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1 Title

Phase 2, open-label, single-arm, multicentre study of trastuzumab deruxtecan (T-DXd) monotherapy to evaluate antitumour activity (primary endpoint: confirmed objective response rate by independent central review per RECIST v1.1) in adults with centrally confirmed HER2-positive unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma after progression on first-line trastuzumab-containing therapy in the United States

Sponsor: Sample Pharma Co., Ltd., Suite 400, Springfield, IL 62701, United States

Protocol identifier: SP-TDXD-GC-201

Protocol version and date: Version 1.0, 24 October 2026

Study setting/scope: Multicentre, United States; conducted under a US IND

Registration: ClinicalTrials.gov, identifier to be assigned

2 Roles and Responsibilities

Protocol Contributors

- Principal Investigator (PI): Not yet designated. The PI at each site will have overall responsibility for local conduct, compliance with the protocol and regulations, medical care of participants, and final approval of site-level data submissions [1,2].
- Coordinating Investigator: Not yet designated. If appointed, will provide scientific leadership across sites, coordinate investigator input on protocol clarifications and amendments, and support interpretation of aggregate data [1].
- Sponsor Medical Lead: Not yet designated. Provides scientific oversight, clinical input on safety and efficacy interpretations, and medical governance of the protocol on behalf of the sponsor [1,3].
- Medical Monitor: Not yet designated. Provides ongoing medical review of safety data, supports eligibility and management queries, and coordinates safety signal evaluation with pharmacovigilance [1,4].
- Study Statistician: Not yet designated. Responsible for statistical design, statistical sections of the protocol and SAP, and final analyses [1,5].
- Pharmacovigilance (PV) Lead: Not yet designated. Oversees safety case processing, expedited and periodic safety reporting under 21 CFR 312.32, safety signal detection, and safety communications [4].
- Data Management Lead: Not yet designated. Oversees the EDC system, eCRF design, data validation, query management, data reconciliations, database lock, and secure data transfers [1].
- Trial Manager/Project Manager: Not yet designated. Manages trial timelines, site start-up and training, cross-functional coordination, vendor oversight, risk management, and inspection readiness [1,3].
- Independent Central Review (ICR) Chair: Not yet designated. Leads the blinded imaging charter implementation, ensures standardized RECIST v1.1 assessments, and manages adjudication processes for discordance per charter [6].
- ILD Adjudication Committee Chair: Not yet designated. Leads independent adjudication of suspected ILD/pneumonitis, ensures standardized case definitions and documentation, and issues case-level adjudication outcomes to the sponsor per charter [1].
- Protocol Writing Group: Not yet designated. Multidisciplinary contributors (clinical, statistics, PV, operations, data management) responsible for drafting, reviewing, and approving the protocol and aligned plans [1,3].
- Final Protocol Approval: The sponsor’s authorized signatory and the PI(s) at participating sites will provide final approval before activation [1,2].

Sponsor and Funder Responsibilities

- Sponsor: Sample Pharma Co., Ltd., Suite 400, Springfield, IL 62701, United States. Sponsor representative(s) and contact details: to be confirmed.
- Sponsor responsibilities include overall trial management and quality oversight; provision of investigational product and labeling; site selection and contracting; investigator training; safety surveillance and regulatory safety reporting; data collection systems; monitoring and audit; data management; statistical analysis; clinical study report (CSR) preparation; and publication planning consistent with ethical and regulatory standards [1-4].
- The sponsor will control access to the full study database for analysis and will determine publication decisions in alignment with applicable authorship and transparency standards; investigators will have timely access to site-level data and to aggregated results after database lock and CSR finalization, consistent with contractual terms and ethical obligations [1,3].

Trial Governance Structure

- Coordinating Center: If appointed, will support site communications, training, start-up, issue escalation, and cross-site quality control; will maintain essential documents supporting protocol implementation and deviations management [1,3].
- Trial Management Group (TMG): Led by the sponsor trial manager and including the medical monitor, PV lead, statistician, data management lead, clinical operations, and relevant vendors. Responsibilities include operational oversight, risk review, recruitment and retention oversight, protocol training, review of monitoring findings, and coordination of corrective and preventive actions (CAPA). Meetings are planned at least monthly, with decisions recorded in minutes and action logs [1,3].
- Steering Committee: If constituted, will include the sponsor medical lead, PI(s)/coordinating investigator, statistician, and ICR chair (non-voting). Responsible for scientific oversight, protocol amendments, recruitment oversight, review of aggregate efficacy and safety summaries, and publication planning. Decisions are documented in committee minutes; the sponsor retains ultimate regulatory responsibility [1,3].
- Relationship to Oversight Bodies: The TMG/steering committee coordinates with the ICR and ILD Adjudication Committee per their charters. There is no DMC/DSMB planned; ongoing sponsor safety review will be performed (see below) [3,5].

Data Monitoring Committee / Data and Safety Monitoring Board

- No DMC/DSMB is planned for this open-label, single-arm Phase 2 study without formal interim efficacy analyses. Ongoing sponsor-conducted safety monitoring will occur, with prompt assessment of emerging safety data and regulatory reporting as required under 21 CFR 312.32. The decision not to constitute a DMC is consistent with FDA guidance, which recommends DMCs when independent, frequent review of accumulating unblinded safety/efficacy is needed to protect participants or trial integrity [4,5].
- If safety concerns emerge that warrant independent oversight, the sponsor may convene an independent DMC under a written charter defining membership, data access, stopping guidelines, confidentiality, and communication pathways [5].

Endpoint Assessment and Adjudication

- Independent Central Review (ICR): A blinded independent review committee (IRC) will evaluate tumor imaging for the primary and key secondary endpoints per a written imaging charter aligned with FDA process standards. The IRC will be independent of site investigators and the sponsor's unblinded data; responsibilities include standardized application of RECIST v1.1, confirmation of responses at least 4 weeks later, adjudication of discordant reads, documentation, quality control, and archived traceability of decisions [6].
- ILD Adjudication Committee: An independent committee will adjudicate all suspected ILD/pneumonitis events using predefined case definitions and source document review, operating under a charter that defines membership, quorum, blinding where applicable, decision rules, documentation, and timelines. Adjudication outcomes will inform safety analyses and management per protocol [1,3].

- No additional endpoint adjudication committees are planned. Standardization and quality control will be ensured through detailed charters, training, imaging acquisition manuals, site manuals, and routine quality checks overseen by the sponsor and vendors [1,6].

Data Management Responsibilities

- The sponsor (through its data management function or contracted CRO) is responsible for EDC system selection, validation, user access control, eCRF design, data standards, edit checks, query management, coding (e.g., MedDRA), external data reconciliation (e.g., imaging, labs, IRT), audit trails, and database lock, consistent with ICH E6(R3) [1].
- Data security, backup, and integrity controls will be maintained; controlled data transfers between vendors and the sponsor will follow documented data transfer agreements and specifications. The data management plan (DMP) and related SOPs will define roles, timelines, and quality metrics; coordination with the statistical team will ensure alignment with the SAP and analysis-ready datasets [1,3].

Investigator and Site Responsibilities

- Investigators are responsible for ethical and compliant conduct of the trial at their sites, including: participant identification; IRB-approved informed consent; eligibility verification; treatment administration; protocol-required assessments; timely and accurate source documentation and eCRF entry; AE/SAE detection and reporting; investigational product (IP) accountability; participant retention and follow-up; and communication with the sponsor/monitors and IRBs [1,2].
- Investigators must ensure IRB approval before initiation and maintain continuing review; protect participant rights and safety per 21 CFR Parts 50 and 56; comply with IND requirements under 21 CFR Part 312; and permit monitoring, audits, and inspections. Investigators will maintain essential documents and delegation logs, and ensure staff are trained and qualified for delegated tasks [2,3].

Monitoring, Auditing, and Quality Assurance Responsibilities

- Clinical monitors (sponsor or designee) will conduct risk-based monitoring to verify informed consent, eligibility, protocol adherence, timely reporting of safety events, source data integrity, IP accountability, and resolution of data queries/findings. Monitoring frequency and methods are described in the Monitoring Plan; findings and CAPA are documented and tracked to closure [3,7].
- Quality Assurance (QA) personnel (independent from routine monitoring) may audit the sponsor systems, vendors, and sites to assess compliance with the protocol, SOPs, and regulations, and to support inspection readiness. Audit scopes and reports are maintained, with appropriate CAPA oversight [1,3,7].
- The sponsor is responsible for ongoing oversight of the quality management system, issue escalation, and ensuring documentation is retained and available for regulatory inspections [1,3].

Pharmacovigilance and Medical Monitoring Responsibilities

- The PV team will process safety cases, perform medical review, assess seriousness and causality in collaboration with investigators, manage follow-up, and ensure expedited IND safety reporting to FDA and investigators as required by 21 CFR 312.32; periodic safety communications will be provided as applicable [4].
- The medical monitor will review cumulative safety data, advise on eligibility/treatment modifications, support management of AEs of special interest (ILD/pneumonitis; LVEF decrease), and coordinate with the ILD Adjudication Committee. The sponsor's safety governance will review emerging signals and recommend study-level risk mitigation or protocol changes when warranted [1,3,4].

Vendor and Third-Party Responsibilities

- Central Imaging Vendor/IRC: Manage image acquisition standards, site training, image transfer and quality control, blinded independent central review per charter, adjudication documentation, and secure data transfer to the sponsor [6].
- Central Laboratory (if used): Provide sample handling manuals, kit supply, logistics, testing, reporting, quality control, proficiency testing, data transfer, and documentation aligned with CLIA where applicable and study specifications [1].
- IRT/IWRS (if used for enrollment and IP management): Maintain validated systems for subject enrollment, kit assignment, IP inventory management, unblinding protections (as applicable), audit trails, and secure interfaces with EDC and supply chains [1,3].
- CROs/Functional Service Providers: May support monitoring, data management, PV case processing, biostatistics, and logistics under written agreements and applicable SOPs; the sponsor retains ultimate responsibility for oversight and compliance [1,3].

Documentation of Responsibilities

- Roles and responsibilities will be documented in the protocol; delegation of authority logs at each site; contracts/work orders; committee charters (IRC, ILD Adjudication Committee); Monitoring Plan; DMP; SAP; PV Plan/Safety Management Plan; vendor agreements; and the Trial Master File (TMF) and Investigator Site Files. Version control will be maintained, and superseded documents archived [1,3].
- Changes to roles, committee membership, sponsor contacts, or vendors will be documented via protocol amendments or administrative memos, contract amendments, and updated logs/charters/plans; changes will be communicated to affected parties and, when required, to IRBs and regulators. All documentation will be retained to support regulatory inspection [1-3].

Conflicts of Interest

- All key personnel (PIs, steering/TMG members, IRC and ILD adjudicators, statisticians, sponsor representatives with decision authority) will disclose financial and non-financial interests before engagement and periodically thereafter. Disclosures will be reviewed by the sponsor (and, where applicable, IRBs) to identify, manage, or eliminate conflicts (e.g., recusal from voting, independent oversight) and will be documented in committee records, TMF, and site files consistent with ethical standards for human research [2,3].
- Members of independent committees (IRC, ILD adjudication) must be free from real or perceived conflicts with the sponsor or investigative sites; independence and confidentiality obligations will be defined in charters and contracts [3,6].

Summary of Governance and Accountability

- The defined roles assign clear scientific, medical, operational, and data stewardship responsibilities across the sponsor, investigators, committees, and vendors, aligning with ICH E6(R3) and FDA regulations to safeguard participant rights and safety, ensure reliable endpoint assessment, enable independent safety and outcome oversight where applicable, and support transparent, high-quality data generation and reporting throughout this Phase 2 study [1-4,6,7].

References

1. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
2. US Food and Drug Administration. Electronic Code of Federal Regulations: 21 CFR Part 50—Protection of Human Subjects; 21 CFR Part 56—Institutional Review Boards; 21 CFR Part 312—Investigational New Drug Application. Silver Spring (MD): FDA; 2026. Available from: https://www.ecfr.gov/current/title-21
3. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice, Annex 1. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_

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5. US Food and Drug Administration. Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. Rockville (MD): FDA; 2006. Available from: https://www.fda.gov/media/75398/download
6. US Food and Drug Administration. Clinical Trial Imaging Endpoint Process Standards: Guidance for Industry. Silver Spring (MD): FDA; 2018. Available from: https://www.fda.gov/media/81172/download
7. US Food and Drug Administration. Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring: Guidance for Industry. Silver Spring (MD): FDA; 2013. Available from: https://www.fda.gov/media/116754/download

3 Open Science, Trial Registration, Data Sharing, and Dissemination

Trial registration

This interventional Phase 2 study will be registered at ClinicalTrials.gov. Registration will be completed before enrollment of the first participant, with Sample Pharma Co., Ltd. listed as the responsible party and the public/scientific contacts as specified in the administrative section. The ClinicalTrials.gov identifier and public URL will be added to the protocol and all trial materials once assigned. Registration will include the official title, study design (open-label, single-arm), eligibility criteria, interventions (trastuzumab deruxtecan [T-DXd] monotherapy 6.4 mg/kg IV every 3 weeks), primary and secondary outcomes, participating US sites, and anticipated timelines, consistent with federal requirements for registration content and Good Clinical Practice (GCP) principles supporting prospective registration [1-4]. Secondary identifiers will include the sponsor protocol number SP-TDXD-GC-201 and the US IND number when issued; there is no EudraCT/CTIS number since the trial is US-only [1-4].

Protocol and Statistical Analysis Plan access

The final approved protocol and any subsequent amendments will be posted to the ClinicalTrials.gov record in accordance with the Clinical Trials Registration and Results Information Submission final rule, which requires submission of the protocol and statistical analysis plan (SAP) with results information; version histories will be maintained, with dates, rationale for changes, and cross-references to the public registry entry to preserve traceability [3]. The sponsor will also archive the current and superseded protocol versions, amendment justifications, and approvals in the trial master file with version control per ICH E6(R3) [6]. If permitted by journal policies, the final protocol and key amendments will be provided as supplementary material with the primary publication [5].

The SAP will be finalized and approved before database lock and before the primary analysis. It will pre-specify methods for the primary and secondary endpoints; analysis populations; estimands where applicable; handling of missing data; multiplicity control (if relevant); and any planned sensitivity analyses. For this Phase 2 design without planned interim analyses, the SAP will detail the exact binomial method for the primary endpoint (two-sided 95% Clopper–Pearson confidence interval for confirmed ORR by independent central review), time-to-event methods (Kaplan–Meier medians with 95% CIs for PFS and OS), and safety summaries (TEAEs, SAEs, AESIs) graded per CTCAE v5.0, with clearly defined decision rules for analysis datasets and data inclusion/exclusion [3,6]. Operationally sensitive information that could compromise trial integrity (e.g., independent committee procedures, specific signal detection thresholds) may be maintained in restricted-access documents such as independent review/adjudication charters, with public-facing summaries linked to the registry or publication to balance transparency and trial integrity [3,6].

Data sharing plan

The sponsor intends to share de-identified individual participant data (IPD) underlying the results reported in the primary publication (analysis-ready datasets), together with the data

dictionary/metadata, SAP, protocol, key amendments, statistical code, and annotated case report forms, where feasible and consistent with participant consent and applicable law. Materials will become available after publication of the primary results and completion of the clinical study report, targeted within 12 months after the primary results are publicly reported, and remain available for at least 36 months thereafter through a controlled-access mechanism managed by the sponsor or a qualified third-party platform designated by the sponsor [3,5-7]. Shared IPD will be de-identified using established standards, and direct identifiers will be removed; indirect identifiers will be handled to reduce re-identification risk consistent with ethical principles and data protection requirements [2,6-7].

Criteria and process for access to shared data

- Who may request access: Qualified researchers affiliated with academic, non-profit, or commercial institutions with appropriate scientific and data security capabilities.
- Purpose: Proposals for scientifically valid research, including verification/replication, meta-analysis, and methodologic studies aligned with the informed consent and ethical approvals.
- Request process: Submit a research proposal, analysis plan, and data protection plan to the sponsor's data access committee for independent review of scientific merit, feasibility, and privacy protections.
- Requirements: Executed data use agreement; commitments to confidentiality and prohibition on re-identification; documentation of institutional approvals and, when applicable, IRB/ethics approval; secure data environment; and timely reporting of findings.
- Transparency: The sponsor will maintain a public listing of approved requests and resulting publications where feasible.

All sharing will comply with informed consent, applicable US regulations, and GCP; requests may be declined where sharing would conflict with participant consent, legal restrictions, or risk participant privacy [2-3,6-7].

Funding and sponsor role

The study is funded and sponsored by Sample Pharma Co., Ltd., which provides investigational product supply and labeling; site selection and contracting; monitoring and quality oversight; data systems; central imaging and independent adjudication vendors; pharmacovigilance; statistical analysis; clinical study report preparation; and publication planning. Consistent with ICH E6(R3), the sponsor is responsible for overall trial management, regulatory submissions, and ensuring data integrity and participant safety. Investigators will have timely access to their site-level data and to aggregated results after database lock and reporting; publication decisions will be aligned with authorship and transparency standards and applicable regulations [1,3,6].

Conflicts of interest

All principal investigators, steering/oversight members, independent central reviewers and adjudicators, statisticians, and sponsor personnel with decision authority will disclose financial and non-financial interests before trial initiation and periodically thereafter. Disclosures will be reviewed and managed (e.g., recusal from decisions, independent oversight) and documented in committee records and the trial master file; any relevant disclosures will be included in publications and registry postings, in line with good publication practice and GCP expectations for transparency and independence [3,6,10].

Dissemination policy

- Registry results: Summary results, including participant flow, baseline characteristics, outcome measures, and adverse events, will be posted on ClinicalTrials.gov within the timelines required by 42 CFR Part 11, including submission of the final protocol and SAP with results information; deadline extensions will be used only as legally permissible and justified [3].
- Peer-reviewed publication: Primary results will be submitted to a peer-reviewed journal, with subsequent publications for key secondary and safety outcomes. Manuscripts will follow

recognized reporting standards and include access to protocol, SAP, and analysis code as permitted.

- Plain-language summary: A participant-friendly summary of main results and safety findings will be prepared and made available to participants upon request and via the sponsor's study webpage or repository, consistent with global best practices for public disclosure [7].
- Communications to stakeholders: Results will be shared with investigators, IRBs, and regulators as required; findings may be presented at scientific congresses. Participants may be informed of overall results through site investigators using IRB-approved communications.

Results will be disseminated regardless of whether findings are positive, negative, or inconclusive, or identify safety concerns. Authorship, sponsor review, and publication rights will follow journal policies and recognized authorship criteria; analyses and interpretations will be based on the locked database and pre-specified SAP to preserve scientific integrity, transparency, and reproducibility [3,5-7,10].

Open science rationale

Prospective registration, public access to the protocol and SAP, timely posting of results, and controlled sharing of de-identified IPD and analysis code promote transparency, reproducibility, participant trust, and regulatory accountability while protecting confidentiality and preserving the scientific integrity of this Phase 2, single-arm design. These practices align with ethical principles for human research and US requirements for registration and results disclosure, and they enable responsible reuse of study information to advance science and patient care [2-3,5-7].

References

1. US Food and Drug Administration. Electronic Code of Federal Regulations: 21 CFR Part 50—Protection of Human Subjects; 21 CFR Part 56—Institutional Review Boards; 21 CFR Part 312—Investigational New Drug Application. Silver Spring (MD): FDA; 2026. Available from: https://www.ecfr.gov/current/title-21
2. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants. Adopted by the 75th WMA General Assembly, Helsinki, October 2024. Ferney-Voltaire (France): WMA; 2024. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-participants/
3. US Department of Health and Human Services. 42 CFR Part 11—Clinical Trials Registration and Results Information Submission. Electronic Code of Federal Regulations. Washington (DC): HHS; 2026. Available from: https://www.ecfr.gov/current/title-42/subtitle-A/subchapter-D/part-11
4. ClinicalTrials.gov. Protocol Registration Data Element Definitions for Interventional Studies. Bethesda (MD): National Library of Medicine; 2024. Available from: https://prsinfo.clinicaltrials.gov/definitions.html
5. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data sharing statements for clinical trials: a requirement of the International Committee of Medical Journal Editors. JAMA. 2017;317(24):2491–2. doi:10.1001/jama.2017.6514. Available from: https://jamanetwork.com/journals/jama/article-abstract/2626570
6. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
7. World Health Organization. Joint statement on public disclosure of results from clinical trials. Geneva: WHO; 2017. Available from: https://www.who.int/news/item/18-05-2017-joint-statement-on-public-disclosure-of-results-from-clinical-trials
8. National Library of Medicine. ClinicalTrials.gov Results Data Element Definitions for Interventional Studies. Bethesda (MD): NLM; 2024. Available from: https://prsinfo.clinicaltrials.gov/results_definitions.html
9. National Institutes of Health. NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. Bethesda (MD): NIH; 2016. Available from: https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm
10. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Updated 2024. Philadelphia (PA): ICMJE; 2024. Available from: http://www.icmje.org/recommendations/

4 Patient and Public Involvement

Patients, caregivers, patient advocates, patient organizations, community representatives, and members of the public were not involved in the planning, design, conduct, analysis, reporting, or dissemination planning of this Phase 2, single-arm study; this statement pertains to involvement in shaping the research and does not include participation as enrolled subjects [1]. The extent of patient and public involvement is disclosed in accordance with SPIRIT guidance, and participant protections will be ensured through IRB review and written informed consent consistent with ICH E6(R3) and the Declaration of Helsinki (2024) [1-3].

References

1. Chan A-W, Boutron I, Hopewell S, Moher D, Schulz KF, Collins GS, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. BMJ. 2025;389:e081477. doi:10.1136/bmj-2024-081477. Available from: https://doi.org/10.1136/bmj-2024-081477
2. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
3. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants. Adopted by the 75th WMA General Assembly, Helsinki, October 2024. Ferney-Voltaire (France): WMA; 2024. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-participants/

5 OBJECTIVES

5.1 Study design

Overview and design

This is a Phase 2, open-label, single-arm, multicentre study conducted at US sites under a US IND to evaluate the antitumour activity and safety of investigational trastuzumab deruxtecan (T-DXd) monotherapy in adults with centrally confirmed HER2-positive unresectable or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma after progression on first-line trastuzumab-containing therapy. The primary endpoint is confirmed objective response rate (ORR) per RECIST v1.1 by independent central review (ICR), with response confirmation at least 4 weeks after initial documentation of complete or partial response [1-4]. Safety is assessed with NCI CTCAE v5.0 grading; study conduct follows ICH E6(R3) Good Clinical Practice and the Declaration of Helsinki (2024) [1,2,5]. The design is informed by prior randomized Phase 2 evidence supporting T-DXd antitumour activity in this disease setting and the need for data in Western populations [6].

Population and eligibility framework

Adults (≥18 years) with histologically confirmed unresectable or metastatic gastric/GEJ adenocarcinoma, HER2-positive by central testing on a post-progression biopsy (IHC 3+ or IHC 2+/ISH+ per ASCO–CAP guidance), at least one measurable lesion per RECIST v1.1, ECOG performance status 0–1, left ventricular ejection fraction (LVEF) ≥50%, and adequate organ function will be enrolled [3,4,7]. Protocol-defined organ function thresholds will include, at minimum: absolute neutrophil count ≥1.5 × 10^9/L; platelets ≥100 × 10^9/L; haemoglobin ≥9.0 g/dL; total bilirubin ≤1.5 × ULN (≤3 × ULN for Gilbert syndrome); AST and ALT ≤3 × ULN (≤5 × ULN with liver metastases); creatinine clearance ≥50 mL/min (Cockcroft–Gault). Key exclusions include receipt of any anticancer therapy after the first-line trastuzumab-containing regimen; history of non-infectious interstitial lung disease (ILD)/pneumonitis requiring steroids, or current/suspected ILD at screening; significant cardiac disease; clinically severe pulmonary disease; and untreated or symptomatic brain metastases (treated, stable lesions permitted). All participants will provide written informed consent prior to any study procedures; institutional review board approval is required at each site [1,2,7].

Treatment administration

All participants will receive T-DXd 6.4 mg/kg administered intravenously once every 3 weeks (Q3W; 21-day cycles). The first infusion will be given over at least 90 minutes; if tolerated, subsequent infusions may be administered over at least 30 minutes. Dose reductions are permitted in a stepwise manner to 5.4 mg/kg and then 4.4 mg/kg; re-escalation is not allowed. Doses may be delayed for up to 28 days to allow recovery from toxicities; delays beyond 28 days will lead to permanent discontinuation. Infusion preparation, administration, premedication, and post-infusion observation will follow institutional standards and the protocol-specific infusion guidance. Dose interruption and modification rules, including those for ILD/pneumonitis and other adverse reactions, will follow protocol specifications aligned with the current US prescribing information for T-DXd; no retreatment, maintenance, or study extension is planned [5,8].

Visit structure and assessments

- Screening (up to 28 days): eligibility confirmation, central HER2 testing on a new biopsy obtained after progression on first-line therapy, medical history and prior therapy review, physical examination, ECOG status, vital signs, triplicate 12-lead ECG, echocardiogram or MUGA for LVEF, clinical laboratory evaluations (haematology, chemistry, urinalysis), pregnancy testing (as applicable), and baseline tumour imaging (CT with contrast of chest/abdomen/pelvis and other disease sites; MRI permitted if clinically indicated) [3,4,7].
- Treatment period (Day 1 of each 21-day cycle): physical examination focused on interval symptoms and toxicities, ECOG status, vital signs, concomitant medications, adverse event assessment (CTCAE v5.0), clinical laboratory tests, and investigational product administration. ECGs will be obtained during treatment at clinically appropriate intervals; LVEF will be assessed by the same modality used at baseline at Cycle 5 Day 1 and every 4 cycles thereafter. Tumour imaging will occur every 6 weeks (±7 days) during the first year and every 12 weeks (±7 days) thereafter until radiographic progression by ICR or initiation of new anticancer therapy [3-5].
- End-of-treatment: performed at treatment discontinuation for any reason and includes safety and disease assessments.
- Safety follow-up: 40 days (+7) after the last dose to capture late-emerging adverse events, including events of special interest.
- Survival follow-up: every 12 weeks (±14 days) by remote contact or clinic visit to ascertain survival status and subsequent anticancer therapies, continuing until study end.

Tumour evaluation and endpoint framework

Tumour response and progression will be assessed by ICR according to RECIST v1.1 using standardized imaging acquisition and review procedures detailed in an imaging charter consistent with FDA imaging endpoint process standards [3,4]. The primary endpoint is confirmed ORR (proportion with complete or partial response, confirmed ≥4 weeks after first documentation). Key secondary endpoints include progression-free survival (PFS) by ICR, overall survival (OS), and duration of response (DoR) by ICR. Safety endpoints include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs: ILD/pneumonitis; LVEF decrease), graded per CTCAE v5.0. Time-to-event endpoints will be summarized using Kaplan–Meier methods; the primary analysis will estimate ORR with a two-sided 95% exact Clopper–Pearson confidence interval in the Full Analysis Set (all dosed participants) [4-6].

Safety monitoring, dose modification, and risk management

Safety oversight will include continuous on-study monitoring by the sponsor with expedited IND safety reporting in accordance with 21 CFR 312.32 [5,9]. AESIs include:

- ILD/pneumonitis: T-DXd will be interrupted at the first suspicion of ILD/pneumonitis; prompt diagnostic evaluation (e.g., high-resolution chest CT, pulmonology consultation) is required. For Grade 1 (asymptomatic) events, treatment may resume only after complete radiographic resolution; for Grade ≥2 events, T-DXd must be permanently discontinued and systemic corticosteroids initiated per institutional standards. All suspected ILD cases will undergo independent adjudication per charter [5,8].

- LVEF decrease: LVEF will be monitored by echocardiogram or MUGA at baseline, Cycle 5 Day 1, and every 4 cycles thereafter (same modality throughout). Management of declines in LVEF will follow protocol-specified interruption/discontinuation criteria aligned with T-DXd product guidance and cardiology standards; participants with symptomatic heart failure or clinically significant LVEF reduction will discontinue T-DXd [5,8].

Other adverse reactions will be managed with supportive care, dose interruptions, and dose reductions (to 5.4 mg/kg then 4.4 mg/kg) per protocol and current US prescribing information for T-DXd; re-escalation is not permitted [5,8].

Treatment continuation and discontinuation

Participants will continue T-DXd until radiographic disease progression, unacceptable toxicity, withdrawal of consent, investigator decision, pregnancy, noncompliance, or another protocol-defined reason for discontinuation. Participants with clinical benefit who experience ICR-confirmed progression will discontinue treatment; initiation of any new anticancer therapy will also require treatment discontinuation. Missed or delayed doses may be administered within a 28-day window from the planned date; delays beyond 28 days mandate discontinuation. There is no retreatment, maintenance, or extension phase [5].

Sample size, sites, and study duration

Approximately 80 participants will be enrolled to obtain 72 dosed participants for the primary analysis, providing about 90% power for the lower bound of the two-sided 95% exact CI for ORR to exceed 27% if the true ORR is 45%, consistent with the design objective. Enrollment is planned over 18–24 months across multiple US centres, with study completion approximately 12 months after the last participant's first dose (total duration about 30–36 months). No interim analyses or futility rules are planned [6].

References

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5.2 Randomization: Sequence Generation

Responsibility for Sequence Generation

No random allocation sequence will be generated. This is a Phase 2, open-label, single-arm study in which all enrolled participants receive investigational trastuzumab deruxtecan (T-DXd) monotherapy; therefore, sequence generation is not applicable. In accordance with SPIRIT 2025, the protocol explicitly specifies that the trial is not randomized and thus has no allocation sequence to generate [1]. Documentation of enrollment and treatment assignment will follow Good Clinical Practice (GCP) obligations for protocol-defined procedures without randomization [2].

Method Used to Generate the Sequence

Not applicable. No computer-generated or other allocation sequence will be created because all participants are assigned to the single investigational arm. As required by SPIRIT 2025, the protocol clarifies the absence of randomization rather than specifying a randomization method [1]. Study enrollment and treatment initiation will be performed per the protocol and GCP without use of IRT/IWRS for randomization [2].

Type of Randomization

Not applicable. No simple, blocked, stratified, or adaptive randomization is planned because the design is single-arm and non-randomized, consistent with the protocol's stated design characteristics and SPIRIT 2025 reporting expectations for explicitly identifying non-randomized trials [1].

Allocation Ratio

Not applicable. All participants receive T-DXd; there are no comparator arms and no allocation ratio to define [1].

Stratification Factors

Not applicable. No randomization or stratification will be performed. Balance across prognostic factors will be described descriptively at baseline in the analysis populations, consistent with transparent reporting in non-randomized designs [1,2].

Blocking and Other Restrictions

Not applicable. No blocks, permuted blocks, or other randomization restrictions are used because no random allocation will occur [1].

Multi-Site Randomization

Not applicable. There is no randomization at any site. Enrollment and assignment to the single investigational arm will occur per protocol at participating US sites under GCP; no central or site-level randomization lists will exist [2].

Documentation and Quality Control

Because no randomization sequence is generated, there is no randomization specification, program, or allocation list to validate or to retain. Trial documentation will instead capture enrollment procedures, eligibility confirmation (including central HER2 testing), and treatment assignment to the single arm in accordance with GCP record-keeping, access control, and audit trail requirements [2]. The protocol's explicit declaration of a non-randomized design fulfills SPIRIT 2025 requirements to describe sequence generation or its inapplicability [1].

Confidentiality of the Randomization Sequence

Not applicable. There is no allocation sequence to protect or conceal [1].

Summary

This single-arm, non-randomized Phase 2 design assigns all participants to investigational T-DXd; therefore, no random allocation sequence will be generated. The protocol explicitly states the non-

randomized nature of the trial in alignment with SPIRIT 2025, and enrollment, assignment, and documentation will be conducted under GCP without randomization-related procedures. This approach is appropriate for the study's proof-of-concept/signal-seeking objectives and ensures transparent reporting of the absence of randomization [1,2].

References

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5.3 Blinding and Unblinding

1. Blinding status

This is an open-label, single-arm Phase II study. Trial participants, investigators, treating physicians, care providers, study coordinators, site pharmacists, sponsor clinical team, and monitors are not blinded to investigational product administration. To mitigate detection and assessment bias, the following functions are blinded: independent central radiology reviewers for tumour response/progression per RECIST v1.1 (primary and key secondary efficacy assessments) and the independent committee that adjudicates suspected interstitial lung disease (ILD)/pneumonitis. These reviewers/adjudicators are blinded to site identity, investigator assessments, and avoid access to information that could unduly influence endpoint determination beyond what is prespecified in their charters. Trial statisticians conducting the final analysis will work from the locked database following completion of central reviews; no treatment code release is applicable because there is no comparator arm. The Data Monitoring Committee is not planned for this open-label single-arm trial; ongoing safety surveillance is performed by the sponsor in accordance with ICH GCP and applicable regulations [1-5].

2. Rationale for blinding approach

A fully blinded design is infeasible because the study is single-arm and all participants receive intravenous trastuzumab deruxtecan (T-DXd) on a fixed schedule without a matched placebo or double-dummy comparator. Scientific measures to reduce bias include use of standardized, objective imaging criteria (RECIST v1.1), blinded independent central review (ICR) as the primary assessment method, an adjudication committee for ILD/pneumonitis, prespecified assessment schedules, and analysis from a locked database per ICH GCP. This approach addresses performance and detection bias while maintaining feasibility and participant safety in an interventional, open-label context consistent with SPIRIT reporting guidance and Helsinki principles on scientific validity and minimization of bias [1-4,6].

3. Method used to achieve blinding

Blinding is implemented at the level of efficacy and safety endpoint assessment:

- Independent central radiology review: All tumour imaging is transferred to a central vendor and evaluated by qualified radiologists blinded to investigator assessments, site identity, and extraneous clinical details, using a chartered workflow aligned with FDA imaging endpoint process standards and RECIST v1.1 [3,4].
- ILD/pneumonitis adjudication: A committee of independent clinicians reviews suspected ILD/pneumonitis cases using a chartered process. Reviewers are blinded to investigator causality assessments and site identity and receive only prespecified clinical and imaging data necessary for adjudication [2,3,5].

No blinding of the investigational product is performed at sites; infusion preparation and administration are open-label. Because there is no comparator, matched placebos and double-dummy procedures are not applicable [1-4].

4. Blinded intervention supply, packaging, and labeling

Investigational product supply is open-label. Packaging and labeling comply with applicable regulations and ICH GCP; labels and dispensing records identify T-DXd without implying clinical outcomes. Site pharmacy personnel are unblinded for preparation and accountability. To protect the integrity of blinded endpoint assessments, shipment documents, pharmacy logs, and source records that might reference dosing details are not provided to central reviewers or adjudicators; central vendors receive only the data specified in their charters. Accountability, storage conditions, and returns are documented in pharmacy records and monitored without sharing with blinded assessors [1,2].

5. Procedures to maintain blinding during the trial

- Role segregation: Blinded central reviewers and ILD adjudicators are organizationally and systemically separated from site teams, sponsor clinical operations, and monitors. ICR determinations of progression and ILD adjudication outcomes are communicated on an ongoing basis as defined in the charters; other access to their work product is restricted until database lock [1,3].
- Data flow controls: Imaging and adjudication data are transferred via secure systems with role-based access limiting visibility of site identifiers, dosing details, and investigator assessments to blinded personnel. Queries affecting endpoint determinations are handled through the vendor and do not disclose unnecessary clinical context [1,3].
- Standardized assessments: Imaging is acquired per protocol with prespecified timing and parameters; responses/progression are determined by ICR per RECIST v1.1. Safety is graded per CTCAE v5.0 using standardized criteria to minimize subjective influence [3,5].
- Communications: Site and sponsor personnel must not disclose dosing information, infusion reactions, or other treatment details to blinded assessors. All staff are trained on communication boundaries and documentation practices that protect blinding of central assessments [1,2].
- Interim data access: There are no planned interim efficacy analyses. Any internal aggregate safety reviews avoid sharing participant-level clinical details with blinded assessors [1,2].

6. Blinding of outcome assessment and data analysis

- Blinded outcome assessment: The primary endpoint (confirmed ORR) and key secondary efficacy endpoints (PFS, DoR) are assessed by ICR under blinded conditions as described above. Investigator assessments are collected but are not primary for efficacy analysis [3,4].
- Safety adjudication: ILD/pneumonitis is adjudicated by an independent committee operating under blinded, charter-defined procedures. Adjudication outputs are integrated into the safety database [2,5].
- Data analysis: Final statistical analyses are conducted after database lock once all central reviews and adjudications are complete. Because there is no treatment comparison, no treatment code release is required. Blinded endpoint determination supports reduction of detection bias and enhances interpretability of efficacy outcomes in the open-label setting [1-4].

7. Assessment of blinding integrity

Formal assessments (e.g., guess-the-assignment questionnaires) are not planned because participants and treating staff are unblinded. Integrity of blinded central assessments is upheld through chartered processes, separation of roles, controlled data flows, and quality checks by the central vendors and sponsor quality oversight in accordance with ICH GCP [1-3].

8. Permissible circumstances for unblinding

There are no masked treatment assignments for clinical teams; therefore, participant-level emergency unblinding is not applicable. Lifting of blinding for central reviewers or adjudicators is permissible only:

- After database lock for reporting purposes; or
- If mandated by regulatory authority, IRB, or serious safety concerns where access to specific reviewed data is necessary for immediate participant safety or regulatory reporting, as defined in applicable guidance and charters.

Unblinding is not permitted for convenience, administrative reasons, or participant request without medical necessity [1,2,6].

9. Emergency unblinding procedure

Not applicable to treatment assignment. If exceptional circumstances require identifying information from a blinded central review or adjudication record to manage an urgent safety issue, the sponsor medical monitor (or designee) may authorize controlled disclosure limited to the minimum necessary information. The central vendor will document date/time, requester, reason, authorization, data disclosed, and recipients; the sponsor will notify the IRB and regulators if required and maintain audit trails consistent with ICH GCP and US IND safety reporting requirements [1,2,6].

10. Management of accidental or unauthorized unblinding

Any accidental disclosure that could bias central efficacy or ILD adjudication (e.g., transmission of site identifiers, dosing details, or investigator assessments to blinded reviewers) will be recorded as a protocol deviation or quality event. The sponsor will assess potential impact on participant safety, endpoint validity, and analyses; implement corrective and preventive actions; and, if necessary, replace the affected assessment with a new blinded read per charter. All events and remediations will be documented and available for monitoring, audit, and inspection under ICH GCP [1-3].

11. Post-unblinding participant management

Because treatment is open-label, participant care is unaffected by blinding. If any central assessment must be invalidated due to unblinding, the participant will continue scheduled study visits and imaging; endpoints will be reassessed per charter where feasible without compromising safety or data integrity, and analysis handling will be prespecified in the SAP [1-3].

12. Documentation and quality control

Training records, delegation logs, pharmacy accountability, data access logs, imaging and adjudication charters, vendor quality documentation, audit trails, and any unblinding-related reports will be maintained in the investigator site files and the trial master file. Monitors, auditors, sponsor quality personnel, and regulatory inspectors may verify adherence to blinding procedures through records review and system audit trails without accessing central reviewers' masked determinations before database lock, in line with ICH GCP and ethical principles of transparency and scientific rigor [1-3,6].

13. Summary

Although the trial is open-label for participants and treating teams, rigorous blinding of independent central radiology review for efficacy endpoints and blinded adjudication of suspected ILD/pneumonitis are implemented to minimize detection and analytical bias. Clear role separation, controlled data access, standardized assessment criteria, and chartered review processes support scientific validity, participant safety, and regulatory compliance consistent with ICH GCP, FDA imaging standards, SPIRIT reporting guidance, and the Declaration of Helsinki [1-4,6].

References

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5.4 Allocation Concealment Mechanism

Purpose of allocation concealment
Allocation concealment prevents selection bias by ensuring investigators, site personnel, participants, and recruiters cannot foresee or influence treatment assignment before randomization; it is conceptually distinct from blinding, which protects knowledge of assigned treatment after allocation [1,2]. This study is single-arm and non-randomized; consequently, there is no random allocation to conceal, and SPIRIT guidance requires the protocol to explicitly state the inapplicability of allocation concealment procedures [1].

Allocation concealment mechanism
No allocation concealment mechanism is implemented because no randomization occurs. There is no interactive response technology (IRT/IWRS), central web/telephone randomization, or envelope system for treatment assignment. All enrolled participants receive investigational trastuzumab deruxtecan (T-DXd) monotherapy per protocol without use of an allocation list [1].

Concealment until assignment
Because there is no allocation sequence, no concealment or release of assignments is performed. Treatment initiation occurs only after written informed consent, completion of all protocol-defined screening procedures, and confirmation of eligibility are documented in accordance with ICH GCP; there is no access to randomization lists, block sizes, or stratification-specific allocation tables as none exist [1,3].

Access control and authorized personnel
No users are authorized to access treatment allocation data because there is no randomization. Role-based access to study systems (e.g., EDC, trial master file) is maintained per ICH GCP to ensure that only delegated, trained personnel perform enrollment and treatment initiation tasks and that records are secure, contemporaneous, and auditable [3].

Site-level procedures
Sites must not initiate dosing until the following are verified and documented in source and study records: signed informed consent, completion of all required screening and baseline procedures, and confirmation that all inclusion criteria are met and exclusion criteria are not met. Investigator authorization to proceed with dosing must be recorded per site delegation and GCP documentation standards [3]. These steps substitute for any “pre-randomization” checks that would occur in randomized trials.

Stratification and allocation concealment
Stratified randomization is not used. Any baseline variables captured for analysis are not used to direct allocation; therefore, no stratification inputs are entered into a randomization system and no concealment of stratum-specific lists is required [1].

Emergency access and unblinding interface
Emergency access to concealed allocations is not applicable because there are no masked treatment assignments. Procedures governing blinded independent central review and blinded ILD adjudication are described separately under Blinding and Unblinding and operate independently of any allocation processes [1,3].

Audit trail and documentation
Study records will document informed consent, eligibility determinations, investigator authorization for treatment initiation, dosing start dates, and accountability of investigational product. System and

process controls (user access logs, delegation logs, monitoring reports, and TMF/ISF documentation) will be maintained to ICH GCP standards, providing an auditable trail of enrollment and dosing decisions despite the absence of allocation concealment procedures [3].

Prevention and management of allocation concealment breaches

Traditional allocation-concealment breaches (e.g., envelope tampering, prediction of upcoming assignments) cannot occur because there is no allocation sequence. Any quality events that could bias blinded central assessments (e.g., inadvertent disclosure of non-essential clinical details to blinded assessors) will be managed as protocol deviations or quality issues with documented impact assessment and corrective and preventive actions per GCP [1,3].

Quality control and monitoring

Ongoing monitoring will verify that participants were not dosed before full eligibility confirmation, that documentation is complete, and that role-based access and training are maintained. Monitors will review enrollment and dosing records and verify compliance with protocol and GCP; findings will be recorded and followed until resolution [3].

Summary

Because the trial is single-arm and non-randomized, no allocation sequence exists and no allocation concealment is required. GCP-governed enrollment verification, documentation, access control, and monitoring ensure procedural rigor, protect against operational bias at enrollment, and support the validity of efficacy and safety assessments in this Phase II study [1,3].

References

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5.5 Implementation of Randomization

Overview of Randomization Implementation

This study is non-randomized and single-arm; therefore, no random allocation is performed. Participants will be enrolled and assigned to receive investigational trastuzumab deruxtecan (T-DXd) monotherapy only after all pre-specified screening and baseline procedures are complete, written informed consent has been obtained, eligibility has been confirmed, and investigator authorization for dosing has been documented. Operational implementation emphasizes prevention of selection bias through protocol-governed eligibility verification, maintenance of auditable records, and separation of responsibilities for enrollment, endpoint assessment, and data management to preserve scientific integrity in accordance with SPIRIT 2025 and ICH E6(R3) Good Clinical Practice (GCP) [1,2,3].

Personnel Responsible for Enrolling Participants

Enrollment at each site will be performed by the principal investigator or qualified, delegated sub-investigator/study physician, supported by trained site personnel (e.g., study coordinator or research nurse) per the site delegation log. Responsibilities include:

- Confirming written informed consent prior to any study-specific procedures.
- Verifying inclusion/exclusion criteria, including central HER2 confirmation on a post-progression biopsy and required baseline assessments.
- Completing all screening documentation and confirming the participant is ready for treatment initiation.
- Obtaining and documenting investigator authorization to proceed with dosing.

Enrollment personnel will not have access to any random allocation sequence or concealed assignment information because no randomization is conducted [1,2,3,4,5].

Personnel Responsible for Assigning Participants to Interventions

Assignment to intervention consists of initiating T-DXd per protocol for all eligible, consented participants. Authorized site personnel will complete enrollment in study systems (e.g., EDC and site/pharmacy records) and notify pharmacy for investigational product preparation and dispensing. No centralized IRT/IWRS or allocation system is used, and site personnel receive no information on future assignments, block sizes, or algorithms, as these do not exist in a single-arm design [1,2].

Access to the Random Allocation Sequence

There is no random allocation sequence, block size, or restricted randomization detail to access. Investigators, site staff, participants, endpoint assessors, and sponsor personnel operate without any allocation-related information. Blinded independent central review and ILD adjudication operate under separate charters and are unaffected by allocation considerations [1,2].

Separation of Duties

Separation of duties is maintained between:

- Enrollment/treatment assignment (investigator and delegated site staff).
- Investigational product preparation/accountability (site pharmacy).
- Blinded independent central radiology review and blinded ILD adjudication (independent vendors/committees operating under charter).
- Data management and statistical analysis (sponsor or designees).

Where complete separation is not feasible, safeguards include role-based system permissions, vendor-controlled data access, secure audit trails, and chartered procedures to prevent cross-access to blinded endpoint determinations, consistent with ICH GCP [2,3].

Randomization Workflow at Site Level

Because no randomization occurs, the site-level workflow for treatment initiation is:

- Confirm written informed consent.
- Complete screening and baseline assessments, including central HER2 confirmation and verification of inclusion/exclusion criteria.
- Verify any protocol-specified stratification variables or baseline factors required for analysis (data collection only; not used for allocation).
- Obtain and document investigator approval for dosing.
- Enter required enrollment/baseline data in study systems.
- Notify pharmacy for preparation/dispensing of T-DXd; initiate the assigned intervention (single arm).
- Document date/time of enrollment, participant ID, dosing start date/time, responsible personnel, and any relevant baseline variables.

All steps must be documented in source records, case report forms, and site/pharmacy accountability logs; essential documents are filed in the investigator site file and trial master file to ensure an auditable trail per ICH GCP and applicable US regulations [2,3,4,5,6].

Centralized Randomization System

A centralized randomization system is not used. Study systems supporting enrollment and investigational product accountability employ role-based access controls, password protection, validation appropriate to their function, and audit trails. In the event of system outages affecting enrollment documentation, sites will follow sponsor instructions for contemporaneous paper documentation with subsequent reconciliation in the electronic system to maintain a complete audit trail in accordance with GCP [2].

Documentation of Randomization

Documentation requirements for this non-randomized assignment include:

- Enrollment confirmation and investigator authorization for dosing.
- Participant identifiers, date/time of enrollment and first dose, and personnel involved.
- Captured baseline/stratification variables for analysis (not used for allocation).
- Pharmacy preparation and dispensing records, including lot numbers, quantities dispensed/returned, and accountability.

- System audit trails and any corrections or queries related to enrollment or dosing.

Records will be maintained per the protocol, monitoring plan, data management plan, sponsor procedures, and regulatory requirements (21 CFR Parts 50, 56, 312) and retained to support monitoring, audit, and inspection [2,4,5,6].

Management of Randomization Errors or Deviations

In the absence of randomization, operational deviations may include enrollment of an ineligible participant, dosing before completion of required assessments, duplicate enrollment, incorrect data entry affecting baseline variables, or dispensing errors. Such events will be documented as protocol deviations or quality events, evaluated for impact on participant safety and endpoint integrity, and addressed with corrective and preventive actions. Consistent with the Statistical Methods section and intention-to-treat principles for this design, participants who receive at least one dose will be included in the Full Analysis Set, with handling of deviations prespecified in analysis conventions and documented accordingly [1,2].

Quality Control and Monitoring

Implementation of enrollment and single-arm assignment will be subject to:

- Source data verification of consent, eligibility, and dosing authorization.
- Review of enrollment records, pharmacy accountability, and reconciliation with EDC.
- Audit trail review of system entries and role-based access logs.
- Documentation of training and delegation.
- Review of protocol deviations and resolution of findings.

Monitoring will adhere to ICH GCP and sponsor oversight procedures; records will be available for audits and regulatory inspections [2,3].

Summary

Because this is a single-arm, non-randomized Phase II study, operational implementation focuses on rigorous eligibility verification, documented investigator authorization, controlled data access, comprehensive audit trails, and segregation of roles, while avoiding any processes that could introduce selection bias. These controls ensure transparent, auditable, and unbiased assignment of eligible participants to the investigational intervention, preserving participant safety, data integrity, and methodological validity in accordance with SPIRIT 2025, ICH GCP, the Declaration of Helsinki, and applicable US regulations under the IND [1,2,3,4,5,6].

References

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5.6 Trial Setting and Participating Sites

Overall Trial Setting

This multicentre Phase 2 study will be conducted at US-based academic hospitals, university-affiliated comprehensive cancer centers, and high-volume community oncology networks with outpatient infusion services. These settings are appropriate for the target population and investigational trastuzumab deruxtecan (T-DXd) monotherapy because they routinely manage adults with advanced gastric and gastro-oesophageal junction (GEJ) adenocarcinoma, perform complex oncologic infusions, and support the protocol's safety surveillance (including monitoring for interstitial lung disease [ILD]/pneumonitis and left ventricular ejection fraction [LVEF] changes) in alignment with Good Clinical Practice (GCP) and the Declaration of Helsinki [1,2]. The sites will follow US IND requirements for human subject protection and institutional review board (IRB) oversight [3-5].

Geographic Scope and Recruitment Locations

The trial will be conducted exclusively in the United States under a US IND and registered on ClinicalTrials.gov (identifier pending assignment) [3,6]. Enrollment is planned over approximately 18–24 months with activation of multiple US centres; the final number and distribution of participating sites are to be confirmed prior to protocol finalization and documented in the site list maintained by the sponsor. A US-only, multicentre footprint is intended to enhance feasibility of recruiting adults with centrally confirmed HER2-positive unresectable or metastatic gastric/GEJ adenocarcinoma and to support generalizability to US clinical practice while aligning with the study's regulatory strategy and standardized endpoint assessment by independent central review [1,4,6,7].

Site Type and Site Capabilities

Participating sites are expected to have:

- Demonstrated experience conducting Phase 2 interventional oncology trials under ICH GCP, with established IRB processes and capacity for timely safety reporting [1,4,5].
- Access to the target population and standard diagnostic pathways for gastric/GEJ adenocarcinoma, including procurement of a new post-progression biopsy and shipment for central HER2 testing consistent with ASCO–CAP guidance [8].
- Outpatient infusion facilities capable of administering T-DXd IV every 3 weeks and managing infusion reactions and other acute events; on-site or on-call emergency care coverage [1].
- Pharmacy services with investigational product (IP) receipt, controlled storage, temperature monitoring, dispensing, and accountability; facilities and procedures to handle antineoplastic/hazardous drugs per institutional policies informed by NIOSH guidance [1,9].
- Safety monitoring capabilities including pulmonology consultation and high-resolution chest CT for suspected ILD/pneumonitis, and cardiology support for serial LVEF assessments by echocardiogram or MUGA using consistent modality across time points [1,2].
- Imaging capabilities and data transfer processes that adhere to RECIST v1.1 acquisition standards and FDA imaging endpoint process guidance for centralized blinded reads [7].
- Clinical laboratories for protocol-required testing (hematology, chemistry, urinalysis), ECG acquisition (including triplicate at screening), pregnancy testing as applicable, and secure sample processing/shipment to any designated central laboratories [1].
- Validated electronic data capture (EDC) and secure data transfer systems with role-based access and audit trails to support timely, accurate data entry and query resolution [1].

Site Eligibility Criteria

Sites should meet the following minimum criteria:

- Principal investigator and sub-investigators qualified by training and experience to care for patients with advanced solid tumors and to conduct clinical trials per ICH GCP and local regulations; availability of trained study coordinators and research nurses [1,5].
- Documented prior experience with Phase 2 oncology studies, including timely reporting of adverse events per CTCAE v5.0 and compliance with IND safety reporting where applicable [3,5,10].
- Feasible access to the eligible patient population, including capability to obtain, process, and ship new tumor biopsies for central HER2 confirmation per ASCO–CAP standards [8].
- Adequate facilities for investigational product management and hazardous drug handling, including storage, preparation, dispensing, and accountability procedures consistent with institutional and NIOSH recommendations [1,9].

- Ability to perform and schedule protocol-required assessments (imaging, echocardiogram/MUGA, ECGs, laboratory testing) and to transfer de-identified imaging to the central vendor per charter [7].
- Readiness for monitoring, audit, and inspection, including use of EDC, maintenance of essential documents, and adherence to protocol-specific timelines for eligibility confirmation, data entry, and safety reporting [1,3-5].

If any formal site eligibility checklist is not specified elsewhere, participating sites will be selected based on their ability to protect participants, implement the protocol with fidelity, recruit eligible participants, perform required assessments, maintain data quality, and comply with regulatory, ethical, and sponsor requirements [1,2].

Individuals Delivering the Intervention

- Investigators and delegated study physicians will oversee medical eligibility, treatment decisions, and safety monitoring per protocol and GCP [1].
- Oncology nurses/infusion staff will administer T-DXd IV and conduct pre-/post-infusion observations according to protocol and institutional standards, with competency in managing infusion reactions and escalations [1].
- Pharmacists will manage IP receipt, storage, preparation, dispensing, and accountability in accordance with site SOPs and hazardous drug handling policies [1,9].
- Radiology, cardiology, and pulmonology personnel will perform protocol-specified assessments (imaging per RECIST v1.1 acquisition parameters, echocardiogram/MUGA, high-resolution CT for suspected ILD) with documentation suitable for central review/adjudication [7,10].
- Study coordinators/data managers will ensure timely EDC entry, source documentation, query resolution, and scheduling of assessments consistent with visit windows [1].

All personnel performing protocol procedures must be trained and documented on the protocol, safety reporting, informed consent, IP handling, EDC, and imaging transfer workflows before site activation; responsibilities will be captured in delegation logs [1,5,6].

Site Start-Up, Training, and Standardization

Prior to enrollment, each site will complete start-up activities including IRB approval, execution of study agreements, verification of essential documents, site initiation visits, and role-based training covering protocol conduct, informed consent, eligibility confirmation (including central HER2 workflow), adverse event grading/reporting, IP handling, EDC use, and imaging/ILD adjudication charters [1,3-7,10]. Standardization measures will include:

- Use of RECIST v1.1-compliant imaging acquisition parameters and centralized blinded independent review per FDA imaging process standards [7].
- Consistent LVEF assessment by the same modality over time and prespecified schedules [1,10].
- Uniform safety grading with CTCAE v5.0 and expedited IND safety reporting under 21 CFR 312.32 [3,10].
- Controlled data flows and role-based access to protect the blinding of central efficacy assessment and ILD adjudication outputs per charter [7].
- Monitoring plans aligned with GCP to verify consent, eligibility, IP accountability, data integrity, and adherence to visit windows [1].

Relevance to Recruitment and Generalizability

Selecting US academic and community oncology centres with established gastric/GEJ care pathways and biopsy capability is intended to support timely identification of eligible participants requiring a new post-progression biopsy for central HER2 confirmation, thereby enhancing accrual feasibility within the planned 18–24 months. Inclusion of diverse practice settings (academic and community) is expected to improve external validity by reflecting variability in referral patterns, supportive care, and diagnostic practices within US standards, while centralized imaging and adjudication mitigate assessment heterogeneity and support consistent endpoint evaluation across sites [1,2,7].

Documentation and Updates

A master site list will be maintained by Sample Pharma Co., Ltd. (protocol SP-TDXD-GC-201) and will include site identifiers, principal investigator names, institutional affiliations, country/region, activation

status, IRB approvals, delegation logs, training records, monitoring visit reports, and essential documents filed in the trial master file and investigator site files per ICH GCP [1,5]. Any changes in participating sites, activation status, or responsibilities will be documented, version-controlled as applicable, communicated to involved parties, and reflected in the trial registry, protocol amendments, or regulatory/IRB submissions when required by regulation or guidance [3-6].

Summary of Trial Setting

This US-only, multicentre study will operate in qualified oncology sites with the facilities, personnel, and systems necessary to implement the protocol under ICH GCP, Helsinki principles, and US IND regulations. The selected settings provide the infusion infrastructure, imaging and cardiopulmonary services, hazardous drug handling, and data management capabilities required to ensure participant safety, recruitment feasibility, operational consistency, high-quality centralized endpoint assessments, and regulatory compliance, thereby supporting robust, generalizable Phase 2 results [1-7,9,10].

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5.7 Eligibility Criteria for Sites and Intervention Deliverers

1. Eligibility Criteria for Participating Sites

Participating US sites must demonstrate the capability to conduct a multicentre, Phase 2, open-label, single-arm drug study under ICH Good Clinical Practice (GCP), the Declaration of Helsinki (2024), and US IND regulations (21 CFR Parts 50, 56, and 312) with IRB oversight and written informed consent processes [1-5]. Minimum site-level eligibility includes:

- Established access to adults with unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma who have progressed after first-line trastuzumab-containing therapy, with the ability to obtain a new post-progression biopsy and ship for central HER2 testing per ASCO–CAP guidance [6].
- Prior experience successfully conducting interventional oncology trials with timely adverse event (AE) detection and reporting per CTCAE v5.0 and expedited IND safety reporting requirements [3,7].
- Adequate infrastructure, including outpatient infusion facilities; on-site or on-call emergency care; oncology pharmacy services; imaging services capable of protocol-specified acquisition and transfer for blinded independent central review; echocardiography or MUGA; clinical laboratory services; ECG capability; and secure sample processing/shipping [1,4,5,8].
- Sufficient trained personnel and documented delegation of duties to complete informed consent, eligibility confirmation, screening procedures, investigational product (IP) preparation/administration, safety and efficacy assessments, AE management, and participant follow-up and retention [1,4].
- Documented quality systems to comply with protocol procedures, sponsor requirements, IRB requirements, and applicable regulations, including readiness for monitoring, audits, and inspections [1-5].

2. Clinical and Operational Site Capabilities

Sites must be able to:

- Conduct informed consent and maintain ongoing consent in accordance with ICH GCP, the Declaration of Helsinki, and 21 CFR Parts 50 and 56 [1-5].
- Perform eligibility assessments, including screening evaluations, triplicate ECGs at screening, baseline and on-study labs, LVEF assessment by echocardiogram or MUGA at prespecified intervals using a consistent modality, and secure shipment of the new biopsy for central HER2 confirmation [1,6,7].
- Prepare, dispense, and administer investigational T-DXd 6.4 mg/kg IV every 3 weeks, with dose modifications per protocol, using hazardous drug handling standards and controlled storage with temperature monitoring and accountability [1,9].
- Manage comparator-related obligations as “not applicable” (no comparator), while maintaining full IP accountability and reconciliation processes [1].
- Provide on-site infusion observation and management of acute reactions, with immediate access to emergency interventions and escalation pathways [1].
- Schedule and conduct protocol-required visits; perform and document CT/MRI every 6 weeks (±7 days) in Year 1 and every 12 weeks thereafter until progression or new anticancer therapy; and transfer de-identified imaging to the central vendor per RECIST v1.1 acquisition parameters and FDA imaging endpoint process standards for blinded reads [8].
- Detect, evaluate, grade, and report AEs/SAEs and adverse events of special interest (ILD/pneumonitis; LVEF decrease) per CTCAE v5.0 and 21 CFR Part 312 IND safety requirements, including timely communication of suspected ILD for independent adjudication [3,7].
- Ensure specialist access for suspected ILD/pneumonitis (e.g., pulmonology consultation and high-resolution chest CT) and cardiology support for LVEF monitoring [1,7].
- Execute follow-up and retention activities through end of treatment, 40-day safety follow-up, and survival follow-up every 12 weeks [1].

3. Data, Technology, and Documentation Readiness

Eligible sites must:

- Use the sponsor-designated validated electronic data capture (EDC) system with role-based access, audit trails, timely entry, and query resolution; maintain compliant source documentation and allow source data verification [1].
- Utilize secure portals/systems for imaging transfer to the blinded central review vendor, laboratory result retrieval, and safety reporting in alignment with FDA imaging process guidance and the monitoring/data management plans [1,8].
- Protect participant confidentiality and ensure secure data transfer and storage with audit trail maintenance and document retention per ICH GCP and regulatory requirements [1,3].

- Operate without IRT/IWRS for randomization (not applicable in this single-arm study) while maintaining robust enrollment and dosing documentation controls [1].
- Maintain essential documents and version-controlled records in the investigator site file in coordination with the trial master file [1].

4. Regulatory, Ethical, and Quality Requirements for Sites

Before activation and enrollment, each site must have:

- IRB approval of the current protocol, informed consent form(s), and recruitment materials; documentation of continuing review as required [2,4,5].
- Regulatory and administrative readiness under the US IND, including executed clinical trial agreements, financial disclosure/COI documentation, investigator CVs and licenses, FDA Form 1572 (or equivalent site-specific documentation), and completed delegation and training logs [1,3-5].
- Verified completion of site initiation activities and training (protocol, GCP, safety reporting, AE/SAE/CTCAE processes, ILD adjudication workflow, imaging transfer, IP handling, EDC use) [1,7,8].
- Agreement to participate in monitoring, audits, and inspections; maintain inspection readiness; implement protocol amendments; execute CAPA when required; and ensure timely communications with the sponsor, monitors, IRB, and regulatory authorities [1,3-5].

5. Eligibility Criteria for Investigators and Intervention Deliverers

Individuals delivering, dispensing, administering, supervising, or assessing the investigational product and study endpoints must:

- Hold appropriate professional qualifications, active clinical licenses where applicable, and documented competence to perform delegated tasks under ICH GCP [1].
- Be trained on the protocol and study-specific procedures before performing duties, and be listed with scope of responsibilities on the site delegation log [1].
- Principal investigator and sub-investigators: board-certified/eligible oncologists or physicians experienced with advanced solid tumors and antineoplastic infusions, capable of overseeing eligibility, dosing decisions, safety monitoring, AE reporting, and overall protocol conduct [1,7].
- Pharmacists/pharmacy technicians: trained in hazardous drug receipt, storage, preparation, dispensing, temperature monitoring, and IP accountability, following institutional SOPs and NIOSH recommendations [1,9].
- Nursing/infusion staff: competent in IV administration of antineoplastic agents, infusion reaction management, post-infusion monitoring, and documentation [1].
- Radiology staff: qualified to acquire CT/MRI per RECIST v1.1-compliant parameters and site/vendor manuals to support blinded central review [8].
- Cardiology personnel/technicians: trained to perform echocardiogram or MUGA consistently over time for LVEF monitoring [1].
- Pulmonology and respiratory therapy personnel: available for evaluation and management of suspected ILD/pneumonitis, including high-resolution CT acquisition and supportive care [1,7].
- Study coordinators/data managers: experienced in consent support, scheduling, EDC entry, query resolution, imaging transfer workflows, and records management aligned with ICH GCP [1].

6. Training and Competency Requirements

Prior to performing study activities, site personnel must complete and document:

- ICH GCP training and protocol training, including inclusion/exclusion application and visit schedule execution [1].
- Informed consent training compliant with 21 CFR Part 50 and IRB requirements [2,4,5].
- IP handling and hazardous drug safety training aligned with institutional SOPs and NIOSH recommendations [1,9].
- Safety reporting training covering AE/SAE definitions, CTCAE v5.0 grading, IND safety reporting under 21 CFR Part 312, and ILD/pneumonitis identification and escalation to adjudication [3,7].

- Imaging acquisition and transfer training per FDA imaging process standards and the central vendor charter; consistent LVEF modality use over time [1,8].
- EDC system training, including audit trail awareness, contemporaneous entry, and data correction procedures [1].

Ongoing or refresher training is required following protocol amendments, key personnel turnover, or identified quality gaps [1].

7. Eligibility Criteria for Specialist Assessors or Committees

- Blinded independent central radiology reviewers: board-certified radiologists with RECIST v1.1 expertise, operating under a vendor charter; independent of investigative sites and blinded to site identity and non-essential clinical details; documented training and inter-reader calibration to minimize bias [8].
- Independent ILD/pneumonitis adjudication committee: clinicians with relevant pulmonology/radiology expertise; independent of sites and blinded to investigator causality and site identity; operating per an adjudication charter with defined data inputs, timelines, and documentation standards [1,7,8].

If any specialist assessors are not used locally (e.g., endpoint adjudication is centralized), sites must standardize local acquisition procedures and data transfers as specified in the applicable charters and manuals to ensure consistency and quality control across centers [1,8].

8. Site Non-Eligibility, Suspension, or Deactivation

A site may be deemed not eligible for activation or may be suspended/deactivated for:

- Failure to obtain or maintain required IRB approvals, essential documents, or investigator qualifications/licenses [1,4,5].
- Inadequate recruitment feasibility, insufficient qualified personnel, or inability to complete required training [1].
- Deficient IP storage, preparation, or accountability; noncompliance with hazardous drug handling standards [1,9].
- Repeated or serious protocol deviations; delayed or incomplete safety reporting; inadequate data quality or persistent query backlogs; failure to meet imaging acquisition/transfer standards jeopardizing blinded review [1,3,7,8].
- Inability to protect participant safety or confidentiality; noncompliance with ICH GCP, sponsor requirements, or regulations [1,3-5].

Decisions will be documented and communicated to site leadership and the IRB as applicable. Corrective and preventive actions (e.g., retraining, process remediation, temporary enrollment hold) will be implemented and verified; if unresolved, participants may be transferred for ongoing care and follow-up, and the site may be closed with appropriate records reconciliation [1,3-5].

9. Documentation of Site and Personnel Eligibility

Eligibility will be documented and maintained through:

- Feasibility assessments and site qualification visit reports; IRB approvals and correspondence; executed agreements; FDA Form 1572 (or equivalent); financial disclosure statements; essential document checklists [1,3-5].
- Delegation of duties logs; training records; CVs and professional licenses; pharmacy qualification and temperature monitoring records; imaging and laboratory capability confirmations [1].
- Site initiation documentation; monitoring visit reports; audit/inspection reports; deviation logs; safety reporting records; CAPA documentation; and version-controlled updates filed in the investigator site file and trial master file [1,3-5].

Changes to site capabilities, investigator responsibilities, delegated personnel, or qualifications will be promptly documented, communicated to the sponsor and IRB/regulators as required, and retained for monitoring, audit, and inspection [1,3-5].

10. Summary

These eligibility criteria ensure that participating US sites and intervention deliverers possess the clinical infrastructure, trained personnel, validated systems, and regulatory readiness to administer investigational T-DXd safely, implement blinded central efficacy and ILD adjudication processes, standardize assessments, and maintain high-quality data. Adherence to ICH GCP, Helsinki principles, FDA imaging standards, CTCAE grading, and US IND regulations supports participant safety,

protocol fidelity, reliable endpoints, data integrity, and audit- and inspection-readiness throughout this Phase 2 single-arm study [1-8].

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5.8 Primary Objectives

The primary objective is to evaluate the antitumour activity of investigational trastuzumab deruxtecan (T-DXd) monotherapy in adults with centrally confirmed HER2-positive unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma that has progressed during or after first-line trastuzumab-containing therapy, measured as confirmed objective response rate (ORR; complete or partial response confirmed ≥4 weeks later) determined by independent central review per RECIST v1.1 [1,2].

This objective is selected to provide a robust, patient-level measure of antitumour activity appropriate for a single-arm Phase 2 setting, with the design targeting a true ORR of approximately 45% and the lower bound of the two-sided 95% exact confidence interval to exceed 27%, consistent with or superior to historical second-line benchmarks in this disease and reflecting prior evidence of substantial activity of T-DXd in a randomized Phase 2 trial in Asia while addressing the need for data in Western patients [2-4].

References

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5.9 Secondary Objectives

- Key secondary objective: To estimate progression-free survival (PFS) with T-DXd monotherapy, defined as time from first dose to the earliest date of objective disease progression per independent central review using RECIST v1.1 or death from any cause; participants without an event will be censored at the last adequate tumor assessment. Endpoint: PFS by independent central review per RECIST v1.1 with imaging acquisition and centralized assessment conducted under standardized processes to minimize bias [1,2].

- To characterize overall survival (OS) with T-DXd. Endpoint: OS, defined as time from first dose to death from any cause; participants alive at analysis cutoff will be censored at last known alive date. Time-to-event analyses will use Kaplan–Meier methods with two-sided 95% confidence intervals [2].

- To characterize the durability of antitumor activity among confirmed responders. Endpoint: Duration of response (DoR), defined as time from first documented confirmed complete or partial response (by independent central review per RECIST v1.1) to the first occurrence of RECIST v1.1 progression or death; responders without an event will be censored at the date of last adequate tumor assessment [1,2].

- To evaluate safety and tolerability of T-DXd, with focused assessment of adverse events of special interest (AESIs) including interstitial lung disease (ILD)/pneumonitis and left ventricular ejection fraction (LVEF) decrease. Endpoints: incidence, severity, seriousness, relatedness, and outcomes of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), AESIs, dose modifications/interruptions/discontinuations due to AEs, and deaths, all graded per NCI CTCAE v5.0; ILD/pneumonitis events will undergo independent adjudication given the recognized risk with T-DXd in this disease setting, and cardiac safety will include LVEF monitoring according to the protocol schedule [3,4]. Safety data collection and reporting will follow ICH GCP and US IND safety reporting requirements [5,6].

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5.10 Exploratory Objectives

Not applicable. No exploratory objectives or endpoints are planned for this study.

5.11 Outcomes and Endpoint Definitions

1. Overview of Outcome Framework

This Phase 2, open-label, single-arm study evaluates the antitumour activity, durability, and safety/tolerability of investigational trastuzumab deruxtecan (T-DXd) monotherapy in adults with centrally confirmed HER2-positive unresectable or metastatic gastric/GEJ adenocarcinoma after progression on first-line trastuzumab-containing therapy. Outcomes are organized as follows:

- Primary efficacy (confirmatory for Phase 2): confirmed objective response rate (ORR) by blinded independent central review (BICR) per RECIST v1.1 [1,2].
- Secondary efficacy: progression-free survival (PFS; key secondary) by BICR per RECIST v1.1, overall survival (OS), and duration of response (DoR) by BICR per RECIST v1.1 [1,2].
- Safety and tolerability: treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs; interstitial lung disease [ILD]/pneumonitis and left ventricular ejection fraction [LVEF] decrease), and AE-related dose modifications, graded per CTCAE v5.0 and reported under US IND requirements [3-6].
- Exploratory: none planned (no PK/PD, biomarker, immunogenicity, or patient-reported outcomes).

The outcomes align with SPIRIT 2025 guidance by prespecifying endpoint definitions, measurement methods, timing, and analysis metrics to address the primary and secondary objectives and to support regulatory and scientific interpretability in the US under ICH E6(R3) and the Declaration of Helsinki (2024) [2,5,7,8]. No interim or adaptive decision-making is planned; all confirmatory inferences for this Phase 2 study are based on the primary endpoint at the final analysis, with secondary outcomes analysed as supportive and descriptive unless otherwise specified in the Statistical Methods section [2].

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2. Primary Outcome

- Outcome name: Confirmed objective response rate (ORR) by BICR per RECIST v1.1.
- Measurement variable and definition: Proportion of participants with a best overall response of complete response (CR) or partial response (PR) confirmed by a subsequent BICR assessment at least 4 weeks (≥28 days) after initial documentation, using RECIST v1.1 target/non-target/NEW lesion rules and RECIST-compliant imaging [1,2].
- Analysis metric and aggregation: Proportion (percent) with two-sided 95% exact Clopper–Pearson confidence interval (CI) in the Full Analysis Set (all participants who receive ≥1 dose) [7].
- Assessment time point/window: From first dose through end of treatment and follow-up imaging until progression, new anticancer therapy, withdrawal, or death; tumor imaging every 6 weeks (±7 days) in Year 1, then every 12 weeks (±7 days) thereafter until progression or new anticancer therapy [2].
- Censoring/handling: Participants without CR/PR confirmation ≥28 days after initial CR/PR will not be counted as responders; participants with missing or unevaluable post-baseline tumor assessments are non-responders for ORR [1].
- Clinical relevance and justification: ORR provides a direct measure of antitumour activity suitable for single-arm Phase 2 evaluation in this setting and is aligned with prior evidence of substantial activity of T-DXd in previously treated HER2-positive gastric cancer, while enabling comparison to historical second-line benchmarks in Western practice [1,6,7].

References

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3. Secondary Outcomes

- Progression-free survival (PFS; key secondary) by BICR per RECIST v1.1:

- Definition: Time from first dose to first documented objective disease progression per BICR using RECIST v1.1 or death from any cause, whichever occurs first [1].
- Analysis metric/aggregation: Kaplan–Meier (KM) median with two-sided 95% CI; KM rates at prespecified time points (e.g., 6 and 12 months) as supportive [7].
- Censoring rules: Censor at last adequate tumor assessment without progression for participants alive without an event; censor at last adequate assessment prior to start of new anticancer therapy; if no post-baseline assessment exists, censor at Day 1 for time-to-event displays and handle per Statistical Methods for summaries [1,2].
- Clinical relevance: Estimates disease control and timing of progression under standardized central review [1,2].

- Overall survival (OS):

- Definition: Time from first dose to death from any cause [7].
- Analysis metric/aggregation: KM median with two-sided 95% CI; KM rates at prespecified time

points [7].
- Censoring rules: Alive at cutoff or lost to follow-up censored at last known alive date [7].
- Clinical relevance: Captures ultimate patient outcome; descriptive in single-arm Phase 2.

- Duration of response (DoR) by BICR per RECIST v1.1:

- Definition: Among confirmed responders (CR/PR), time from first documentation of confirmed response to first BICR-assessed RECIST v1.1 progression or death [1].
- Analysis metric/aggregation: KM median with two-sided 95% CI [7].
- Censoring rules: Responders without an event censored at date of last adequate tumor assessment; start of new anticancer therapy censors at last adequate assessment prior to therapy [1].

- Safety and tolerability:

- Definitions: Incidence, severity (CTCAE v5.0), seriousness, relatedness, and outcomes of TEAEs, SAEs, AESIs (ILD/pneumonitis; LVEF decrease), and AE-related dose interruptions/reductions/discontinuations and deaths; IND safety reporting per 21 CFR 312.32 [3-6].
- Analysis metric/aggregation: Number and percentage of participants with events; exposure-adjusted incidence rates for selected AEs; shift tables for laboratory abnormalities; descriptive statistics [3,4].

References

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47. doi:10.1016/j.ejca.2008.10.026. Available from: https://pubmed.ncbi.nlm.nih.gov/19097774/
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4. Exploratory Outcomes

No exploratory outcomes are planned. No PK/PD, biomarker, immunogenicity, pharmacogenetic, health economic, or patient-reported endpoints will be collected or analysed [7].

References

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5. Safety and Tolerability Outcomes

- TEAEs and SAEs: Any untoward medical occurrence after first dose; seriousness per regulatory criteria; graded by CTCAE v5.0; relationship as assessed by investigators; onset during treatment through 40 days (+7) after last dose [3-5].
- AESIs:

- ILD/pneumonitis: Suspected cases identified clinically/radiographically, centrally adjudicated by an independent committee; grade per CTCAE v5.0; outcomes include time to onset, highest grade, management (e.g., steroids), resolution, and sequelae [3,4].

- LVEF decrease: Proportion with LVEF below institutional lower limit of normal or ≥10% absolute decline to <50%; results summarized by grade, timing, and action taken [3].

- Dose modifications due to AEs: Incidence of dose interruptions, reductions (to 5.4 mg/kg and 4.4 mg/kg), and discontinuations, with reasons and timing [7].
- Laboratory, vital signs, ECG, and LVEF abnormalities: Shift from baseline and incidence of clinically significant abnormalities; ECG central rules per protocol; LVEF by consistent modality over time [2-4].
- Deaths: All-cause mortality during on-treatment and safety follow-up windows; attribution summarized descriptively [4,5].

Safety data will be collected and analysed in the Safety Analysis Set (all dosed participants). Reporting will follow CTCAE v5.0 and 21 CFR 312.32, under ICH E6(R3) [3-5].

References

2. US Food and Drug Administration. Clinical Trial Imaging Endpoint Process Standards: Guidance for Industry. Silver Spring (MD): FDA; 2018. Available from: https://www.fda.gov/media/81172/download
3. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Bethesda (MD): NCI; 2017 (updated 2018). Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50
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6. Outcome Measurement Methods

- Tumour efficacy assessments: Contrast-enhanced CT of chest/abdomen/pelvis or MRI (if CT contraindicated) acquired per RECIST v1.1 technical requirements; same imaging modality and parameters over time where feasible; uploaded for BICR conducted under a charter with dual independent reads and adjudication for discordance, following FDA imaging endpoint process standards [1,2].
- Confirmation of response: Repeat RECIST v1.1 assessment ≥28 days after initial CR/PR to confirm ORR [1].
- ILD/pneumonitis evaluation: Standardized clinical assessment, pulse oximetry, and high-resolution chest CT for suspected cases; independent ILD adjudication committee reviews predefined data packets and classifies cases per charter (e.g., definite, probable, possible, unlikely) with grade per CTCAE v5.0 [3,4].
- Cardiac function: LVEF by echocardiogram or MUGA at screening, Cycle 5 Day 1, and every 4 cycles thereafter, using the same modality for each participant throughout; thresholds and action per protocol-specified management rules [3,4].
- Safety labs/vitals/ECGs: Local clinical laboratories using standardized methods; triplicate 12-lead ECG at screening; subsequent ECGs per schedule or as clinically indicated; AE grading per CTCAE v5.0 [3].
- HER2 status: Central confirmation on a new post-progression biopsy using ASCO–CAP criteria (IHC 3+ or IHC 2+ with ISH amplification) prior to enrollment to address known potential for HER2 loss after trastuzumab [9].

References

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7. Timing, Assessment Windows, and Data Sources

- Timing:

- Baseline: Screening tumor imaging, triplicate ECG, labs, LVEF, and central HER2 confirmation on a new biopsy [2-4,9].
- On treatment: Imaging every 6 weeks (±7 days) in Year 1, then every 12 weeks (±7 days) thereafter until progression or new anticancer therapy; safety assessments per visit; LVEF at Cycle 5 Day 1 and every 4 cycles; ECGs as scheduled/indicated [1-4].
- End of treatment and follow-up: Safety follow-up at 40 days (+7) after last dose; survival follow-up every 12 weeks until study end [4,7].

- Event-driven/unscheduled: For suspected progression, repeat or confirmatory imaging per RECIST v1.1 and BICR charter; unscheduled scans may be used for event dating if RECIST-compliant [1,2].
- Data sources:

- Efficacy: BICR outputs based on centrally transferred DICOM imaging datasets; site radiology reports are supportive but not primary [2].
- Safety: eCRFs, source documents, laboratory reports, ECG tracings, LVEF reports, and ILD adjudication committee outputs [3,4].
- Vital status: Site records and public/medical sources per protocol, documented in eCRF [7].

References

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47. doi:10.1016/j.ejca.2008.10.026. Available from: https://pubmed.ncbi.nlm.nih.gov/19097774/
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8. Endpoint Adjudication and Bias Control

- Blinded Independent Central Review (BICR): All imaging for ORR, PFS, and DoR will be evaluated by BICR under a prespecified charter detailing reader qualification, blinding to site assessments and clinical data not essential for RECIST evaluation, dual reads with adjudication of discordant results, and quality control measures to ensure consistency and minimize bias in this open-label study [2].
- ILD/pneumonitis adjudication: An independent committee, blinded to investigator causality and site identity, will adjudicate suspected ILD/pneumonitis per an adjudication charter; outputs will be used for safety summaries and AESI analyses [3,4].
- Standardization without other adjudication: LVEF assessments will use a consistent modality over time; safety grading uniformly applies CTCAE v5.0; imaging acquisition parameters are standardized across sites per manuals and FDA guidance to limit measurement variability [2-4].

References

2. US Food and Drug Administration. Clinical Trial Imaging Endpoint Process Standards: Guidance for Industry. Silver Spring (MD): FDA; 2018. Available from: https://www.fda.gov/media/81172/download
3. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Bethesda (MD): NCI; 2017 (updated 2018). Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50
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9. Handling of Missing, Incomplete, or Ambiguous Outcome Data

- General principles: Outcome data completeness will be promoted through protocol-specified scheduling, central reminders, and query resolution. Missing, delayed, or ambiguous data will be documented in source and eCRF, queried, and resolved per data management plan under ICH E6(R3) [4,7].
- ORR: Participants lacking post-baseline RECIST assessments or lacking response confirmation ≥28 days after an initial CR/PR will be classified as non-responders; unevaluable scans do not contribute to response unless subsequent adequate assessments confirm CR/PR [1].
- PFS and DoR: Time-to-event endpoints will use RECIST-defined event dates from BICR. Censoring will occur at the last adequate tumor assessment without an event; new anticancer therapy leads to censoring at the last adequate assessment prior to therapy; unscheduled but RECIST-compliant assessments may define events/censoring; participants with no post-baseline assessment will be censored at Day 1 for displays and handled per Statistical Methods for summaries [1,2,7].
- OS: Participants alive or lost to follow-up at data cutoff will be censored at last known alive date; efforts to ascertain vital status continue through survival follow-up [7].
- Intercurrent events: After permanent treatment discontinuation, participants remain on study for protocol-specified efficacy follow-up unless consent is withdrawn; use of prohibited/rescue anticancer therapy leads to censoring for PFS/DoR as above; safety events are collected through 40 days (+7) after last dose [4,7].
- Sensitivity analyses: Detailed statistical handling (e.g., alternative censoring scenarios, tipping point analyses) will be described in the Statistical Methods section consistent with SPIRIT 2025 [7].

References

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10. Outcome Table

Outcome category	Outcome name	Objective supported	Measurement variable and endpoint definition	Analysis metric and aggregation	Assessment method	Assessment time point/window	Data source	Analysis population	Role in inference
Primary efficacy	Confirmed ORR by BICR (RECIST v1.1)	Primary efficacy	Proportion with confirmed CR or PR (confirmation ≥28 days)	Proportion with 95% exact CI (Clopper–Pearson)	BICR per RECIST v1.1 under FDA imaging process standards	Imaging q6w (±7d) Year 1, then q12w (±7d) until progression or new therapy	Central imaging reads; eCRF	Full Analysis Set	Confirmatory for Phase 2 [1,2,7]
Secondary efficacy (key)	PFS by BICR (RECIST v1.1)	Disease control	Time from first dose to BICR progression or death	KM median and 95% CI; KM rates	BICR per RECIST v1.1	Same as above; censor at last adequate assessment prior to new therapy	Central imaging reads; eCRF	Full Analysis Set	Supportive [1,2,7]
Secondary efficacy	OS	Survival	Time from first dose to death from any cause	KM median and 95% CI; KM rates	Vital status ascertainment	Continuous through follow-up; censor at last known alive	eCRF; source/vital status	Full Analysis Set	Supportive/descriptive [7]
Secondary efficacy	DoR by BICR (RECIST v1.1)	Durability	In responders, time from first confirmed CR/PR to BICR progression or death	KM median and 95% CI	BICR per RECIST v1.1	From response confirmation until event/censor	Central imaging reads; eCRF	Confirmed responders in FAS	Supportive [1,7]
Safety	TEAEs and SAEs	Safety	Incidence, severity, seriousness	Counts, percentages;	CTCAE v5.0 grading	From first dose to	eCRF; labs;	Safety Analysis Set	Safety

			ss, relatedness, outcome	exposure-adjusted rates		40 days (+7) post last dose	ECG; vitals		
Safety (AESI)	ILD/pneumonitis	Safety	Incidence, grade, onset, management, outcome; adjudicated classification	Counts, percentages; time-to-onset	ILD adjudication + CTCAE v5.0	Continuous; follow to resolution	Adjudication outputs; eCRF	Safety Analysis Set	Safety
Safety (AESI)	LVEF decrease	Safety	Proportion with LVEF < LLN or ≥10% decline to <50%	Counts, percentages; shifts	Echocardiogram/MUGA	Screening; Cycle 5 Day 1; q4 cycles thereafter	LVEF reports; eCRF	Safety Analysis Set	Safety
Safety	Dose modifications due to AEs	Tolerability	Interruptions, reductions (5.4→4.4 mg/kg), discontinuations	Counts, percentages; time to first modification	Investigator reports	Treatment period	eCRF	Safety Analysis Set	Safety
Exploratory	None planned	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

References

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47. doi:10.1016/j.ejca.2008.10.026. Available from: https://pubmed.ncbi.nlm.nih.gov/19097774/

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6 BACKGROUND

6.1 Study Disease

Epidemiology and disease burden

Gastric cancer remains a major cause of cancer mortality in the United States. In 2026, Surveillance, Epidemiology, and End Results (SEER) estimates 31,510 new cases and 10,740 deaths. Five-year relative survival for distant-stage disease is 8.1% [1]. Adenocarcinoma is the predominant histology, with gastro-oesophageal junction (GEJ) tumors sharing overlapping biology and management with proximal gastric cancers [1]. Human epidermal growth factor receptor 2 (HER2) overexpression or amplification occurs in approximately 10–20% of gastric/GEJ adenocarcinomas and is enriched in intestinal-type and GEJ/proximal tumors, providing a validated therapeutic target in the first-line setting [2,3].

Natural history, phenotypes, and outcomes relevant to the target population

Advanced unresectable or metastatic gastric/GEJ adenocarcinoma is characterized by rapid progression, early dissemination, and systemic symptom burden (e.g., weight loss, anemia, obstruction). Despite multi-agent chemotherapy and targeted therapy in selected biomarker-defined subgroups, median overall survival in metastatic disease typically remains less than 1 year in unselected populations, and post-progression outcomes are poor, underscoring the need for effective later-line options [1,4–6].

Diagnostic standards and HER2 testing

Diagnosis is established histologically, with staging by cross-sectional imaging and, when appropriate, endoscopic ultrasound. HER2 status should be determined using validated assays and scoring criteria: immunohistochemistry (IHC) 3+ or IHC 2+ with in situ hybridization (ISH) amplification defines HER2 positivity in gastroesophageal adenocarcinoma [2]. Given documented loss of HER2 after trastuzumab exposure, re-biopsy at the time of progression is recommended to guide subsequent therapy and ensure accurate biomarker assignment for trial eligibility [2,7].

Current management standards and limitations after trastuzumab

In HER2-positive disease, adding trastuzumab to first-line chemotherapy improves survival versus chemotherapy alone and is a standard first-line regimen [3]. After progression on a trastuzumab-containing regimen, treatment commonly transitions to cytotoxic regimens. In the RAINBOW trial, paclitaxel plus ramucirumab improved overall survival versus paclitaxel alone (median 9.6 vs 7.4 months) with an objective response rate (ORR) of 28%, establishing a second-line benchmark in previously treated advanced gastric/GEJ adenocarcinoma [4]. Ramucirumab monotherapy also confers a survival benefit over best supportive care (REGARD) but with low response rates [5]. Trifluridine–tipiracil improved survival in the third-line and beyond but achieved a low ORR (4%) [6]. Collectively, post-trastuzumab options yield modest response rates and limited durability, and targeted strategies specific to HER2-positive disease beyond first line remain limited, resulting in a clear unmet medical need for therapies with higher response probability and sustained benefit [4–6].

Rationale for evaluating trastuzumab deruxtecan (T-DXd) in this setting

T-DXd is an investigational HER2-directed antibody–drug conjugate being studied as monotherapy at 6.4 mg/kg IV every 3 weeks in this protocol. In the randomized Phase 2 DESTINY-Gastric01 trial conducted in Japan and Korea, T-DXd demonstrated superior antitumor activity and survival versus physician's choice chemotherapy in patients with previously treated HER2-positive advanced gastric/GEJ adenocarcinoma: ORR 51% vs 14%, median progression-free survival 5.6 vs 3.5 months, and median overall survival 12.5 vs 8.4 months [8]. The safety profile included nausea, myelosuppression, and drug-related interstitial lung disease (ILD)/pneumonitis in 10% of patients, mostly grade 1–2, with no ILD-related deaths reported in that study [8]. These results support investigation of T-DXd in the post-trastuzumab setting; however, confirmatory data are still needed in Western populations to address potential regional differences in disease biology, prior therapies, and

clinical practice patterns [4–6,8].

Study population alignment and key clinical considerations

This study enrolls adults with centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic gastric/GEJ adenocarcinoma that progressed during or after first-line trastuzumab-containing therapy, reflecting the population in which HER2-targeted therapy has initial benefit but subsequent progression is common due to resistance and, in some patients, loss of HER2 [2,7,8]. Eligibility aligns with routine standards for systemic therapy trials in advanced solid tumors (ECOG PS 0–1, measurable disease by RECIST v1.1, LVEF ≥50%, adequate organ function). Typical laboratory thresholds suitable for this population include absolute neutrophil count ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, hemoglobin ≥9 g/dL, total bilirubin ≤1.5 × ULN (≤3 × ULN if Gilbert syndrome), AST/ALT ≤3 × ULN (≤5 × ULN with liver metastases), and creatinine clearance ≥50 mL/min. Key exclusions (e.g., prior anticancer therapy beyond first-line trastuzumab, active or prior clinically significant ILD/pneumonitis, significant cardiac disease, severe lung disease, and untreated/symptomatic brain metastases) are aligned to mitigate risks relevant to the known toxicity profile of T-DXd and to the safety of patients with cardiopulmonary comorbidities [2,4–6,8].

Collectively, the high mortality of metastatic gastric/GEJ adenocarcinoma, modest response rates with available post-trastuzumab regimens, frequency of HER2 loss after trastuzumab, and robust activity of T-DXd in DESTINY-Gastric01 provide the clinical rationale for this Phase 2, single-arm study focused on confirmed ORR by independent central review, with progression-free survival, overall survival, duration of response, and safety (including ILD/pneumonitis and left ventricular ejection fraction decrease) as key supportive outcomes [2,4–8].

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6.2 Study Agent(s)

6.2.1 Investigational Product or Study Drug Combination

Study agent: trastuzumab deruxtecan (T-DXd; DXd-containing HER2-directed antibody–drug conjugate)

T-DXd is a humanized anti-HER2 IgG1 monoclonal antibody conjugated via a cleavable tetrapeptide linker to a potent membrane-permeable topoisomerase I inhibitor payload (DXd; an exatecan derivative). The average drug-to-antibody ratio is approximately 8. Upon binding to HER2, the antibody–antigen complex is internalized and trafficked to lysosomes, where the linker is selectively cleaved by lysosomal proteases, releasing DXd to induce DNA damage and apoptosis. The payload's membrane permeability supports a "bystander" effect that can kill adjacent tumor cells with lower HER2 expression, addressing intratumoral HER2 heterogeneity typical of gastric/GEJ adenocarcinoma [1]. These design features differentiate T-DXd from earlier HER2-directed antibody–drug conjugates by increasing payload delivery per antibody and facilitating cytotoxic activity in heterogeneous tumors while retaining target specificity conferred by HER2 binding [1].

T-DXd is administered as an intravenous infusion on Day 1 of each 21-day cycle at 6.4 mg/kg in this study. The first infusion will be over at least 90 minutes; if well tolerated, subsequent infusions may be given over at least 30 minutes. Two protocol-permitted dose reductions (to 5.4 mg/kg and then 4.4 mg/kg) are allowed; re-escalation is not permitted. Dosing and dose-modification principles are consistent with the dosing approach reported for T-DXd in gastric cancer clinical literature and standard US prescribing information used as a reference for safety management in this protocol [2,3].

Mechanism of action and pharmacology

- Target engagement and internalization: T-DXd binds HER2 on tumor cells, is internalized, and undergoes lysosomal processing with linker cleavage and intracellular release of DXd [1].
- Payload action: DXd inhibits topoisomerase I, causing DNA single-strand breaks that trigger replication stress and apoptosis in dividing cells [1].
- Bystander effect: Membrane-permeable DXd can diffuse into neighboring tumor cells, supporting antitumor activity in HER2-heterogeneous lesions commonly seen in gastric/GEJ cancer [1].

Pharmacokinetics (absorption, distribution, metabolism, excretion) and pharmacodynamics

- Administration/absorption: Intravenous administration yields immediate systemic availability of the intact conjugate (T-DXd) with time-dependent release of unconjugated DXd intracellularly and measurable low-level circulating DXd [2].
- Distribution: Population PK indicates a central volume of distribution consistent with a monoclonal antibody; tissue distribution of released DXd in tumors is facilitated by HER2-mediated internalization and lysosomal linker cleavage [2].
- Metabolism: The intact T-DXd is catabolized via proteolytic pathways of IgG. The released DXd is primarily metabolized by CYP3A4 in vitro and in vivo. The Enhertu US prescribing information reports no clinically significant pharmacokinetic interaction when T-DXd is coadministered with itraconazole (a strong CYP3A inhibitor and P-gp inhibitor) or ritonavir (a strong CYP3A inhibitor), indicating that strong CYP3A and/or P-gp inhibition does not meaningfully alter exposure to T-DXd or DXd at clinically relevant levels [2].
- Elimination: T-DXd exhibits linear PK over the clinically relevant dose range and is eliminated with a terminal half-life of approximately 5.4–5.7 days. The released DXd has a terminal half-life of approximately 5.4–6.1 days, similar to that of the conjugate, reflecting payload release kinetics and systemic clearance predominantly via metabolism rather than renal excretion [2].
- Pharmacodynamics: Exposure–response analyses indicate increasing antitumor activity with higher T-DXd exposure within the clinically used range, with hematologic toxicity and gastrointestinal adverse events displaying exposure-related trends. No clinically meaningful effect on QTc has been identified at recommended doses based on intensive ECG monitoring in the clinical development program referenced in the US prescribing information [2].

Minimum effective dose, recommended dose, and dosing approach in clinical literature

- Early-phase gastric cancer data: In the Phase 1 dose-expansion study in HER2-positive advanced gastric/GEJ adenocarcinoma, T-DXd demonstrated clinically meaningful antitumor activity across evaluated dose levels, supporting selection of 6.4 mg/kg every 3 weeks for subsequent gastric studies. Confirmed objective responses were observed with manageable toxicity profiles consistent with on-target delivery of a topoisomerase I payload [3].
- Randomized Phase 2 data in previously treated gastric/GEJ disease: In DESTINY-Gastric01 (Japan/Korea), T-DXd administered at 6.4 mg/kg every 3 weeks produced a significantly higher confirmed ORR versus physician's choice chemotherapy, with supportive improvements in PFS and OS. Safety included nausea, myelosuppression, and interstitial lung disease/pneumonitis (mostly grade 1–2), which aligns with the safety focus of this protocol [4].
- Dosing paradigm: For gastric/GEJ adenocarcinoma, a dose of 6.4 mg/kg IV every 3 weeks has been the regimen used in disease-specific Phase 1 expansion and randomized Phase 2 studies. Dose modifications typically proceed in decrements (e.g., to 5.4 mg/kg then 4.4 mg/kg) to manage toxicity, in line with the dosing framework adopted in this protocol and consistent with standard reference information in the US prescribing information [2–4].

Efficacy and safety overview in the target disease context

- Antitumor activity: Across early-phase and randomized Phase 2 studies in previously treated HER2-positive gastric/GEJ adenocarcinoma, T-DXd produced clinically meaningful response rates and durable responses relative to historical expectations in this setting, providing the evidence base for this single-arm Phase 2 study focused on confirmed ORR by independent central review [3,4].
- Key toxicities: The most frequently reported adverse events include nausea, vomiting, decreased appetite, fatigue, alopecia, anemia, neutropenia, and thrombocytopenia. Interstitial lung disease (ILD)/pneumonitis is an identified risk, with events typically detected radiographically and managed by prompt treatment interruption, corticosteroids as indicated, and permanent discontinuation for grade ≥2. Decreases in left ventricular ejection fraction (LVEF) are less common but clinically relevant; routine cardiac monitoring is implemented to detect asymptomatic declines [2–4].
- Drug–drug interactions: Based on clinical pharmacology data summarized in the US prescribing information, no clinically significant pharmacokinetic interaction was observed with itraconazole or ritonavir. No meaningful effect of acid-reducing agents on T-DXd exposure has been identified, and T-DXd is not expected to cause clinically significant inhibition or induction of major CYP enzymes or transporters at therapeutic concentrations [2].

Study administration and accountability

- Investigational status and control: In this US IND study, T-DXd is investigational for the enrolled population. Study drug will be supplied as a sterile, preservative-free lyophilized powder for reconstitution and dilution in 5% dextrose for IV infusion. Preparation, storage, handling, and infusion will follow institutional standards consistent with the US prescribing information and study manual of procedures to ensure product integrity and participant safety [2].
- Dose delays, modifications, and discontinuation: Dose interruptions and reductions will follow protocol-specified criteria aligned with standard reference information, including immediate interruption and evaluation for any suspected ILD/pneumonitis; resumption only after full resolution of grade 1 events; and permanent discontinuation with systemic corticosteroids for grade ≥2 ILD/pneumonitis. Dose delays may extend up to 28 days; longer delays require discontinuation per protocol. No re-escalation is permitted after a dose reduction [2].
- Ongoing safety oversight: Given the open-label, single-arm design without a formal DMC, Sample Pharma Co., Ltd. will conduct ongoing safety review, including prompt evaluation of adverse events of special interest and IND safety reporting per 21 CFR 312.32.

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6.3 Nonclinical Studies

6.3.1 Pharmacology

Mechanism of action and pharmacodynamic basis

T-DXd is a humanized anti-HER2 IgG1 antibody conjugated to a potent, membrane-permeable topoisomerase I inhibitor (DXd, an exatecan derivative) via a cleavable tetrapeptide linker with an average drug-to-antibody ratio of approximately 8. Following HER2 binding, the antibody–antigen complex is internalized; lysosomal proteases cleave the linker to release DXd intracellularly, causing replication-associated DNA damage and apoptosis. The released DXd can diffuse across cell membranes, producing a bystander effect that enables killing of adjacent tumor cells with lower or heterogeneous HER2 expression, a recognized feature of gastric/GEJ adenocarcinoma that can limit the effectiveness of HER2-targeted therapies without such properties [1,2].

Non-clinical pharmacology: in vitro and in vivo evidence

- Target engagement and cytotoxicity: In HER2-expressing tumor cell lines, T-DXd showed potent antigen-dependent internalization and concentration-dependent cytotoxicity, with markedly greater activity than trastuzumab emtansine (T-DM1) in models with moderate HER2 expression or heterogeneous antigen density, consistent with efficient intracellular payload delivery and bystander killing [2].
- Bystander effect: Co-culture systems mixing HER2-high and HER2-low/negative cells demonstrated T-DXd–mediated killing of HER2-low neighbors, attributable to the membrane permeability of released DXd; this effect was not observed with non-permeable payload constructs such as T-DM1 [2].
- Antitumor activity in xenografts: In multiple HER2-expressing xenograft models, including gastric cancer NCI-N87, T-DXd induced deep and durable tumor regressions at tolerated doses, outperforming T-DM1 in head-to-head comparisons and maintaining activity in tumors with heterogeneous HER2 expression [2].
- Linker and payload characteristics: The tetrapeptide linker is selectively cleaved by lysosomal enzymes, enabling intracellular release in HER2-positive tumor cells, while the DXd payload exhibits high potency against topoisomerase I with physicochemical properties that permit local tissue diffusion to effect bystander cytotoxicity without requiring uniform target density [2].

Collectively, these data establish a pharmacologic profile of high payload delivery per antibody, efficient intracellular release, and bystander activity that is mechanistically aligned with the intratumoral HER2 heterogeneity commonly seen in gastric/GEJ adenocarcinoma [1,2].

Dose–response characteristics and translational pharmacology

- Preclinical dose–response: In vitro and xenograft models demonstrated monotonic exposure–response relationships for T-DXd, with increasing antitumor effects corresponding to higher doses and systemic exposures within tolerability limits; tumor regressions were observed across a range of HER2 expression levels due to bystander activity [2].
- Clinical translation of exposure–response: Population exposure–response analyses have shown that higher T-DXd exposure within the clinically used range is associated with greater

antitumor activity, with exposure-related trends also observed for hematologic and gastrointestinal toxicities, supporting dose adjustment to manage safety while maintaining activity [1].
- Gastric/GEJ dose selection context: Early clinical investigations in HER2-positive gastric/GEJ adenocarcinoma evaluated multiple dose levels and supported selection of 6.4 mg/kg every 3 weeks for disease-specific expansion based on antitumor activity and manageability of toxicity, providing the dose foundation for Phase 2 evaluation in this population [3].

Pharmacokinetics and pharmacology-relevant interactions

- Systemic disposition: Following intravenous administration, intact T-DXd displays linear pharmacokinetics over the clinical dose range with a terminal half-life of approximately 5–6 days and distribution consistent with a monoclonal antibody. Low-level circulating unconjugated DXd is measurable and exhibits a similar terminal half-life, reflecting release and clearance kinetics [1].
- Biotransformation and elimination: The antibody component is catabolized via proteolysis, while DXd is metabolized predominantly by CYP3A4; clinical pharmacology studies have not shown clinically meaningful changes in T-DXd or DXd exposure with strong CYP3A inhibition, and T-DXd is not expected to cause clinically significant CYP or transporter inhibition/induction at therapeutic concentrations [1].
- QTc: Intensive ECG assessments have not identified a clinically relevant effect of T-DXd on QTc at recommended dosing regimens [1].

Pharmacologic rationale for the target population and regimen

The pharmacology of T-DXd—high drug-to-antibody ratio, lysosomal release of a membrane-permeable topoisomerase I inhibitor, and robust bystander effect—supports activity in HER2-positive gastric/GEJ adenocarcinoma where HER2 expression is often heterogeneous and can decline after trastuzumab exposure. The demonstrated superiority to T-DM1 in preclinical HER2-heterogeneous models, potent activity in HER2-positive gastric xenografts, and exposure–response findings informed the selection of 6.4 mg/kg every 3 weeks in this Phase 2 study to balance efficacy and safety in patients with centrally confirmed HER2-positive disease after progression on trastuzumab-containing therapy [1–3].

Pharmacology-informed safety focus

From a pharmacology perspective, on-target HER2 engagement and efficient payload delivery underpin risks of class-relevant cardiac effects (monitoring of LVEF) and payload-related toxicities including myelosuppression and gastrointestinal adverse events; careful monitoring for interstitial lung disease/pneumonitis is warranted given experience with topoisomerase I–containing ADCs and the identified risk in clinical use of T-DXd, although a definitive mechanistic basis remains to be fully elucidated [1,3,4]. The protocol's safety assessments and dose-modification rules are aligned with these pharmacology-informed risks.

References

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6.3.2 Toxicology

Overview of the nonclinical toxicology package

The nonclinical toxicology profile of trastuzumab deruxtecan (T-DXd) has been characterized primarily in repeat-dose studies in rats and cynomolgus monkeys, complemented by genotoxicity testing of the DXd payload. Across species, target organ toxicities were consistent with the pharmacology of a topoisomerase I–inhibiting antibody–drug conjugate and included myelosuppression, gastrointestinal injury, lymphoid depletion, and lung injury (interstitial pneumonitis) in monkeys [1]. No dedicated long-term carcinogenicity studies have been conducted. No animal reproductive or developmental toxicity studies have been conducted with T-DXd; based on its mechanism of action, fetal harm is expected. Contraception is required for females of reproductive potential during treatment and for 7 months after the last dose, and for male patients with female partners of reproductive potential during treatment and for 4 months after the last dose [1].

Safety pharmacology

- Cardiovascular: No specific nonclinical safety pharmacology studies have identified direct cardiovascular liabilities; in clinical development, T-DXd has not demonstrated a clinically meaningful effect on QTc at recommended dosing regimens, supporting a low risk of drug-induced QT prolongation for this program's monitoring plan [1].
- Respiratory: Interstitial pneumonitis (ILD) was observed in cynomolgus monkeys after T-DXd administration, establishing a nonclinical signal for lung injury concordant with clinical risk; this informs the protocol's heightened ILD surveillance and management plan [1].
- Central nervous system: No dedicated nonclinical CNS safety pharmacology signal has been highlighted beyond class-consistent constitutional effects secondary to systemic toxicity in repeat-dose studies [1].

General toxicology and target-organ effects

Repeat-dose toxicity studies in rats and cynomolgus monkeys identified the following treatment-related findings that are pertinent to Phase 2 safety monitoring:

- Hematologic/bone marrow: Myelosuppression manifested as neutropenia, anemia, and thrombocytopenia with bone marrow hypocellularity, consistent with the DXd payload's antiproliferative effects [1].
- Gastrointestinal: Degeneration/necrosis of gastrointestinal mucosa with corresponding clinical signs (e.g., decreased appetite, diarrhea), reflecting rapidly proliferating epithelial susceptibility [1].
- Lymphoid/immune system: Lymphoid tissue depletion (thymus, spleen, lymph nodes) observed in repeat-dose studies [1].
- Respiratory (lung): Interstitial pneumonitis in monkeys, including inflammatory infiltrates and alveolar damage, supporting a species-relevant signal for ILD risk that warrants proactive clinical monitoring and early intervention [1].
- Hepatic: Mild, generally reversible hepatocellular changes and/or transaminase elevations were observed; severe intrinsic hepatotoxicity was not a prominent nonclinical feature, but routine liver test monitoring is warranted [1].
- Renal: No primary nephrotoxicity was identified as a consistent target-organ effect in repeat-dose studies; renal findings, when present, were generally limited and often occurred in the context of systemic toxicity [1].
- Dermatologic/appendageal: Changes consistent with effects on rapidly dividing cells (e.g., alopecia in species where assessable) were noted [1].
- Reproductive organs: Fertility studies were not performed with T-DXd; based on findings in animal toxicity studies, T-DXd may impair male reproductive function and fertility [1].

Collectively, these nonclinical data delineate a toxicity profile centered on proliferative compartments (bone marrow, GI mucosa, lymphoid tissues) and the lung (monkey ILD), aligning with the protocol's monitoring emphasis on cytopenias, gastrointestinal adverse events, hepatic laboratory abnormalities, and ILD/pneumonitis [1]. The lung findings in monkeys represent an organ toxicity signal identified in nonclinical models that is clinically actionable and may precede overt respiratory symptoms,

reinforcing imaging-based detection strategies and adjudication in this study [1].

Genetic toxicology

- Bacterial reverse mutation (Ames): The DXd payload was not mutagenic in standard bacterial assays [1].
- Mammalian cell and chromosomal damage assays: The DXd payload was clastogenic, demonstrating induction of micronuclei/structural chromosomal damage in mammalian systems; topoisomerase I inhibitors are mechanistically associated with aneugenic/clastogenic effects [1].
- In vivo: The DXd payload demonstrated genotoxic potential in in vivo assays consistent with its pharmacology [1].

These results support a conclusion that while point mutations are not induced in bacterial systems, the DXd payload causes chromosomal damage consistent with topoisomerase I inhibition, informing contraception requirements and the absence of a carcinogenicity package [1].

Reproductive and developmental toxicity

No animal reproductive or developmental toxicity studies have been conducted with T-DXd. Based on its mechanism of action and genotoxic profile, fetal harm is expected if exposure occurs during pregnancy. Females of reproductive potential must use effective contraception during treatment and for 7 months after the last dose; males with female partners of reproductive potential must use effective contraception during treatment and for 4 months after the last dose [1]. Fertility studies have not been performed; based on animal toxicity findings, T-DXd may impair male reproductive function and fertility [1].

Long-term carcinogenicity

No long-term carcinogenicity studies have been conducted with T-DXd or the DXd payload. Given the genotoxic/clastogenic activity of the payload and the clinical context of use, a carcinogenicity assessment was not pursued in the nonclinical package; the clinical risk–benefit in this patient population justifies proceeding without such studies while implementing rigorous clinical safety monitoring [1].

QTc interval and cardiovascular safety considerations

Intensive ECG evaluations from the clinical development program summarized in the reference prescribing information have not shown a clinically meaningful effect of T-DXd on QTc at recommended dosing levels. Nonclinical data do not indicate a primary ion-channel liability for the conjugate at relevant exposures, supporting the study's standard ECG surveillance without specialized proarrhythmia testing beyond protocol-specified assessments [1].

Interpretation for the Phase 2 study

The nonclinical profile indicates dose-dependent, exposure-related toxicities in rapidly proliferating tissues and a species-relevant ILD signal in monkeys, while not identifying intrinsic proarrhythmic risk. Accordingly, this protocol's safety strategy prioritizes early detection and management of ILD/pneumonitis, monitoring and dose modification for myelosuppression and gastrointestinal toxicity, routine hepatic laboratory assessment, and standard cardiac surveillance including LVEF and ECGs. Absence of reproductive/developmental and carcinogenicity studies and the clastogenic potential of the payload support stringent contraception requirements and exclusion of pregnant or breastfeeding individuals [1].

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6.4 Clinical Studies

6.4.1 Human Pharmacokinetics

Overview and measured analytes

Following intravenous infusion of trastuzumab deruxtecan (T-DXd), two principal analytes are characterized systemically: intact conjugate (T-DXd) and unconjugated DXd payload. Peak serum concentrations of T-DXd occur at end of infusion, with measurable low-level circulating DXd reflecting time-dependent intracellular release and limited systemic deconjugation [1].

Dose–exposure relationships and time course

Across the clinically relevant range, T-DXd exhibits approximately linear pharmacokinetics with dose-proportional increases in exposure following every-3-week dosing. After a 6.4 mg/kg infusion, the terminal elimination half-life (t1/2) for intact T-DXd is approximately 5–6 days; DXd shows a similar terminal half-life governed by release and metabolic clearance kinetics [1]. T-DXd Cmax is achieved at infusion completion; unconjugated DXd typically reaches its maximum concentration after the infusion, consistent with intracellular linker cleavage and subsequent appearance in circulation [1,2]. Modest accumulation is observed with repeated dosing every 3 weeks, and steady state is generally approached within the first few cycles; first-dose versus steady-state differences are not large and reflect expected accumulation based on the ~5–6-day half-life [1,2].

Published first-in-human/expansion data and the prescribing reference consistently show a monoclonal antibody–like disposition for T-DXd with time-dependent DXd appearance, dose proportionality over the clinical range, and modest accumulation with q3w dosing; taken together, these support the fixed mg/kg q3w regimen used in this study [1,2].

Absorption and food effect

As an intravenously administered product, T-DXd has complete systemic availability at the end of infusion; food has no effect on exposure or absorption and no food-effect studies are required for drugs administered solely by the intravenous route [3].

Distribution

Population pharmacokinetic analyses indicate a central volume of distribution consistent with IgG1 monoclonal antibodies, with limited extravascular distribution of intact T-DXd. Systemic DXd concentrations are low relative to the conjugate and reflect localized intracellular release with limited systemic distribution of unconjugated payload [1].

Metabolism, biotransformation, and drug–drug interactions

The antibody component undergoes proteolytic catabolism to small peptides and amino acids. DXd is primarily metabolized by CYP3A4 in vitro and in vivo; clinical drug–drug interaction evaluations with strong CYP3A and P-glycoprotein (P-gp) inhibitors (e.g., itraconazole, ritonavir) did not produce clinically meaningful changes in exposure to T-DXd or DXd, indicating that strong CYP3A and/or P-gp inhibition does not meaningfully alter systemic exposure at therapeutic dosing [1]. T-DXd is not expected to cause clinically significant inhibition or induction of major CYP enzymes or transporters at clinically relevant concentrations [1].

Elimination pathways

Clearance of intact T-DXd occurs predominantly via reticuloendothelial catabolism typical of IgG-based therapeutics. Renal excretion is not a meaningful pathway for intact T-DXd. The released DXd is cleared primarily by hepatic metabolism; renal elimination of DXd is a minor pathway based on clinical pharmacology evaluations [1].

Renal impairment

Clinical pharmacology and population PK analyses indicate no clinically meaningful differences in exposure to T-DXd or DXd in patients with mild (creatinine clearance 60–89 mL/min) or moderate (30–59 mL/min) renal impairment relative to normal renal function; however, a higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment, and these patients should be monitored more frequently [1]. Data in severe renal impairment (creatinine clearance <30 mL/min) and end-stage renal disease, including patients on dialysis, are limited or absent; in these populations, the impact on DXd exposure and safety is uncertain and requires clinical judgment with enhanced monitoring if treatment is undertaken [1]. Given the minimal renal

contribution to intact T-DXd clearance and primarily metabolic clearance of DXd, large renal function–driven changes in exposure are not expected; however, evidence in severe impairment/dialysis is insufficient to define dosing with confidence [1].

Hepatic impairment

In clinical pharmacology assessments, mild hepatic impairment (commonly defined in the T-DXd program as total bilirubin ≤ ULN with AST > ULN or total bilirubin >1.0–1.5 × ULN with any AST) did not result in clinically meaningful changes in exposure to T-DXd or DXd compared with normal hepatic function. Limited data suggest that moderate hepatic impairment (total bilirubin >1.5–3 × ULN with any AST) may increase DXd exposure; the magnitude of increase has not necessitated a standard dose adjustment recommendation but warrants closer safety monitoring. Effects in severe hepatic impairment (total bilirubin >3 × ULN) have not been characterized, and dosing recommendations cannot be made for this group based on available evidence [1]. Clinical studies commonly classify hepatic function using Child-Pugh classes A, B, and C or bilirubin/AST-based categories; increases in systemic exposure with worsening hepatic dysfunction are a general expectation for payloads cleared hepatically and may elevate the risk of toxicity, supporting cautious use and enhanced monitoring when hepatic function is impaired [1].

First-dose versus steady-state exposure

With q3w dosing, exposure to T-DXd and DXd increases modestly between the first dose and subsequent cycles, consistent with the half-life and limited accumulation. No phenomenon of time-dependent clearance has been identified; steady-state trough and peak concentrations stabilize within the first several cycles without evidence of clinically relevant autoinduction or autoinhibition [1,2].

Clinical implications for dosing in this protocol

- Intravenous administration obviates food-effect considerations [3].
- No dose adjustment is indicated for mild or moderate renal impairment, but patients with moderate renal impairment should be monitored more frequently for ILD/pneumonitis; evidence is insufficient in severe impairment or dialysis, requiring individualized risk–benefit assessment and enhanced safety monitoring if treated [1].
- In mild hepatic impairment, no adjustment is indicated; in moderate impairment, potential for increased DXd exposure supports heightened monitoring for toxicity. Use in severe hepatic impairment cannot be recommended based on current evidence [1].
- The ~5–6-day half-life supports the every-3-week regimen and informs the 40-day safety follow-up window after the last dose in this protocol [1].

References

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6.4.2 Clinical Efficacy Studies

Overview of prior human efficacy evidence with trastuzumab deruxtecan in HER2-positive gastric/GEJ adenocarcinoma

Two multicentre studies have reported clinically meaningful antitumour activity of trastuzumab deruxtecan (T-DXd) monotherapy in patients with heavily pretreated, HER2-positive advanced gastric/GEJ adenocarcinoma: a randomized Phase 2 trial conducted in Japan and Korea (DESTINY-Gastric01) and a Phase 1 dose-expansion cohort that included a dedicated gastric/GEJ population. Both studies used the 6.4 mg/kg every-3-weeks regimen and assessed efficacy with RECIST v1.1

and independent central review, providing concordant evidence of high objective response rates, durable responses, and improvements in progression-free and overall survival versus chemotherapy in the randomized setting [1–3].

Summary of key published clinical efficacy studies

Study	Design and setting	Population	T-DXd regimen	Primary/Key efficacy assessments	Efficacy results
Shitara et al., 2020 (DESTINY-Gastric01) [1]	Open-label, randomized Phase 2 (T-DXd vs physician's choice chemo); Japan/Korea; independent central review	HER2-positive (IHC 3+ or IHC 2+/ISH+); unresectable/metastatic gastric/GEJ adenocarcinoma; prior trastuzumab and ≥2 prior regimens	6.4 mg/kg IV q3w	Primary: ORR by independent central review; key secondary: OS, PFS, DOR	ORR (confirmed and unconfirmed) 51.3% (95% CI 41.9–60.5) with T-DXd vs 14.3% (95% CI 6.4–26.2) with chemo; confirmed ORR 42.9% vs 12.5%; median DOR 11.3 months with T-DXd; median PFS 5.6 vs 3.5 months (HR 0.47); median OS 12.5 vs 8.4 months (HR 0.59)
Shitara et al., 2019 (Phase 1 gastric cohort) [2]	Multicentre, Phase 1 dose-expansion; single arm; independent central review	HER2-positive advanced gastric/GEJ adenocarcinoma; prior trastuzumab; ≥2 prior regimens (typical)	6.4 mg/kg IV q3w in gastric cohort	Primary: safety/tolerability; key efficacy: ORR, DOR, PFS	ORR 43% (95% CI 28–59); median DOR 7.0 months (95% CI 4.4–16.6); median PFS 5.6 months (95% CI 3.0–8.3)

Endpoint definitions and assessment methods

- Objective response rate (ORR): Confirmed complete or partial responses by RECIST v1.1 with independent central review; confirmation required on a subsequent assessment at least 4 weeks after initial documentation [1,2].
- Duration of response (DOR), progression-free survival (PFS), and overall survival (OS): Time-to-event outcomes estimated using Kaplan–Meier methods; hazard ratios derived from stratified Cox models in the randomized trial [1].

Magnitude and precision of antitumour activity

Across studies, T-DXd 6.4 mg/kg q3w achieved high ORR with durable responses in a trastuzumab-pretreated, predominantly third-line-or-later population. DESTINY-Gastric01 demonstrated a 51.3% ORR (confirmed and unconfirmed; 95% CI 41.9–60.5; confirmed ORR 42.9%) by independent central review and superiority over chemotherapy in PFS (HR 0.47) and OS (HR 0.59), with median DOR of 11.3 months, establishing clinically meaningful benefit in an Asian population [1]. The Phase 1 gastric cohort showed an ORR of 43% (95% CI 28–59), median DOR 7.0 months, and median PFS 5.6 months, supporting reproducible activity with the same regimen in a single-arm setting [2]. Together, these data indicate consistent, robust tumour shrinkage and response durability at the 6.4 mg/kg q3w dose used in this protocol [1,2].

Subgroup and response-pattern observations

Efficacy was observed across HER2 IHC 3+ and IHC 2+/ISH+ categories in both studies, with numerically higher ORR in IHC 3+ tumours, consistent with target-dependent activity; however, responses also occurred in IHC 2+/ISH+ disease, aligning with preclinical bystander-effect pharmacology [1,2]. DESTINY-Gastric01 reported responses regardless of prior stability to trastuzumab and in patients with measurable disease across organ sites, supporting broad activity

within HER2-positive gastric/GEJ adenocarcinoma after trastuzumab exposure [1]. These subgroup findings are descriptive and should be interpreted cautiously given limited sample sizes in certain strata [1,2].

Limitations and remaining uncertainties

- Geography and line of therapy: The randomized evidence derives from East Asian sites and later lines of therapy (≥3L), with potential differences in prior therapies, supportive care, and tumour biology relative to Western practice [1].
- Single-arm evidence outside the randomized setting: The Phase 1 gastric cohort was uncontrolled, limiting comparative inference [2].
- Generalizability to earlier post-trastuzumab settings: While activity after multiple prior regimens is established, additional data are warranted in Western patients treated immediately after failure of first-line trastuzumab-containing therapy to refine estimates of response and durability [1,2].

Relevance to protocol SP-TDXD-GC-201

The selected dose and schedule (6.4 mg/kg q3w) replicate those associated with high ORR and durable responses in the Phase 1 gastric cohort and the randomized Phase 2 trial demonstrating superiority over chemotherapy in Japanese and Korean patients pretreated with ≥2 regimens including trastuzumab [1,2]. This protocol focuses on Western patients earlier in the post-trastuzumab sequence (progression during or after first-line trastuzumab-containing therapy), where prospective, single-arm confirmation of antitumour activity is needed. The primary endpoint of confirmed ORR by independent central review and the sample size are designed so that, if the true ORR is approximately 45% as observed across studies, the lower bound of the 95% confidence interval will reliably exceed 27%, a commonly cited historical second-line benchmark in this disease context [1,2].

References

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6.4.3 Overall Safety Summary

Integrated safety database and exposure

Safety data for investigational trastuzumab deruxtecan (T-DXd) monotherapy at 6.4 mg/kg every 3 weeks in HER2-positive gastric/gastro-oesophageal junction (GEJ) adenocarcinoma derive primarily from a randomized Phase 2 trial (DESTINY-Gastric01; T-DXd n=125) and a Phase 1 dose-expansion gastric cohort (n=44), for an aggregate of approximately 169 treated patients across two studies, supplemented by the current US prescribing information, which summarizes adverse reactions and risks observed with T-DXd, including at the 6.4 mg/kg dose used in gastric cancer [1–3]. Across these sources, T-DXd was associated with a characteristic adverse event profile centered on gastrointestinal and hematologic toxicities and a consistent risk of interstitial lung disease (ILD)/pneumonitis, with cardiac dysfunction (decreased left ventricular ejection fraction [LVEF]) observed infrequently but warranting routine surveillance [1–3].

Overall incidence and pattern of TEAEs with monotherapy

Treatment-emergent adverse events (TEAEs) were common. In DESTINY-Gastric01, most patients receiving T-DXd experienced at least one TEAE, and grade 3–4 events occurred frequently, driven largely by myelosuppression and gastrointestinal toxicity; serious adverse events (SAEs) included infections, ILD/pneumonitis, and neutropenic complications [2]. The Phase 1 gastric cohort demonstrated a similar pattern, with predominantly gastrointestinal and hematologic TEAEs and manageable non-hematologic toxicity with dose holds/modifications as needed [3]. The current prescribing information corroborates these patterns at 6.4 mg/kg, highlighting ILD/pneumonitis,

myelosuppression (neutropenia, anemia, thrombocytopenia), and gastrointestinal adverse reactions (nausea, vomiting, decreased appetite, diarrhea, constipation) as characteristic risks of T-DXd that require proactive monitoring and dose modification per protocol [1].

Most frequent TEAEs (≥20% incidence)

Across gastric datasets, the most commonly reported TEAEs (occurring in ≥20% of patients) included:

- Nausea, vomiting, decreased appetite, diarrhea, and constipation [1–3]
- Anemia, neutropenia, leukopenia, and thrombocytopenia [1–3]
- Fatigue and alopecia [1–3]
- Pyrexia [1,2]

These events were typically grade 1–2 for non-hematologic toxicities, whereas hematologic events showed a higher proportion of grade ≥3 severity, consistent with the topoisomerase I payload–related myelosuppressive profile [1–3].

Grade 3–4 toxicities and SAEs

Grade 3–4 TEAEs most commonly involved hematologic laboratory abnormalities and clinical events (neutropenia, anemia, and thrombocytopenia), with febrile neutropenia reported less frequently but constituting a clinically important SAE when present [1–3]. Non-hematologic grade ≥3 events included gastrointestinal toxicities (e.g., severe nausea/vomiting, diarrhea) and ILD/pneumonitis; infections (including pneumonia) were among the more frequent SAEs, often in the setting of cytopenias [1–3]. The prescribing information emphasizes the need for dose interruptions/reductions for myelosuppression and supportive care (e.g., growth factors per institutional standards) to mitigate risks of severe hematologic toxicity and infection [1].

Events of special interest

- ILD/pneumonitis: ILD/pneumonitis is a well-characterized, potentially fatal risk of T-DXd. In DESTINY-Gastric01, adjudicated drug-related ILD/pneumonitis occurred in approximately 10% of T-DXd–treated patients, mostly grade 1–2, with no ILD-related deaths; time to onset was variable, and early recognition with treatment interruption and corticosteroids was critical [2]. The current prescribing information reports ILD/pneumonitis across the T-DXd program, including at 6.4 mg/kg, and underscores prompt investigation of new/worsening respiratory symptoms, permanent discontinuation for grade ≥2 events, and systemic corticosteroid treatment per severity [1]. The Phase 1 gastric cohort observed a concordant signal with mostly low-grade events and rare severe cases, reinforcing the need for vigilant monitoring and early management [3].
- Cardiac effects (LVEF decrease): Decreased LVEF and cardiac failure events were uncommon but observed; routine LVEF monitoring is recommended. The prescribing information reports infrequent LVEF decreases and rare cardiac failure events, advising baseline and periodic assessments (e.g., echocardiogram or MUGA) and treatment interruption/discontinuation based on severity and absolute LVEF changes [1]. In gastric studies, clinically significant cardiac events were uncommon, but the risk warrants adherence to scheduled LVEF evaluations specified in this protocol [2,3].
- Infections and febrile neutropenia: Serious infections, including pneumonia, and febrile neutropenia occurred and were more likely in the setting of grade ≥3 neutropenia; supportive care and dose modifications per toxicity guidelines mitigated risk [1–3].

Dose modifications, interruptions, and discontinuations

Dose interruptions and reductions were commonly used to manage TEAEs, particularly hematologic (neutropenia, anemia, thrombocytopenia) and gastrointestinal toxicities (nausea, vomiting, diarrhea), and were generally effective in enabling continued treatment [1–3]. Permanent discontinuations due to adverse events occurred in a subset of patients across gastric studies; ILD/pneumonitis was among the most frequent reasons for permanent discontinuation, consistent with program-wide guidance mandating discontinuation for grade ≥2 ILD/pneumonitis [1–3]. The prescribing information provides dose-modification algorithms for hematologic and non-hematologic toxicities and mandates immediate interruption and evaluation for any suspected ILD/pneumonitis, aligning with this protocol's rules (e.g., restart only after complete resolution of grade 1; permanent discontinuation for grade ≥2)

[1].

Overall safety interpretation for the Phase 2 study population

Taken together, safety data from approximately 169 T-DXd–treated patients with HER2-positive gastric/GEJ adenocarcinoma across two clinical studies, supported by the current prescribing information, delineate a consistent safety profile characterized by frequent gastrointestinal and hematologic TEAEs, a clinically significant risk of ILD/pneumonitis (including rare fatal events), and infrequent but monitorable decreases in LVEF [1–3]. These findings justify the protocol's focused surveillance for ILD/pneumonitis (with independent adjudication), routine cardiac monitoring (LVEF assessments and ECGs), and proactive management of myelosuppression and gastrointestinal toxicity through dose interruptions/reductions and supportive care. The anticipated tolerability profile in this single-arm Phase 2 US study is aligned with prior experience at 6.4 mg/kg, with the greatest risks being ILD/pneumonitis and hematologic toxicity; the safety monitoring plan and dose-modification schema are designed to mitigate these risks while maintaining treatment continuity where clinically appropriate [1–3].

References

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6.4.4 Adverse events

Overview

Adverse events (AEs) will be collected from first dose through 40 days (+7) after the last dose and graded per NCI CTCAE v5.0. The safety profile of investigational trastuzumab deruxtecan (T-DXd) monotherapy at 6.4 mg/kg every 3 weeks in HER2-positive gastric/gastro-oesophageal junction adenocarcinoma is characterized by gastrointestinal toxicities, myelosuppression, and interstitial lung disease (ILD)/pneumonitis as a clinically significant risk; decreases in left ventricular ejection fraction (LVEF) occur infrequently but warrant routine surveillance [1–3]. Serious adverse events (SAEs) include ILD/pneumonitis, infections (including pneumonia), and neutropenic complications; dose interruptions/reductions are commonly used to manage toxicities [1–3].

Hematologic toxicities (neutropenia, anemia, thrombocytopenia)

Myelosuppression is common with T-DXd, consistent with a topoisomerase I–inhibiting payload. Neutropenia, anemia, and thrombocytopenia occur frequently; grade 3–4 neutropenia and anemia are among the most common high-grade laboratory abnormalities, with febrile neutropenia less frequent but clinically important [1–3]. Symptoms warranting early evaluation include fever (especially with neutropenia), dyspnea or new cough (infection), bleeding/bruising or petechiae (thrombocytopenia), and fatigue, dizziness, or pallor (anemia) [1–3]. Management includes dose interruption/modification per protocol, growth factor support per institutional guidelines, transfusions as indicated, and infection workup and treatment when febrile neutropenia or documented infection occurs [1].

Gastrointestinal toxicities (nausea, vomiting, diarrhea, constipation, decreased appetite)

Nausea, vomiting, diarrhea, constipation, and decreased appetite are among the most frequent AEs; non-hematologic events are typically grade 1–2, though severe nausea/vomiting and diarrhea can occur and may require antiemetics, antidiarrheals, intravenous fluids, and dose modification [1–3]. For grade ≥3 non-hematologic toxicity (excluding alopecia, nausea/vomiting controlled with optimal therapy, or ILD/pneumonitis), interrupt until grade ≤1, then resume at a reduced dose; permanently

discontinue for life-threatening (grade 4) non-hematologic toxicity [1].

Pulmonary toxicity (ILD/pneumonitis)

ILD/pneumonitis is an identified, potentially fatal risk of T-DXd. Events have occurred across grades, most commonly grade 1–2 in gastric cancer experience, with variable time to onset; prompt interruption at first suspicion and early corticosteroids are critical [1–3]. Monitoring includes baseline symptom assessment, pulse oximetry and targeted imaging when clinically indicated, with a low threshold for chest CT if new or worsening cough, dyspnea, fever, or hypoxia occurs. Per protocol and product guidance: interrupt immediately for any suspected ILD/pneumonitis; for grade 1, treat and resume only after complete resolution; for grade ≥2, permanently discontinue and initiate systemic corticosteroids and supportive care; follow all cases to resolution [1–3].

Cardiac safety (LVEF decrease, arrhythmias, QT)

- LVEF decrease and heart failure: Clinically significant decreases in LVEF are uncommon but have been observed; baseline and serial assessments (echocardiogram or MUGA) are required. Management follows the dose-modification algorithm below [1–3].
- Atrial fibrillation and other arrhythmias: No clinically meaningful effect on QTc has been observed with T-DXd at recommended dosing, and a consistent proarrhythmic signal has not been identified; atrial fibrillation or other arrhythmias have been reported infrequently in clinical development and routine oncology practice. Evaluate palpitations, dizziness/syncope, and exertional intolerance; obtain ECG and manage per standard cardiology care, considering anticoagulation for persistent atrial fibrillation based on stroke risk and bleeding risk in the setting of thrombocytopenia [1]. For concomitant QT-prolonging drugs, monitor ECG and electrolytes and correct hypokalemia, hypomagnesemia, and hypocalcemia.

Dermatologic and hypersensitivity reactions

Alopecia and rash are common; most events are mild to moderate and manageable with topical agents and dose modification only when severe or persistent [1–3]. Infusion-related reactions and hypersensitivity have been reported and are generally manageable with infusion interruption, symptomatic treatment, and resumption at slower rates when appropriate [1]. Severe cutaneous adverse reactions (SCARs) have not emerged as a consistent signal with T-DXd; promptly evaluate any widespread or blistering rash with mucosal involvement and manage per institutional standards. Evidence for SCARs with T-DXd remains limited [1].

Infections (common and opportunistic)

Bacterial infections, including pneumonia, occur and are more frequent with higher-grade neutropenia; febrile neutropenia has been reported and requires urgent broad-spectrum antibiotics and supportive care [1–3]. Opportunistic infections are uncommon, and routine antimicrobial prophylaxis is not mandated; consider antiviral or antifungal prophylaxis only for patients with prolonged, profound neutropenia or other risk factors per institutional guidelines. Rare, serious neurologic infections have not been identified as a product-specific signal with T-DXd; maintain vigilance in immunocompromised states and evaluate new focal neurologic deficits or encephalopathy promptly. Current evidence for opportunistic and neurologic infection risk with T-DXd is limited [1–3].

Hepatic, renal, and metabolic laboratory abnormalities

Asymptomatic transaminase elevations and hypoalbuminemia have occurred; severe intrinsic hepatotoxicity is not a prominent feature, but routine liver tests are recommended and dose modification for grade ≥3 events should follow the general non-hematologic algorithm [1–3]. Clinically meaningful changes in renal function are uncommon; monitor creatinine and electrolytes per standard oncology practice [1].

Hypertension and vascular events

Hypertension has been reported but is not a characteristic toxicity of T-DXd; manage per standard algorithms with antihypertensives, ensuring control before subsequent dosing. Evaluate for secondary causes (pain, anxiety, fluid shifts) and consider dose interruption for severe, uncontrolled hypertension until stabilized. Thromboembolic events have not been a consistent signal with T-DXd in gastric cancer; evaluate new dyspnea or limb swelling promptly, especially in immobilized or high-risk

patients [1–3].

Secondary malignancies and non-melanoma skin cancers

Across clinical studies and the current safety database, secondary primary malignancies, including non-melanoma skin cancers, have not emerged as a consistent signal with T-DXd. Routine age- and risk-appropriate cancer screening is recommended; counsel patients to report new or changing skin lesions and consider periodic skin assessments during long-term therapy. Evidence for treatment-emergent non-melanoma skin cancers with T-DXd remains limited [1–3].

Drug–drug interactions and concomitant therapy considerations

- Metabolism and transport: The antibody component undergoes proteolysis; the DXd payload is primarily metabolized by CYP3A4. Clinical evaluations show no clinically meaningful changes in T-DXd or DXd exposure with strong CYP3A and/or P-glycoprotein inhibitors, and T-DXd is not expected to cause clinically significant CYP inhibition or induction [1].
- Strong CYP3A inhibitors/inducers: Based on available data, coadministration with strong CYP3A or P-gp inhibitors does not necessitate T-DXd dose adjustment; clinically meaningful effects of strong CYP3A inducers have not been demonstrated. Monitor for expected toxicities if such agents are coadministered [1].
- Dietary considerations: No dietary restrictions (e.g., grapefruit) are required given the absence of a clinically meaningful inhibitor effect on exposure in studies conducted to date [1].
- QT-prolonging agents: Although T-DXd has not shown a clinically meaningful QTc effect, when coadministered with QT-prolonging drugs, obtain baseline and follow-up ECGs and monitor/correct electrolytes [1].

Dose modifications and treatment interruptions

- General rules: For any suspected ILD/pneumonitis, interrupt immediately and evaluate; permanently discontinue for grade ≥2 ILD/pneumonitis; for grade 1, resume only after complete resolution. For other grade ≥3 non-hematologic toxicity (excluding alopecia, nausea/vomiting responsive to optimal therapy), interrupt until grade ≤1, then resume at a reduced dose; permanently discontinue for life-threatening toxicity [1–3].
- Neutropenia:

- Grade 3: Interrupt until grade ≤2, then resume at the same dose [1].
- Grade 4: Interrupt until grade ≤2, then reduce by one dose level [1].
- Febrile neutropenia: Interrupt until resolved, then reduce by one dose level [1].

- Thrombocytopenia:

- Grade 3: Interrupt until grade ≤1, then resume at the same dose [1].
- Grade 4: Interrupt until grade ≤1, then reduce by one dose level [1].

- LVEF management:

- LVEF >45% with absolute drop of 10–20% from baseline: Continue; repeat assessment per schedule [1].
- LVEF 40–45% with absolute drop <10%: Continue and repeat LVEF within 3 weeks [1].
- LVEF 40–45% with absolute drop 10–20%: Interrupt and repeat within 3 weeks; if LVEF recovers to within 10% of baseline, resume at the same dose; otherwise permanently discontinue [1].
- LVEF <40% or absolute drop >20%: Interrupt, repeat within 3 weeks, and permanently discontinue if confirmed [1].
- Symptomatic congestive heart failure: Permanently discontinue [1].

- Maximum of two dose reductions are permitted (to 5.4 mg/kg then 4.4 mg/kg); no re-escalation. Doses may be delayed up to 28 days for toxicity; longer delays require discontinuation [1].

AE monitoring and reporting in this study

- Monitoring: Vital signs and symptom review each visit; complete blood counts and chemistry including liver tests prior to each cycle; ECG at screening and during treatment per protocol; LVEF at screening, Cycle 5 Day 1, and every 4 cycles thereafter with consistent modality; ILD vigilance with prompt imaging when symptomatic. An independent ILD adjudication

committee will review all potential ILD cases. Pregnancy testing is required for participants of childbearing potential [1–3].

- Regulatory reporting: Suspected unexpected serious adverse reactions (SUSARs) and other safety information will be reported in accordance with 21 CFR 312.32. Sample Pharma Co., Ltd. will conduct ongoing safety review throughout the study.

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6.4.5 Rationale for the study

Scientific and clinical justification

Patients with HER2-positive unresectable or metastatic gastric/gastro-oesophageal junction (GEJ) adenocarcinoma who progress during or after first-line trastuzumab-containing therapy face limited second-line options with modest objective response rates (ORR) and short progression-free survival (PFS), underscoring a need for agents that can induce deeper and more durable remissions. In the RAINBOW trial, paclitaxel plus ramucirumab achieved an ORR of 28% and median PFS of 4.4 months versus 16% and 2.9 months with paclitaxel alone, illustrating incremental benefit with intensified cytotoxic/antiangiogenic therapy yet highlighting constraints in durability and tolerability, particularly hematologic toxicity [6]. Concurrently, continued anti-HER2 strategies after trastuzumab failure are challenged by on-treatment resistance mechanisms, including intratumoral HER2 heterogeneity and dynamic loss of HER2 amplification/overexpression; post-trastuzumab rebiopsy studies reported HER2 loss in approximately one-third of patients, supporting mandatory reassessment to identify those most likely to benefit from HER2-directed approaches [3,4].

Trastuzumab deruxtecan (T-DXd), a HER2-directed antibody–drug conjugate, has demonstrated substantial antitumour activity in HER2-positive gastric/GEJ cancer previously treated with trastuzumab. In a randomized phase 2 study in Japan and Korea (DESTINY-Gastric01), T-DXd produced superior ORR (confirmed and unconfirmed 51.3%; confirmed 42.9%), longer PFS (median 5.6 vs 3.5 months; HR 0.47), and improved overall survival (OS; median 12.5 vs 8.4 months; HR 0.59) compared with physician’s choice chemotherapy in heavily pretreated patients [1]. A phase 1 dose-expansion gastric cohort reported an ORR of 43%, median duration of response (DOR) 7.0 months, and median PFS 5.6 months at the same 6.4 mg/kg every-3-weeks regimen, corroborating robust activity in a similar post-trastuzumab population [2]. These data collectively support the investigational evaluation of T-DXd monotherapy at 6.4 mg/kg every 3 weeks in the proposed second-line, post-trastuzumab U.S. population, with the study powered to show a lower bound of the 95% ORR confidence interval exceeding a historical benchmark around 27% derived from standard second-line regimens [1,2,6].

Why deeper and more durable remissions matter after trastuzumab failure

Following progression on first-line trastuzumab-containing therapy, prognosis is poor and clinical trajectories can be rapid due to cumulative disease burden and declining performance status. In this setting, achieving rapid, deep tumour shrinkage can restore organ function and permit continuation of systemic treatment, while durable responses may translate into longer OS and delay the need for more toxic cytotoxic combinations [1,6]. The randomized T-DXd data demonstrated not only high ORR but also meaningful DOR and OS gains versus chemotherapy, aligning with the therapeutic goal

of inducing substantive and sustained disease control in patients whose cancers have already demonstrated resistance to prior HER2-targeted plus chemotherapy regimens [1].

Central confirmation of HER2 positivity on post-progression biopsy

Given the documented frequency of HER2 loss after trastuzumab and the prognostic and predictive impact of HER2 heterogeneity, central confirmation of HER2 status on a new biopsy obtained after first-line progression is essential to enrich for patients most likely to benefit from HER2-directed therapy [3]. The ASCO–CAP guideline provides validated, standardized criteria for classifying HER2 status in gastro-oesophageal adenocarcinoma (IHC 3+ or IHC 2+/ISH+), ensuring analytic rigor and clinical interpretability across sites and minimizing false-positive assignment in a biologically heterogeneous disease [4].

Target population, subgroup considerations, and treatment-intensity context

Treatment goals and tolerance differ across patient subgroups. Younger patients with ECOG PS 0–1 and adequate marrow reserve may realize incremental benefit from intensified cytotoxic regimens such as paclitaxel plus ramucirumab but experience higher rates of grade ≥3 neutropenia and require growth factor support and dose modifications, whereas older or more comorbid patients may be less able to tolerate prolonged doublet therapy [6]. The single-agent ADC approach aims to deliver high antitumour activity with a toxicity profile that can be proactively monitored and managed via standardized dose-interruption/reduction algorithms, potentially broadening applicability across fitness strata while preserving efficacy signals seen in prior studies [1,2,5]. Early randomized and cohort data with T-DXd suggest responses across HER2 IHC 3+ and 2+/ISH+ tumours, with numerically higher activity in IHC 3+, supporting inclusion of both categories with stratified interpretation and reinforcing the requirement for rigorous, central HER2 confirmation in this protocol [1,2,4].

Safety-focused design elements and monitoring rationale

T-DXd is associated with characteristic toxicities including gastrointestinal events, myelosuppression, and a clinically important risk of interstitial lung disease (ILD)/pneumonitis, with uncommon decreases in left ventricular ejection fraction (LVEF) necessitating surveillance [1,2,5]. Close early monitoring for pulmonary symptoms with prompt treatment interruption at first suspicion of ILD/pneumonitis and permanent discontinuation for grade ≥2 events reflects established risk-mitigation strategies supported by clinical experience and product guidance [5]. Routine cardiac monitoring with baseline and periodic LVEF assessments and proactive management of myelosuppression and gastrointestinal adverse events through dose interruptions/reductions and supportive care are standard phase 2 safety practices appropriate for this setting [1,5]. The open-label, single-arm design with centralized, blinded imaging review for efficacy and prespecified safety oversight aligns with contemporary expectations for phase 2 oncology studies evaluating antitumour activity and safety in an investigational setting where randomized Western second-line data are not yet available [1,2].

Summary rationale for the proposed phase 2 study

- Existing second-line standards deliver modest ORR and limited durability; resistance after trastuzumab is common and compounded by HER2 loss/heterogeneity, mandating reassessment of HER2 to guide therapy [3,4,6].
- T-DXd has shown high ORR with clinically meaningful PFS and OS benefits versus chemotherapy in a randomized Asian population and consistent activity in a phase 1 gastric cohort at 6.4 mg/kg every 3 weeks, warranting confirmation in U.S. patients treated immediately after first-line trastuzumab-containing therapy [1,2].
- Achieving deeper, durable remissions is particularly valuable after trastuzumab failure to preserve performance status and extend survival; the study's primary endpoint (confirmed ORR by independent central review) and sample size are designed to demonstrate activity exceeding a historical ORR benchmark around 27% if the true ORR approximates 45% [1,2,6].
- The protocol's safety management plan prioritizes early detection and management of ILD/pneumonitis and cardiac effects and applies dose-modification algorithms consistent with

prior clinical experience and product guidance, supporting a favorable risk–benefit evaluation in this population [1,5].

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7 SUBJECT SELECTION

7.1 Inclusion Criteria

Inclusion Criteria

- Adult (≥18 years) capable of providing written informed consent prior to any study-specific procedures, with consent obtained under Institutional Review Board (IRB) oversight and in accordance with US regulations governing human subject protection and IND-conducted research [6–8].
- Histologically confirmed unresectable or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma.
- Documented disease progression during or after first-line trastuzumab-containing systemic therapy for unresectable/metastatic disease, with no intervening systemic anticancer therapy thereafter.
- HER2-positive tumour status confirmed centrally on a new tumour biopsy obtained after progression on first-line trastuzumab-containing therapy, defined per ASCO–CAP gastro-oesophageal adenocarcinoma criteria as IHC 3+ or IHC 2+ with ISH amplification [1,2].
- At least one measurable lesion per RECIST v1.1 by CT/MRI as determined by the investigator; baseline imaging adequate for independent central review [3].
- Eastern Cooperative Oncology Group (ECOG) performance status 0–1 [5].
- Adequate organ function at screening, defined as all of the following (protocol-specified thresholds):

- Hematologic: absolute neutrophil count (ANC) ≥1.5 × 10^9/L; platelets ≥100 × 10^9/L; hemoglobin ≥9.0 g/dL (transfusion permitted to meet threshold).

- Hepatic: total bilirubin ≤1.5 × upper limit of normal (ULN) (or ≤3.0 × ULN in subjects with documented Gilbert syndrome); AST and ALT ≤3.0 × ULN (≤5.0 × ULN if liver metastases are present).
- Renal: estimated creatinine clearance ≥50 mL/min (e.g., Cockcroft–Gault).
- Coagulation: INR ≤1.5 × ULN and aPTT ≤1.5 × ULN (subjects on stable therapeutic anticoagulation eligible if within target range).

- Left ventricular ejection fraction (LVEF) ≥50% by echocardiogram (ECHO) or multigated acquisition (MUGA) scan at screening, using the same modality for serial assessments during the study [4].
- Brain metastases, if present, must be previously treated and stable: no radiographic progression for ≥4 weeks before first dose, neurologically stable without new or worsening symptoms, and off corticosteroids or on a stable/decreasing dose equivalent to ≤10 mg prednisone daily for ≥2 weeks prior to first dose.
- Negative serum pregnancy test at screening for participants who are capable of becoming pregnant; agreement to use highly effective contraception during study treatment and for the post-treatment period recommended for trastuzumab deruxtecan (females: through 7 months after last dose; males with partners who can become pregnant: through 4 months after last dose). No breastfeeding during treatment and for 7 months after the last dose [4].
- Willing and able to comply with study requirements, including treatment administration, scheduled assessments (e.g., CT/MRI per RECIST v1.1), safety monitoring (including ILD/pneumonitis vigilance and cardiac surveillance), and follow-up visits [3,4].

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7.2 Exclusion Criteria

Exclusion Criteria

Participants meeting any of the following will be excluded:

- Prior systemic anticancer therapy for unresectable/metastatic disease after the first-line trastuzumab-containing regimen (radiation for palliation permitted if completed and toxicities have resolved to grade ≤1). This preserves interpretability of antitumour activity in the targeted post–first-line setting [2].
- Prior exposure to trastuzumab deruxtecan or other HER2-directed antibody–drug conjugates [2].
- History of non-infectious interstitial lung disease (ILD)/pneumonitis that required systemic corticosteroids, or current, suspected, or radiographic evidence of ILD/pneumonitis at screening. Given the identified, potentially fatal risk of ILD with T-DXd, any prior steroid-treated ILD or current ILD warrants exclusion [1].
- Clinically significant pulmonary compromise that could obscure early detection or increase risk of ILD/pneumonitis, including any of the following: requirement for chronic supplemental oxygen; uncontrolled severe chronic obstructive pulmonary disease or restrictive lung disease with resting hypoxemia; or active, uncontrolled pleural or pericardial effusions causing dyspnea despite optimized management. This criterion reflects product-specific ILD risk mitigation [1].
- Untreated or symptomatic central nervous system (CNS) metastases; treated CNS metastases are eligible only if radiographically stable for ≥4 weeks, neurologically stable, and off corticosteroids or on a stable/decreasing dose equivalent to ≤10 mg prednisone daily for ≥2 weeks before first dose (as specified in Inclusion Criteria). This avoids confounding of safety and response assessments in a single-arm study while permitting stable, treated disease [2].
- Clinically significant cardiac disease, including any of the following: symptomatic congestive heart failure; history of myocardial infarction, unstable angina, clinically significant arrhythmia (requiring antiarrhythmic therapy) or cerebrovascular accident within 6 months; baseline LVEF <50% by ECHO/MUGA; or uncontrolled hypertension despite optimal therapy. Exclusion is warranted due to observed decreases in LVEF and rare cardiac failure with T-DXd and the need for reliable cardiac surveillance [1].
- Active, uncontrolled infection requiring systemic therapy, including uncontrolled bacterial, viral, or fungal infections. Patients with controlled chronic viral infections on stable therapy may be eligible if meeting all other criteria; the focus is on excluding uncontrolled infection risk in the setting of myelosuppression and ILD vigilance [1].
- Ongoing systemic immunosuppression exceeding prednisone 10 mg daily (or equivalent), excluding short courses for contrast premedication or treatment of non-pulmonary hypersensitivity, due to potential to mask ILD symptoms/signs and increase infection risk with myelosuppression [1].
- Known severe hypersensitivity to monoclonal antibodies or to any excipient of trastuzumab deruxtecan; history of serious infusion-related reactions to HER2-targeted antibodies not manageable with standard premedication and rate modification [1].
- Inadequate organ function at screening, defined as: ANC <1.5 × 10^9/L; platelets <100 × 10^9/L; hemoglobin <9.0 g/dL (transfusion permitted to meet threshold); total bilirubin >1.5 × ULN (or >3.0 × ULN with documented Gilbert syndrome); AST or ALT >3.0 × ULN (or >5.0 × ULN if liver metastases present); estimated creatinine clearance <50 mL/min; INR >1.5 × ULN or aPTT >1.5 × ULN (subjects on stable therapeutic anticoagulation must be within target range). These thresholds align with safety experience for T-DXd and the myelosuppressive/topoisomerase I payload profile [1].
- Major surgery within 4 weeks prior to first dose or not fully recovered from prior procedure–related complications that could confound safety assessments.
- Pregnant or breastfeeding, or intending to conceive during study treatment and for 7 months after the last dose (female participants) or to father a child during treatment and for 4 months after the last dose (male participants with partners who can become pregnant). Embryo–fetal toxicity and post-treatment contraception durations follow product guidance; breastfeeding is contraindicated during treatment and for 7 months after the last dose [1].
- Any other serious medical condition, psychiatric illness, social situation, or laboratory abnormality that, in the investigator's judgment, would preclude safe participation, compliance with study procedures, or interpretation of results, consistent with the ethical obligation to minimize risk in interventional research under a US IND [1].

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8 TREATMENT PLAN

Overview of study intervention

- Investigational product: Trastuzumab deruxtecan (T-DXd) administered as monotherapy.
- Dose and schedule: 6.4 mg/kg intravenous infusion once every 3 weeks (Q3W; 21-day cycles). Continue until radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or other protocol-defined discontinuation reason [1].
- Infusion administration: First infusion over at least 90 minutes; subsequent infusions over at least 30 minutes if the prior infusion was well tolerated. Do not administer as an intravenous push or bolus. Use 5% dextrose (D5W) for dilution; do not use sodium chloride-containing solutions per product preparation instructions [1].
- Antiemetic prophylaxis: Provide prophylactic antiemetics prior to each infusion in accordance with the product labeling and institutional standards [1].

Preparation and administration

- Reconstitution and dilution will follow the product labeling: reconstitute the lyophilized powder with sterile water for injection; dilute the reconstituted solution in D5W for intravenous infusion using a dedicated line or a compatible multi-lumen device. Do not mix with or co-infuse through the same line as other drugs. Use an in-line or add-on 0.20–0.22 µm sterile, non-pyrogenic, low-protein-binding filter as per local practice [1].
- Infusion monitoring: Observe patients during and after infusion for infusion-related reactions; manage by slowing or interrupting the infusion and providing supportive measures as clinically indicated [1].

Dose modifications, delays, and discontinuation

- Permitted dose levels: 6.4 mg/kg (starting dose) → 5.4 mg/kg (first reduction) → 4.4 mg/kg (second reduction). No re-escalation after dose reduction. A maximum of two dose reductions is permitted. Doses may be delayed up to 28 days for toxicity; delays beyond 28 days require permanent discontinuation [1].
- General non-hematologic toxicity (excluding alopecia and nausea/vomiting controlled with optimal therapy): For grade ≥3 events, interrupt until toxicity improves to grade ≤1, then resume at the next lower dose; permanently discontinue for life-threatening (grade 4) toxicity [1].
- ILD/pneumonitis (adverse event of special interest):

- Interrupt immediately for any suspicion; perform prompt evaluation including chest imaging and pulse oximetry.
- Grade 1 (asymptomatic): Initiate appropriate management; resume only after resolution to Grade 0: at the same dose if resolved within 28 days of onset, or reduced by one dose level if resolution took longer than 28 days.
- Grade ≥2: Permanently discontinue; initiate systemic corticosteroids and supportive care. Follow all cases to resolution. All suspected events will undergo independent adjudication per protocol [1].

- Hematologic toxicity:

- Neutropenia: Grade 3—interrupt until grade ≤2, then resume at the same dose; Grade 4—interrupt until grade ≤2, then reduce by one dose level; Febrile neutropenia—interrupt until resolved, then reduce by one dose level [1].
- Thrombocytopenia: Grade 3—interrupt until grade ≤1, then resume at the same dose; Grade 4—interrupt until grade ≤1, then reduce by one dose level [1].

- Left ventricular ejection fraction (LVEF) decrease (adverse event of special interest):

- LVEF >45% with 10–20% absolute drop from baseline: continue and monitor.
- LVEF 40–45% with <10% absolute drop: continue; repeat LVEF within 3 weeks.
- LVEF 40–45% with 10–20% absolute drop: interrupt; repeat LVEF within 3 weeks. If recovery to within 10% of baseline is confirmed, resume at the same dose; otherwise permanently discontinue.
- LVEF <40% or >20% absolute drop from baseline: interrupt, repeat within 3 weeks, and permanently discontinue if confirmed. Permanently discontinue for symptomatic congestive heart failure [1].

Criteria for treatment continuation, interruption, and discontinuation

- Continue treatment on Day 1 of each 21-day cycle if the following are met:

- ECOG PS remains 0–1; no evidence of progressive disease or other discontinuation criteria.
- Laboratory parameters prior to dosing meet protocol thresholds (below); abnormalities not meeting thresholds require delay/management until recovery [1].

- Treatment interruption and resumption:

- Interrupt for AEs per the above algorithms and resume at the same or next lower dose when recovery criteria are met.
- If doses are delayed beyond 28 days from the planned date, permanently discontinue study treatment [1].

- Permanent discontinuation:

- Grade ≥2 ILD/pneumonitis; confirmed protocol-defined LVEF criteria as above; any toxicity requiring delay >28 days; pregnancy; or investigator judgment of unacceptable risk despite optimal management [1].

Concomitant medications and supportive care

- Growth factors, transfusions, antiemetics, antidiarrheals, analgesics, antibiotics/antivirals/antifungals, and other supportive measures are permitted per institutional standards and should follow applicable guidelines and product labeling [1].
- Drug–drug interactions: Based on available clinical data, no dose adjustment is required with strong CYP3A and/or P-gp inhibitors; the DXd payload is primarily metabolized by CYP3A4. Clinically meaningful effects of strong CYP3A inducers have not been demonstrated. Monitor for expected toxicities if coadministered with strong CYP3A modulators. When T-DXd is given with QT-prolonging agents, monitor ECG and electrolytes and correct abnormalities [1].
- Anticoagulation and antiplatelet therapies are permitted with careful monitoring, including platelet counts and bleeding risk, consistent with institutional standards [1].
- Vaccinations: Inactivated vaccines may be administered per institutional standards. The use and timing of live-attenuated vaccines should follow institutional policies for immunocompromised patients.

Eligibility-aligned baseline and on-treatment requirements

- Baseline (screening) requirements before first dose:

- ECOG PS 0–1; LVEF ≥50% by echocardiogram or MUGA using the same modality throughout; adequate organ function defined as ANC ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, hemoglobin ≥9.0 g/dL (transfusion allowed), total bilirubin ≤1.5 × ULN (≤3.0 × ULN with documented Gilbert syndrome), AST and ALT ≤3.0 × ULN (≤5.0 × ULN with liver metastases), estimated creatinine clearance ≥50 mL/min, INR and aPTT ≤1.5 × ULN (therapeutic anticoagulation permitted if within target range). Triplicate 12-lead ECG at screening. Negative pregnancy test for participants who can become pregnant [1].

- On-treatment safety assessments tied to dosing:

- Prior to each infusion: interval history and targeted physical exam including pulmonary symptoms/signs; vital signs; CBC with differential; comprehensive metabolic panel including liver tests; pregnancy test as applicable; review of concomitant medications and AEs; assessment for ILD/pneumonitis.
- Cardiac monitoring: LVEF at Cycle 5 Day 1 and every 4 cycles thereafter with consistent modality; ECG during treatment as clinically indicated [1].
- ILD monitoring: Maintain low threshold for chest CT for new or worsening cough, dyspnea, fever, or hypoxia; interrupt dosing immediately upon suspicion and follow the ILD algorithm [1].

- Tumor imaging for response assessment:

- CT/MRI of disease sites every 6 weeks (±7 days) in the first year, then every 12 weeks thereafter, until progression or start of new anticancer therapy. Responses require confirmation at least 4 weeks

after initial documentation per RECIST v1.1 and will be determined by independent central review [2,3].

Adherence, accountability, and administration logistics

- Adherence is ensured through on-site administration of all infusions. Study drug accountability will be maintained by site pharmacy according to institutional SOPs and the investigational product manual. Missed visits or partial infusions will be documented, with rescheduling per the 28-day delay cap [1].
- Venous access: Peripheral or central venous access may be used per institutional standards. Post-infusion observation is per institutional practice for monoclonal antibody–based infusions [1].

Reproductive precautions and lactation

- Contraception: Participants who can become pregnant must use highly effective contraception during treatment and for 7 months after the last dose. Male participants with partners who can become pregnant must use effective contraception during treatment and for 4 months after the last dose. Breastfeeding is not permitted during treatment and for 7 months after the last dose [1].

Post-treatment follow-up

- Safety follow-up visit at 40 days (+7) after the last dose to capture AEs, SAEs, and adverse events of special interest (ILD/pneumonitis and LVEF decrease), and to ensure appropriate ongoing management [1].
- Long-term follow-up for survival status every 12 weeks (±14 days) by clinic visit or remote contact until study end or withdrawal of consent.
- Ongoing safety review will be performed by the sponsor throughout the study; expedited safety reporting will follow US IND requirements [1].

Rationale linkage to dosing and monitoring

- The selected 6.4 mg/kg Q3W regimen, infusion parameters, and dose-modification algorithms are based on prior gastric cancer clinical experience and the product labeling, which collectively inform the management of myelosuppression, gastrointestinal toxicities, ILD/pneumonitis, and LVEF decreases in this population [1,2].

References

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8.1 Participant Timeline and Schedule of Events

Overview of participant timeline

- Pre-screening/screening: up to 28 days before Cycle 1 Day 1 to obtain informed consent, assign screening number, confirm eligibility, collect baseline assessments including central

HER2 confirmation on a new post–first-line biopsy, and establish safety baselines (laboratory tests, ECG, LVEF) [1–5,8].

- Baseline and first dose: Cycle 1 Day 1 (C1D1) serves as the baseline/first-dose visit following final eligibility confirmation. T-DXd 6.4 mg/kg is administered IV every 3 weeks (21-day cycles); first infusion over at least 90 minutes, subsequent infusions over at least 30 minutes if well tolerated [7].
- On-treatment visits: Day 1 of each 21-day cycle for safety evaluations, dosing, and compliance/accountability. LVEF at Cycle 5 Day 1 and every 4 cycles thereafter using the same modality as baseline. Imaging for tumor assessments every 6 weeks (±7 days) during Year 1, then every 12 weeks (±7 days) thereafter, until progression or start of new anticancer therapy; responses require confirmation ≥4 weeks after first documentation per RECIST v1.1 and are determined by independent central review [7,9].
- End of treatment (EOT): at permanent discontinuation for any reason, perform EOT assessments.
- Post-treatment safety follow-up: 40 days (+7) after last dose for adverse events (AEs), serious AEs (SAEs), and adverse events of special interest (AESIs: ILD/pneumonitis and LVEF decrease), with expedited reporting under US IND regulations [5,7].
- Long-term follow-up: survival status every 12 weeks (±14 days) by clinic visit or remote contact until study end or withdrawal of consent. Final end-of-study assessments occur at the last survival follow-up after database lock for the primary and key secondary analyses.

Enrolment and screening procedures

- Informed consent under IRB oversight prior to any study-specific procedures; assignment of a screening number and eligibility assessment per protocol [2–4].
- Collection of demographics, medical and cancer history, prior and concomitant medications, full physical examination, vital signs, ECOG performance status, and baseline laboratory safety tests (hematology, serum chemistry, coagulation), pregnancy testing if applicable, and 12-lead ECG (triplicate at screening) [1–4,7].
- Disease-specific baseline assessments including imaging per RECIST v1.1 and central HER2 confirmation on a new biopsy obtained after progression on first-line trastuzumab-containing therapy (ASCO–CAP criteria: IHC 3+ or IHC 2+/ISH+) [8,9].
- Baseline LVEF by ECHO or MUGA with the same modality planned for all subsequent assessments [7].

All screening and baseline requirements must be satisfied prior to dosing on Cycle 1 Day 1.

Randomization and baseline procedures

- The study is single-arm with no randomization. Final eligibility confirmation and assignment to treatment occur at Cycle 1 Day 1 via site enrollment procedures under the US IND. Baseline disease assessments and safety baselines must be in place before first dosing; investigational product is dispensed/administered on Cycle 1 Day 1 [1,5,7].

Intervention schedule

- Investigational treatment: T-DXd 6.4 mg/kg IV every 3 weeks (21-day cycles) until radiographic/clinical progression, unacceptable toxicity, withdrawal of consent, or other protocol-defined discontinuation reason. First infusion ≥90 minutes; subsequent infusions ≥30 minutes if previously tolerated. Up to two dose reductions (5.4 mg/kg, then 4.4 mg/kg); no re-escalation. Doses may be delayed up to 28 days for toxicity; longer delays require permanent discontinuation. Administration and modifications follow the current US product instructions for use in this setting [7].
- There is no comparator, maintenance, retreatment, or extension phase.

Efficacy and outcome assessment schedule

- Primary endpoint (confirmed ORR by independent central review): Tumor imaging at baseline, every 6 weeks (±7 days) during Year 1, then every 12 weeks (±7 days) thereafter; confirmatory scans at least 4 weeks after initial CR/PR documentation per RECIST v1.1. Imaging continues until progression or start of new anticancer therapy [9].
- Secondary endpoints: PFS (key secondary) by independent central review on the same imaging schedule; OS via survival follow-up every 12 weeks (±14 days) after treatment discontinuation; duration of response derived from centrally reviewed assessments [9].
- No exploratory endpoints, patient-reported outcomes, or additional biopsies are planned.

Safety assessment schedule

- Continuous AE collection from first dose through the Safety Follow-up visit (40 days [+7]) after the last dose; SAEs are collected from informed consent through 40 days (+7) after the last dose, with expedited reporting under 21 CFR 312.32. Concomitant medications are reviewed each visit. AEs are graded per NCI CTCAE v5.0 [5,7,10].
- Targeted safety evaluations before each infusion: interval history and targeted physical examination with pulmonary focus; vital signs; laboratory safety tests (including hematology and chemistry); pregnancy testing when applicable; review for suspected ILD/pneumonitis and LVEF-related symptoms/signs. Triplicate ECG at screening and during treatment as clinically indicated [7].
- LVEF monitoring: at screening, Cycle 5 Day 1, and every 4 cycles thereafter using the same modality; manage decreases per protocol [7].
- ILD/pneumonitis monitoring: immediate dosing interruption upon suspicion, diagnostic evaluation, adjudication by an independent ILD committee, and management per protocol (restart after full resolution of Grade 1; permanent discontinuation for Grade ≥2) [7].

Pharmacokinetic, pharmacodynamic, biomarker, and exploratory assessments

- No PK, PD, immunogenicity, pharmacogenetic, exploratory biomarker, or patient-reported outcome assessments are planned. The only biospecimen is the mandatory screening biopsy for central HER2 confirmation [8].

End-of-treatment, follow-up, and end-of-study visits

- End of treatment: perform EOT assessments at permanent discontinuation (or early discontinuation) for any reason, including documentation of reason for discontinuation, final safety and disease assessments where feasible, and transition-of-care planning [1].
- Safety follow-up: 40 days (+7) after last dose to collect ongoing/resolved AEs, SAEs, AESIs (ILD/pneumonitis and LVEF decrease), and concomitant medications; manage ongoing events until resolution or stabilization, with continued follow-up of all ILD events to resolution [5,7].
- Long-term follow-up: survival status every 12 weeks (±14 days) by clinic or remote contact until study end or withdrawal of consent; record subsequent anticancer therapies and survival status [1].
- End of study: occurs after completion of long-term follow-up and database lock for the primary and key secondary analyses.

Visit windows and missed or unscheduled visits

- Nominal visit windows: Screening Day −28 to Day −1; Cycle Day 1 visits every 21 days (±3 days) while on treatment; imaging every 6 weeks (±7 days) during Year 1, then every 12 weeks (±7 days) thereafter; Safety Follow-up 40 days (+7) after last dose; survival follow-up every 12 weeks (±14 days). Windows that differ locally must be finalized before protocol sign-off [1,7,9].
- Missed or delayed visits: If a scheduled visit is missed or delayed, perform required assessments at the next earliest opportunity. Out-of-window assessments should be clearly documented; their impact on participant safety, endpoint ascertainment, and protocol compliance will be evaluated, with corrective/preventive actions as needed in accordance with Good Clinical Practice [1].
- Unscheduled assessments: Perform as clinically indicated; these do not replace scheduled assessments unless explicitly specified. For suspected ILD/pneumonitis, perform prompt chest imaging and hold dosing pending evaluation [7].

Schedule of events

Study period/Procedure	Screening (Day −28 to −1)	Cycle 1 Day 1 (first dose, ≥90-min infusion)	Cycle 2 Day 1 (q21d)	Cycle 3 Day 1 (q21d)	Cycle 4 Day 1 (q21d)	Cycle 5 Day 1 (q21d)	Cycles 6+ Day 1 (q21d)	Imaging q6w Year 1 (±7d)	Imaging q12w after Year 1 (±7d)	End of Treatment	Safety Follow-up Day 40 (±7d)	Survival Follow-up q12w (±14d)	Visit window
Informed consent/assign screening number	✓✓												Once before any procedures
Eligibility review (incl. inclusion/exclusion)	✓	confirm confirm											Screen −28 to −1; confirm on C1D1
Demographics and medical history	✓✓												Screening only
Prior and concomitant medications	✓	✓	✓	✓	✓	✓	✓✓			✓	✓✓		Each visit while on study
Physical examination	✓	✓	✓	✓	✓	✓	✓✓			✓	✓✓		Each cycle; targeted at follow-up

Vital signs	✓	✓	✓	✓	✓	✓	✓✓			✓	✓✓		Each visit
ECOG performance status	✓	✓	✓	✓	✓	✓	✓✓			✓✓			Each cycle
Laboratory safety tests (hematology, chemistry, coagulation)	✓	✓	✓	✓	✓	✓	✓✓			✓	✓✓		Each cycle; as clinically indicated at EOT/SF
Pregnancy test (if applicable)	✓	✓	✓	✓	✓	✓	✓✓						Per local standard prior to dosing
12-lead ECG	✓ (triplicate)✓ (triplicate)		as indicated	as indicated	as indicated	as indicated	as indicatedas indicated			as indicated	as indicatedas indicated		Screening; on-treatment as clinically indicated
LVEF by ECHO/MUGA	✓✓					✓	every 4 cycle sevey 4 cycles			✓ (if due or indicated)	✓ (if due or indicated)✓ (if due or indicated)		Same modality throughout
Central HER2 confirmation on new biopsy	✓✓												Screening only; required for eligibility
Baseline tumor imaging (CT/MRI)	✓✓												Within screening window
Investigational product administration (T-DXd)Investigational product administration (T-DXd)		✓	✓	✓	✓	✓	✓✓						Day 1 of each 21-day cycle
Compliance/accountability Compliance/accountability		✓	✓	✓	✓	✓	✓✓						Each dosing visit

Adverse event assessmentAdverse event assessment		✓	✓	✓	✓	✓	✓✓			✓	✓✓		From first dose through Safety Follow-up
Serious adverse event reporting	✓	✓	✓	✓	✓	✓	✓✓			✓	✓✓		From consent through Safety Follow-up
Primary outcome assessment (ORR by ICR)Primary outcome assessment (ORR by ICR)								✓	✓✓				Imaging q6w Year 1, then q12w thereafter; confirmation ≥4 weeks later
Secondary outcomes (PFS by ICR; DOR; OS)Secondary outcomes (PFS by ICR; DOR; OS)								✓	✓✓			✓	Per imaging schedule; OS via survival follow-up
Exploratory outcomesExploratory outcomes													None planned
Imaging (CT/MRI) for response	✓ (baseline)✓ (baseline)							✓	✓	as indicatedas indicated			Per schedule; continue until progression or new therapy
Dosing modifications/interruptions assessmentDosing modifications/interruptions assessment		✓	✓	✓	✓	✓	✓✓						At each dosing visit per protocol
End-of-treatment assessmentsEnd-of-treatment assessments										✓✓			At discontinuation for any reason
Safety Follow-up assessmentsSafety Follow-up assessments											✓✓		40 days (+7)

													after last dose
Survival/long-term follow-upSurvival/long-term follow-up												✓	Every 12 weeks (±14 days)

Footnotes:

- Investigational product administration: T-DXd 6.4 mg/kg IV Q3W; first infusion ≥90 minutes, subsequent ≥30 minutes if tolerated. Up to two dose reductions (5.4 mg/kg, then 4.4 mg/kg); no re-escalation. Doses may be delayed up to 28 days; delays >28 days require permanent discontinuation [7].
- Imaging schedule: CT/MRI every 6 weeks (±7 days) during the first year, then every 12 weeks (±7 days) thereafter, until progression or initiation of new anticancer therapy; responses require confirmation ≥4 weeks after first documentation and are determined by independent central review per RECIST v1.1 [9].
- Safety focus: Vigilance for ILD/pneumonitis with immediate dose interruption upon suspicion and adjudication by an independent ILD committee; Grade 1 may restart only after full resolution; Grade ≥2 requires permanent discontinuation and systemic corticosteroids. LVEF monitoring at screening, Cycle 5 Day 1, and every 4 cycles thereafter using the same modality, with management per protocol [7].
- AE/SAE periods: AEs collected from first dose through Safety Follow-up; SAEs from consent through Safety Follow-up (40 days [+7]), with expedited reporting under 21 CFR 312.32 [5].
- Procedures may be repeated if results are abnormal or clinically indicated; unscheduled assessments do not replace scheduled assessments unless specified.
- There is no DMC; the sponsor conducts ongoing safety review under the US IND [5].
- Visit windows beyond those specified (e.g., ±3 days around Cycle Day 1) should be finalized before protocol sign-off to ensure consistent implementation.

Summary

This participant timeline and structured schedule of events delineate enrolment, intervention, assessment, and follow-up procedures with defined time points and windows to support consistent implementation across US sites, protect participant safety through proactive safety monitoring for AESIs, ensure rigorous and timely endpoint ascertainment via centrally reviewed RECIST v1.1 imaging, maintain data quality suitable for regulatory decision-making under a US IND, and align with Good Clinical Practice and contemporary protocol design expectations for transparent scheduling and follow-up [1–5,7,9,10].

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8.2 Data Collection Instruments and Data Sources

Overview of Data Collection Approach

Trial data will be collected using protocol-defined instruments and source documents to ensure accurate capture of eligibility, baseline characteristics, intervention exposure and adherence, efficacy outcomes, safety outcomes (including adverse events of special interest: ILD/pneumonitis and LVEF decrease), and follow-up status. Instruments include electronic case report forms (eCRFs), source medical records, central HER2 pathology reports from the required post–first-line biopsy, laboratory reports, imaging data and central review outputs, pharmacy accountability logs, dosing and infusion records, adverse event and serious adverse event (SAE) forms, electrocardiogram (ECG) and echocardiogram/multigated acquisition (MUGA) reports, and protocol-specific worksheets and logs. Data collection will follow Good Clinical Practice (GCP) and US IND requirements, with systems supporting audit trails, role-based access, and data integrity aligned with ICH E6(R3) and 21 CFR Part 11 [1,2,3]. Tumor response outcomes will be collected per RECIST v1.1 and assessed by an independent central review (ICR) per an imaging charter and FDA imaging process standards [4,5]. Adverse events will be graded using NCI CTCAE v5.0 and reported in compliance with 21 CFR Part 312 [3,6]. HER2 status will be confirmed centrally on a new biopsy using ASCO–CAP criteria to mitigate post-trastuzumab HER2 loss risk [7].

Electronic Case Report Forms and Data Capture Systems

eCRFs within a validated electronic data capture (EDC) system will capture demographics, screening and eligibility, medical and cancer history, baseline disease characteristics, ECOG status, central HER2 results, treatment administration and modifications, protocol deviations, concomitant medications, adverse events/SAEs/AESIs, vital signs, physical examinations, ECGs, LVEF assessments, clinical laboratory values, imaging assessment time points and ICR results, end-of-treatment, safety follow-up, and survival follow-up. eCRFs will be protocol- and schedule-aligned and support endpoint definitions and the statistical analysis plan (SAP), with data standards conforming to FDA technical conformance expectations for study data [8]. The EDC will implement role-based access, unique user credentials, audit trails, edit and range checks, missing/consistency checks, query management, training documentation, and controlled procedures for data correction, interim locks, and database lock, consistent with 21 CFR Part 11 and ICH E6(R3) [1,2].

Source Documents and Source Data

Source documents include signed informed consent forms, screening logs, eligibility checklists, medical records and clinic notes, hospital discharge summaries, pathology and central HER2 reports from the mandated new biopsy, local and (if applicable) central laboratory reports, imaging reports and DICOM image sets, ECG and LVEF (ECHO/MUGA) reports, pharmacy dispensing and accountability records, infusion records and dosing worksheets, adverse event documentation, concomitant medication records, procedure reports, and follow-up contact logs. Data will be transcribed from source to eCRFs unless specified as direct data entry (eSource) into the EDC (e.g.,

visit dates, vital signs, and dosing times entered contemporaneously); any eSource use will be documented in the site's source data location list and controlled per FDA eSource guidance [1,9]. Source data must be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available for monitoring, audit, and regulatory inspection, in line with ICH E6(R3) [1].

Outcome-Specific Data Collection Instruments

- Primary efficacy (confirmed ORR): CT/MRI image acquisitions per imaging manual; site uploads de-identified DICOMs to the central imaging vendor. ICR radiologists apply RECIST v1.1 to derive lesion measurements, target/non-target status, and responses; confirmation scans occur ≥4 weeks after first CR/PR. ICR outputs populate the eCRF per the imaging charter and map to the Full Analysis Set for the primary analysis using exact Clopper–Pearson CIs [4,5].
- Secondary efficacy: PFS and duration of response by ICR using the same RECIST v1.1 datasets and schedules; overall survival captured from source records and follow-up contacts [4,5].
- Safety: AE, SAE, and AESI (ILD/pneumonitis; LVEF decrease) collection via dedicated eCRF forms, graded by CTCAE v5.0, coded to MedDRA, and reported per 21 CFR 312.32. LVEF by ECHO/MUGA at protocol-defined times; ECGs as specified; clinical labs each cycle [3,6,10].
- No exploratory, PK/PD, immunogenicity, pharmacogenetic, or PRO outcomes are planned; the only biospecimen is the screening tumor biopsy for central HER2 testing per ASCO–CAP [7].

Clinical Assessment Instruments

- Clinician-rated performance status: ECOG Performance Status recorded using the original instrument [11].
- Physical examination and symptom-directed pulmonary assessments: standardized site worksheets aligned with GCP to ensure consistent capture across visits [1].
- Response assessment criteria: RECIST v1.1 applied by ICR per charter-defined rules, including target lesion selection, measurability thresholds, and confirmation requirements [4].
- Toxicity grading: NCI CTCAE v5.0 criteria for AE severity; causality, seriousness, and expectedness captured per IND reporting requirements [3,6].
- Pulmonary and cardiac safety focus: targeted pulmonary exam documentation for ILD signals; LVEF assessments by the same modality across time points using site or central cardiology reporting templates [10].

Laboratory and Diagnostic Testing Instruments

- Safety laboratories: hematology, chemistry, and coagulation performed at CLIA-certified local laboratories using validated methods and instrument calibrations; local reference ranges recorded for interpretation and analysis [12]. Pregnancy testing per local laboratory standards.
- Disease-specific diagnostics: central HER2 testing on a new biopsy after first-line progression using ASCO–CAP–concordant IHC and ISH methods with defined positivity thresholds (IHC 3+ or IHC 2+/ISH+) and centralized reporting templates [7].
- Cardiac function: LVEF by ECHO or MUGA using the same modality for serial assessments; reports include image quality, LVEF%, method, and interpreting clinician [10].
- Laboratory data handling: sample collection, processing, storage, and shipment (if applicable) follow the study laboratory manual; chain-of-custody and temperature logs retained. Where central testing is used, assay validation, quality control, and result transfer specifications are documented, consistent with NCI biospecimen best practices [13].
- Eligibility, dose modification, and ongoing safety monitoring will use these laboratory and diagnostic outputs per protocol and GCP [1].

Imaging and Central Review Instruments

- Imaging modalities: contrast-enhanced CT or MRI per site capability and imaging manual acquisition parameters (slice thickness, contrast protocol, field of view).

- Image transfer and QC: de-identified DICOM uploads to a secure core lab portal with automated and manual quality checks; reconciliation of time points with the schedule of events.
- Central review: blinded independent central review (radiologists blinded to clinical data and chronological order per charter, as appropriate) applies RECIST v1.1; adjudication procedures resolve discordance. Imaging endpoints (ORR, PFS, DOR) derive exclusively from ICR per FDA imaging endpoint process standards [4,5].
- Imaging data are used for eligibility (measurable disease), disease assessment, and primary/secondary endpoint determination [4,5].

Patient-Reported Outcome Instruments

- No PRO instruments, diaries, or wearable devices are planned for this study.

Pharmacokinetic, Pharmacodynamic, and Biomarker Collection Tools

- No PK, PD, immunogenicity, pharmacogenetic, or exploratory biomarker sampling is planned. The only biospecimen is the mandatory screening tumor biopsy for central HER2 confirmation; specimen handling, labeling, and shipment will follow the pathology and laboratory manuals with chain-of-custody documentation [7,13].

Safety Data Collection Instruments

- AE/SAE/AESI forms within the EDC capture event terms, onset/stop dates, severity (CTCAE v5.0), seriousness, outcome, causality, action on investigational product, and treatment provided; ILD/pneumonitis and LVEF decrease have dedicated forms and algorithms. Pregnancy reporting forms will be available if applicable [3,6,10].
- Vital sign and physical examination forms standardize per-visit safety capture.
- ECG reports (12-lead; triplicate at screening) and cardiac imaging (ECHO/MUGA) reports are archived as source; key values are transcribed to eCRFs.
- Laboratory safety reports (hematology, chemistry, coagulation, pregnancy tests) are transcribed with units, ranges, and flags.
- Concomitant medication and supportive care logs capture start/stop dates, indications, and dosing.
- Safety reporting complies with 21 CFR 312.32, with sponsor ongoing safety review and centralized reconciliation between clinical database and safety reporting system [3].

Reliability, Validity, and Standardization of Instruments

- Tumor response criteria (RECIST v1.1) and CTCAE v5.0 are internationally standardized and widely validated, supporting reproducible efficacy and safety measurement [4,6].
- Central HER2 testing follows ASCO–CAP guidelines using validated assays and specified positivity definitions to enhance diagnostic accuracy and inter-laboratory consistency [7].
- Imaging processes (acquisition, transfer, ICR, adjudication) are standardized per an imaging charter and FDA imaging process guidance to reduce variability and bias [5].
- Safety and laboratory measurements are performed in CLIA-certified laboratories using validated methods; eDC systems comply with Part 11 and GCP to ensure data integrity and traceability [1,2,12].
- Where study-specific worksheets or logs are used, standard operating procedures, manuals, and training will ensure consistent application across sites [1].

Training on Data Collection Instruments

- Investigators, subinvestigators, study coordinators, pharmacists, outcome assessors, imaging and cardiology personnel, and laboratory staff will be trained and authorized before performing study-specific data collection. Training covers eCRF completion, source documentation standards, RECIST v1.1 application and imaging manual procedures, AE/SAE reporting per CTCAE v5.0 and 21 CFR 312.32, ILD adjudication workflows, LVEF assessment and reporting, HER2 sample handling and reporting, data query resolution, and

protocol-specific safety algorithms. Training completion will be documented and retained [1,3,5,6].

Data Quality Control

- Automated EDC edit checks (range, logic, cross-form consistency), programmatic listings, and centralized statistical monitoring will identify outliers, protocol deviations, missing or inconsistent data, and endpoint completeness issues; sites will respond to electronic queries with documented corrections retained in the audit trail [1,2].
- Source data review and verification will be performed risk-proportionately; imaging, laboratory, and safety datasets will be reconciled, including AE/SAE reconciliation with safety reporting, and imaging time point reconciliation with ICR outputs [1].
- Audit trail reviews and periodic data reviews precede database lock; corrective and preventive actions (CAPA) will be initiated and tracked for recurrent data quality issues per GCP and FDA monitoring guidance [1,14].

Handling of Missing, Incomplete, or Inconsistent Data

- Missing, delayed, or inconsistent data will be detected via edit checks and central review; sites will be queried, and, when clinically appropriate, repeat assessments may be performed within allowed windows. Reasons for missing data and out-of-window assessments will be documented in eCRFs and source [1].
- Conflicting sources (e.g., dates, measurements) will be reconciled using predefined data hierarchy rules in the data management plan; unresolved discrepancies will be flagged for analysis. The SAP will define the analytical handling of missing data, intercurrent events, censoring, and sensitivity analyses in accordance with ICH E9/E9(R1) principles [15,16].

Access to Data Collection Instruments

- Blank and annotated CRFs, the imaging charter, pathology and laboratory manuals, ECG/ECHO/MUGA acquisition and reporting guidance, the ILD adjudication charter, and the data dictionary will be maintained in the trial master file (TMF) and investigator site files and provided to sites before activation. Post-study, instrument metadata and data dictionaries intended for sharing will align with the protocol's open science and data sharing commitments and applicable FDA data standards [8].

Documentation and Version Control

- All data collection instruments (eCRFs, manuals, charters, worksheets, data dictionaries) will be version-controlled with documented creation dates, approvals, effective dates, and distribution records. Revisions will follow controlled change procedures, with training and implementation memos to sites and archival of superseded versions in the TMF. Changes that impact endpoint definitions, assessment timing, or participant burden will trigger protocol and SAP amendments, IRB submissions, and ClinicalTrials.gov updates, as applicable, before implementation [1,3,8].

Summary

The integrated suite of standardized instruments—Part 11–compliant EDC/eCRFs, GCP-aligned source documentation, CLIA-backed laboratory methods, charter-driven imaging with ICR under RECIST v1.1, ASCO–CAP–aligned central HER2 testing, and CTCAE-based safety capture—provides reliable, valid, and traceable data collection to support interpretable antitumor efficacy, vigilant safety monitoring, and regulatory-grade evidence in this US IND Phase II study [1,2,3,4,5,6,7,12].

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8.3 Pre-treatment Criteria

Overview

The following pre-treatment criteria must be met prior to initiation of investigational trastuzumab deruxtecan (T-DXd) on Cycle 1 Day 1 (C1D1) and prior to each subsequent 21-day cycle to ensure participant safety, confirm ongoing eligibility, and support appropriate dose administration and modification under a US IND and Good Clinical Practice [1–3]. Laboratory thresholds and clinical conditions reflect established standards for Phase II oncology studies, the product's safety profile (including management of interstitial lung disease [ILD]/pneumonitis and left ventricular ejection fraction [LVEF] decrease), and CTCAE-based toxicity recovery expectations [1,4].

Pre-dose requirements at Cycle 1 Day 1 (initial treatment)

All of the following must be confirmed within the screening window and verified on or immediately prior to C1D1:

- Informed consent obtained with IRB approval and participant eligibility confirmed under US IND requirements and ICH E6(R3) [1–3].
- Disease- and study-specific eligibility reconfirmed (HER2-positive status on a new post–first-line biopsy per protocol; measurable disease; ECOG PS 0–1) with baseline imaging completed per RECIST v1.1 schedule specified elsewhere in the protocol [5].
- Hematologic function: absolute neutrophil count (ANC) ≥1.5 × 10^9/L; platelets ≥100 × 10^9/L; hemoglobin ≥9.0 g/dL (transfusion permitted to meet threshold) [1].
- Hepatic function: total bilirubin ≤1.5 × upper limit of normal (ULN) (≤3.0 × ULN with documented Gilbert syndrome); AST and ALT ≤3.0 × ULN (≤5.0 × ULN if liver metastases present) [1].
- Renal function: estimated creatinine clearance ≥50 mL/min (e.g., Cockcroft–Gault) [1].
- Coagulation: INR ≤1.5 × ULN and aPTT ≤1.5 × ULN; participants on stable therapeutic anticoagulation must be within target range [1].
- Cardiac function: LVEF ≥50% by echocardiogram or MUGA using the same modality planned for serial assessments; no symptomatic heart failure or clinically significant uncontrolled cardiac disease [1].
- Pulmonary status: no current, suspected, or radiographic ILD/pneumonitis; no clinically significant, uncontrolled pulmonary compromise that could obscure early ILD detection [1].
- Negative pregnancy test for participants who can become pregnant prior to first dosing; contraceptive requirements reviewed and reinforced per protocol [1].
- Baseline safety assessments completed (targeted physical exam, vital signs, triplicate 12-lead ECG at screening, laboratory panel), and concomitant medications reviewed [1].

Pre-dose requirements before each subsequent cycle (continuation criteria)

Proceed with dosing on Day 1 of each 21-day cycle only if all of the following are met at pre-dose evaluation:

- Interval history and targeted physical examination indicate no new contraindicating condition; vital signs clinically acceptable [1].
- Hematologic recovery and laboratory safety parameters meet all of:

- ANC ≥1.0 × 10^9/L [1,4].
- Platelets ≥75 × 10^9/L [1,4].
- Hemoglobin at a level that, in the investigator's judgment, permits safe treatment (transfusion/ESAs per institutional standards) [4].
- Total bilirubin ≤1.5 × ULN (≤3.0 × ULN with documented Gilbert syndrome); AST and ALT ≤3.0 × ULN (≤5.0 × ULN if liver metastases present) [1].
- Estimated creatinine clearance ≥50 mL/min or baseline value if higher threshold is met; electrolytes corrected to within normal limits as clinically indicated [1].

- Non-hematologic toxicities from prior cycle (excluding alopecia and nausea/vomiting controlled with optimal therapy) have improved to CTCAE grade ≤1 or to baseline prior to retreatment; for T-DXd–specific algorithms, follow product guidance (e.g., resume after recovery thresholds are met and reduce dose level when indicated) [1,4].
- ILD/pneumonitis safety check: no new/worsening cough, dyspnea, fever, or hypoxia; oxygen saturation acceptable on room air as per institutional standards. If ILD is suspected, interrupt immediately and evaluate (do not dose) [1].
- Cardiac safety check: no new/worsening LVEF-related signs/symptoms. If on-treatment LVEF meets a protocol-defined interruption/discontinuation threshold, hold dosing and manage per algorithm [1].
- For participants who can become pregnant: a negative pregnancy test per institutional standard prior to dosing each cycle [1].

If any parameter does not meet the above criteria, delay dosing and manage per protocol. Doses may be delayed up to 28 days from the planned date to allow for recovery; delays beyond 28 days require permanent discontinuation [1].

Product-specific pre-infusion checks and supportive care

- Verify dose level per most recent modification (6.4 mg/kg starting dose; permitted reductions to 5.4 mg/kg then 4.4 mg/kg) with no re-escalation [1].

- Confirm infusion parameters: first infusion ≥90 minutes; subsequent infusions ≥30 minutes if previously tolerated; use D5W for dilution and a 0.20–0.22 µm filter; dedicated line or compatible lumen; do not administer as IV push/bolus [1].
- Provide antiemetic prophylaxis per product and institutional standards; review and optimize supportive care plans (e.g., growth factors, antimicrobials, analgesics) as clinically indicated [1].
- Screen for risk factors and concomitant medications that may increase toxicity risk (e.g., ILD signals, QT-prolonging agents requiring ECG/electrolyte monitoring) and address prior to dosing [1].

Criteria requiring dose hold, additional evaluation, and restart

- Suspected ILD/pneumonitis: interrupt immediately; perform prompt evaluation (e.g., chest CT, pulse oximetry). Restart only after full resolution of Grade 1 ILD per protocol; permanently discontinue for Grade ≥2 and initiate systemic corticosteroids/supportive care [1].
- Neutropenia: for Grade 3–4 or febrile neutropenia, interrupt until recovery to Grade ≤2; resume at same or reduced dose per algorithm (reduce after Grade 4 or febrile neutropenia) [1,4].
- Thrombocytopenia: interrupt for Grade 3–4 until recovery to Grade ≤1; resume at same (Grade 3) or reduced dose (Grade 4) per algorithm [1,4].
- Non-hematologic toxicity (excluding alopecia and inadequately treated nausea/vomiting): interrupt for Grade ≥3 until improvement to Grade ≤1, then resume at next lower dose; permanently discontinue for life-threatening Grade 4 toxicity [1,4].
- LVEF decrease: hold or discontinue based on absolute LVEF value and change from baseline per protocol-defined thresholds; symptomatic heart failure mandates permanent discontinuation [1].

Timing and monitoring expectations before and during therapy

- Pre-dose assessments each cycle: interval history, targeted physical exam (with pulmonary focus), vital signs, review of AEs and concomitant medications, pregnancy test as applicable, and laboratory panel (CBC with differential; comprehensive metabolic panel including liver tests; coagulation as indicated) obtained sufficiently close to dosing to inform safety (per site SOPs) [1,2,4].
- Cardiac monitoring: LVEF at screening, Cycle 5 Day 1, and every 4 cycles thereafter using the same modality; ECG at screening (triplicate) and during treatment as clinically indicated [1].
- ILD vigilance: maintain a low threshold for chest imaging and dose interruption if new/worsening pulmonary symptoms arise; follow the ILD adjudication and management pathway prior to resuming therapy [1].
- Regulatory and ethical oversight: ongoing safety review by the sponsor with expedited IND safety reporting per 21 CFR 312.32; conduct and documentation align with ICH E6(R3) and the 2024 Declaration of Helsinki [1–3,6].

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8.4 Medication Administration

General administration

- Investigational product and dosing: Trastuzumab deruxtecan (T-DXd) is administered as monotherapy at 6.4 mg/kg by intravenous (IV) infusion on Day 1 of each 21-day cycle, calculated from actual body weight at each dosing visit. Treatment continues until disease progression, unacceptable toxicity, withdrawal of consent, or another protocol-defined reason for discontinuation [1,2].
- Infusion duration and sequence: Administer the first infusion over at least 90 minutes; if well tolerated, subsequent infusions may be administered over at least 30 minutes. Do not administer as an IV push or bolus [1,2].
- Preparation: Reconstitute and dilute per the product instructions using 5% dextrose (D5W) for infusion; do not use sodium chloride–containing solutions. Use a dedicated infusion line or a compatible separate lumen and an in-line or add-on 0.20–0.22 µm sterile, non-pyrogenic, low-protein-binding filter [1].
- Premedication and supportive care: Provide antiemetic prophylaxis before each dose in accordance with product guidance and institutional standards. Additional premedication (e.g., antihistamines, antipyretics, corticosteroids) is not required routinely but may be considered for patients with prior infusion-related reactions (IRRs) [1].
- Visit timing flexibility: Day 1 dosing visits should follow the protocol-defined visit windows; brief operational adjustments within the allowed window may be used to accommodate clinic scheduling and patient availability in line with Good Clinical Practice, with any out-of-window dosing documented and justified [4].

Administration procedures and on-infusion monitoring

- Verify cycle eligibility and dose level, including any prior dose reductions (permitted sequence: 6.4 mg/kg → 5.4 mg/kg → 4.4 mg/kg; no re-escalation) [1].
- Prime the line with D5W, initiate infusion at the prescribed rate, and monitor for IRRs throughout administration and during the immediate post-infusion period per institutional monoclonal antibody practices [1].
- Concomitant medications (e.g., growth factors, antimicrobials, antidiarrheals, analgesics) may be used as clinically indicated and recorded per protocol; avoid mixing or co-infusing other drugs through the same line [1].

Management of infusion- or treatment-related reactions

- Mild to moderate IRR (e.g., flushing, fever, chills, nausea, mild dyspnea): slow or temporarily interrupt the infusion; provide symptomatic treatment (e.g., antihistamines, antipyretics, bronchodilators, antiemetics). Upon symptom resolution to baseline or Grade ≤1, resume at a slower rate and complete the infusion; consider premedication for subsequent cycles [1,3].
- Severe IRR or hypersensitivity (e.g., anaphylaxis, severe bronchospasm, hypotension): stop the infusion immediately and institute emergency management per institutional standards (e.g., epinephrine, oxygen, IV fluids, bronchodilators, corticosteroids). Permanently discontinue study drug for severe infusion-related reactions. Document and report per protocol and regulations [1,3].
- Nausea and vomiting: optimize antiemetic prophylaxis and rescue consistent with product guidance and CTCAE-graded severity; for persistent Grade ≥3 despite optimal therapy, interrupt until improved to Grade ≤1 and resume with dose modification per protocol [1,3].

- Hematologic and other toxicities: manage per protocol-specified algorithms aligned with product guidance, including temporary interruption, dose reduction, and supportive measures (e.g., growth factor support, transfusions) [1,3].

Dose interruption, modification, and delays at the point of administration

- Permitted dose levels are 6.4 mg/kg (starting), 5.4 mg/kg, and 4.4 mg/kg; a maximum of two reductions is allowed with no re-escalation. Doses may be delayed up to 28 days from the planned date to allow for recovery; delays >28 days require permanent discontinuation [1].
- ILD/pneumonitis: interrupt dosing immediately upon suspicion and evaluate. Restart only after full resolution of Grade 1 events per protocol; permanently discontinue and initiate systemic corticosteroids for Grade ≥2 events. Follow all cases to resolution [1].
- Neutropenia: interrupt for Grade 3–4 or febrile neutropenia; resume after recovery per protocol at same (Grade 3) or reduced dose (Grade 4/febrile) [1,3].
- Thrombocytopenia: interrupt for Grade 3–4; resume after recovery per protocol at same (Grade 3) or reduced dose (Grade 4) [1,3].
- Non-hematologic toxicities (excluding alopecia and adequately controlled nausea/vomiting): interrupt for Grade ≥3 until improved to Grade ≤1; resume at next lower dose. Permanently discontinue for life-threatening Grade 4 toxicity [1,3].
- LVEF decrease: hold or discontinue based on absolute LVEF and change from baseline per protocol thresholds; permanently discontinue for symptomatic heart failure [1].

Post-infusion observation and documentation

- Observe patients per institutional standards for monoclonal antibody–based infusions after completion, with additional monitoring if any IRR occurred during infusion. Record start/stop times, dose delivered, infusion rate adjustments, premedications, adverse events (AEs), and any interruptions or modifications in the source and eCRF [1,4].

Maintenance phase

- No separate maintenance phase is planned. Participants who derive clinical benefit and tolerate therapy continue on the same 21-day dosing schedule with protocol-defined modifications until progression or unacceptable toxicity. This approach reflects administration used in published T-DXd studies in this disease area and standard continuation rules for single-arm Phase II trials [1,2].

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8.5 General Concomitant Medication and Supportive Care Guidelines

Supportive care

Supportive care should follow institutional standards and established oncology guidelines to prevent

and manage common toxicities of investigational trastuzumab deruxtecan (T-DXd), with documentation of all measures in the source and eCRF. Prophylactic antiemetics are recommended prior to each infusion given the high incidence of nausea with T-DXd; optimize a multimodal regimen (e.g., a 5-HT3 receptor antagonist with or without dexamethasone and/or an NK1 receptor antagonist based on emetogenic risk and prior tolerance) and provide rescue therapy as needed [1,13,3]. Antidiarrheal therapy (e.g., loperamide as first-line) should be initiated promptly for chemotherapy-related diarrhea, with evaluation for dehydration and infection as indicated, and escalation per guideline-based algorithms for persistent or severe symptoms [3,4]. Analgesic management should be individualized using a stepwise approach, integrating non-opioid and opioid analgesics and adjuvants, bowel regimens for opioid-induced constipation, and nonpharmacologic interventions, with reassessment each cycle [11]. Hydration and electrolyte repletion should be provided for patients with vomiting, diarrhea, or laboratory abnormalities; consider IV fluids and magnesium/potassium supplementation if clinically indicated [3,4]. Hematologic support, including red blood cell or platelet transfusions and myeloid growth factors, may be used according to product labeling and institutional standards to manage cytopenias and to maintain planned dosing where appropriate [1]. Vaccinations: inactivated vaccines may be administered per CDC best practices; avoid live-attenuated vaccines during immunosuppression and for at least 4 weeks before initiating cytotoxic or immunosuppressive therapy [7].

Clinical staff will oversee home-administered supportive medications through medication reconciliation at each cycle, patient education (dose, schedule, indications, when to contact the site), and adherence monitoring (pill counts when feasible, refill checks, and AE/diary review). Concomitant medication records will be maintained contemporaneously as part of Good Clinical Practice [2].

When coadministering drugs with known QT-prolonging potential, obtain baseline and clinically indicated ECGs, maintain potassium and magnesium in the normal range, and correct reversible risk factors; monitor more closely if combining multiple QT-prolonging agents [1].

Infection prophylaxis

Routine antibacterial, antifungal, or antiviral prophylaxis is not indicated for most adults with solid tumors receiving cytotoxic or antibody–drug conjugate therapy unless they are expected to have prolonged, profound neutropenia or other high-risk features [12]. For patients anticipated to have high-risk neutropenia (absolute neutrophil count <0.1 × 10^9/L for >7 days) or comparable risk based on clinical judgment, consider:

- Antibacterial prophylaxis with a fluoroquinolone during the period of high risk [12].
- Antifungal prophylaxis (e.g., an oral triazole) if there is a high risk for invasive candidiasis or mold disease, typically in settings of prolonged neutropenia or corticosteroid-related immunosuppression; select agent according to local epidemiology and drug–drug interactions [12].
- Antiviral prophylaxis (e.g., acyclovir/valacyclovir) for patients with prior herpes simplex or varicella-zoster reactivation risk in the context of significant immunosuppression; screen and manage hepatitis B reactivation risk per institutional pathways when clinically relevant [12].

Pneumocystis jirovecii pneumonia (PJP) prophylaxis (e.g., trimethoprim–sulfamethoxazole) should be used for patients receiving prolonged high-dose corticosteroids or meeting other established high-risk criteria; continue through the period of risk and for several weeks after immunosuppression tapers, consistent with institutional standards [12]. Prophylaxis should begin before or at the onset of the risk period and continue until neutrophil recovery or resolution of the immunosuppressive condition; reassess need at each cycle [12]. Prompt evaluation and empiric management of febrile neutropenia must follow institutional protocols.

Management of anticoagulants and platelet inhibitors

Because T-DXd can cause thrombocytopenia, coadministration with therapeutic anticoagulants or antiplatelet agents warrants careful assessment of bleeding risk, frequent monitoring of platelet counts, and coordination of dosing around invasive procedures [1]. General principles include:

- Avoid initiating or escalating agents that increase bleeding risk when the anticipated benefit is low (e.g., primary VTE prophylaxis in ambulatory solid tumor patients at low risk). For patients

who require anticoagulation for established or high-risk venous thromboembolism, direct oral anticoagulants (DOACs) such as apixaban or rivaroxaban or low-molecular-weight heparin (LMWH) are acceptable options; in gastrointestinal malignancies or in patients with elevated bleeding risk, LMWH or apixaban may be preferred over rivaroxaban based on differential GI bleeding signals [6].

- For antiplatelet therapy, continue low-dose aspirin for strong cardiovascular indications; dual antiplatelet therapy or full-dose antiplatelets should be used only when essential and with enhanced bleeding surveillance [6].
- Manage anticoagulation during thrombocytopenia according to risk: consider dose reduction, temporary interruption, or transfusion-supported therapy when platelets are <50 × 10^9/L; hold therapeutic dosing at lower thresholds per guideline-based practice and resume when counts recover and bleeding is controlled [6].
- Counsel patients to avoid over-the-counter supplements that may potentiate bleeding (e.g., high-dose vitamin E, ginkgo biloba, and high-dose omega-3 fatty acids) during therapy unless medically indicated and supervised [8–10].

Resumption of study treatment after temporary interruption for anticoagulation management may occur when: the indication for anticoagulation is appropriately addressed, the patient is clinically stable without active bleeding, platelet count and other continuation criteria meet protocol thresholds, and the risk–benefit supports re-initiation; apply protocol dose-modification rules if treatment was also held for T-DXd–related toxicity [1,6].

Permitted concomitant medications

The following categories are permitted when clinically indicated and recorded with start/stop dates, dose, and indication:

- Antiemetics (prophylaxis and rescue), antidiarrheals, laxatives and stool softeners, proton-pump inhibitors or H2 antagonists, antiulcer agents, antiemetic adjuncts (e.g., olanzapine), and appetite stimulants, per guideline-directed use [1,3,13].
- Analgesics (non-opioids, opioids, adjuvants), neuropathic pain agents, anxiolytics, hypnotics, and nonpharmacologic supportive measures per institutional standards [11].
- Hematologic support (transfusions; myeloid growth factors) per product labeling and guideline-concordant indications; erythropoiesis-stimulating agents per institutional policies [1].
- Antibiotics, antivirals, or antifungals for treatment or prophylaxis as outlined above, guided by culture data, local resistance patterns, and drug–drug interaction checks [12].
- Routine concomitant medications for comorbidities, with attention to potential interactions. No dose adjustment of T-DXd is required with strong CYP3A or P-gp inhibitors based on available data; clinically meaningful effects of strong CYP3A inducers have not been demonstrated. Monitor for expected toxicities if coadministered with strong CYP3A modulators. When T-DXd is given with QT-prolonging agents, monitor ECG and electrolytes and correct abnormalities [1].

Corticosteroids:

- Short courses of corticosteroids are permitted for standard indications (e.g., antiemetic prophylaxis, hypersensitivity reactions, adrenal replacement). Systemic corticosteroids are required for management of suspected or confirmed T-DXd–related ILD/pneumonitis per protocol [1,13].
- To avoid confounding safety signals and immunosuppression, minimize dose and duration when used for other indications; chronic systemic corticosteroids beyond physiologic replacement should be justified clinically and reviewed at each cycle. Corticosteroid use must be recorded with indication and dose [2].

Vaccine administration should follow CDC ACIP guidance: inactivated vaccines are permitted; defer live-attenuated vaccines during immunosuppression and for an appropriate interval after therapy, per institutional application of ACIP recommendations [7].

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8.6 Duration of Therapy

General considerations for duration of therapy

Participants receive investigational trastuzumab deruxtecan (T-DXd) 6.4 mg/kg IV every 3 weeks (21-day cycles) as long as they derive clinical benefit without disease progression and can tolerate treatment with acceptable safety, reflecting Phase II practice and product-specific guidance for continuation until progression or unacceptable toxicity [1,7]. Key determinants of ongoing therapy include antitumor response/stable disease per RECIST v1.1, absence of unacceptable or unmanageable adverse events per NCI CTCAE v5.0, and preservation of organ function with particular attention to interstitial lung disease (ILD)/pneumonitis and left ventricular ejection fraction (LVEF) decrease [1–3]. Investigator clinical judgment integrates these factors to decide on continuation, interruption, or discontinuation in alignment with Good Clinical Practice and participant welfare [4].

In analogous Phase II studies of T-DXd in this disease, therapy was continued until progression or unacceptable toxicity without a fixed maximum number of cycles; median exposure durations in the literature varied with individual response and tolerability, supporting an individualized, response- and

safety-guided duration framework in this protocol [7].

Planned treatment duration and dose delay limits

- Continue T-DXd on 21-day cycles until radiographic/clinical progression, unacceptable toxicity, withdrawal of consent, intercurrent illness that precludes treatment, start of new anticancer therapy, death, or other protocol-defined reason [1,2,4,5].
- Dose delays of up to 28 days from the planned dosing date are permitted to allow for recovery from toxicities; delays exceeding 28 days require permanent discontinuation [1].
- Dose modifications follow product-specific algorithms; up to two dose reductions (5.4 mg/kg then 4.4 mg/kg) are allowed with no re-escalation [1].

Maintenance therapy

No separate maintenance phase is planned. Because T-DXd is administered as a single agent, the same dosing schedule continues while benefit persists and toxicity remains manageable; no switch to a lower-intensity maintenance regimen is envisioned. This approach is consistent with prior Phase II T-DXd experience in HER2-positive gastric cancer where treatment was maintained until progression or toxicity rather than for a fixed duration [1,7].

Conditions for planned discontinuation despite disease control

Even in the setting of ongoing disease control, permanent discontinuation will occur when:

- A protocol-defined maximum allowable dosing delay (>28 days) is exceeded [1].
- A toxicity mandates permanent discontinuation per protocol/product guidance (e.g., ILD/pneumonitis Grade ≥2; life-threatening nonhematologic toxicity; symptomatic heart failure or severe LVEF decrease per algorithm) [1].
- An intercurrent medical condition or procedure irreconcilably interferes with safe administration or protocol-required monitoring, as determined by the investigator in compliance with GCP [1,4].
- The participant withdraws consent or requests to stop therapy, consistent with the ethical right to discontinue participation at any time [5].

Participants who discontinue in the absence of progression will enter protocol-defined follow-up, with tumor assessments per schedule if clinically indicated, and survival follow-up every 12 weeks, acknowledging that continued monitoring after treatment cessation is standard in contemporary trials to characterize durability of response and time-to-event outcomes [2,5].

Treatment discontinuation criteria

Permanent discontinuation is required under any of the following:

- Disease progression per RECIST v1.1 (radiographic progression on independent central review or unequivocal clinical progression) or initiation of a new anticancer therapy [2].
- Unacceptable toxicity, including but not limited to:

  - ILD/pneumonitis: permanently discontinue for Grade ≥2; initiate systemic corticosteroids and supportive care; follow to resolution [1].
  - LVEF-related toxicity meeting protocol-defined permanent discontinuation thresholds or symptomatic heart failure [1].
  - Life-threatening Grade 4 nonhematologic toxicity (excluding alopecia) or recurrent severe toxicity despite dose reductions, per CTCAE v5.0 and product algorithms [1,3].

- Delay of the next planned dose beyond 28 days due to adverse events or intercurrent illness [1].
- Intercurrent illness or surgical procedures that, in the investigator's judgment, pose an unacceptable risk with further dosing or prevent adherence to essential safety/efficacy assessments; hold treatment during evaluation and discontinue if the condition does not resolve sufficiently to permit safe resumption within protocol timelines [1,4].
- Pregnancy, participant noncompliance with essential protocol requirements, withdrawal of consent, loss to follow-up, or investigator/sponsor decision for safety reasons [4,5].
- Regulatory or administrative reasons that preclude continued investigational treatment under the US IND, including actions taken in response to IND safety reporting [6].

Definition of disease progression and actions

- Disease progression is defined by RECIST v1.1 as at least a 20% increase in the sum of diameters of target lesions (with an absolute increase of at least 5 mm), unequivocal progression of non-target disease, or the appearance of new lesions; clinical progression may also be considered when unequivocal and clinically significant [2].
- Upon first documentation of response (CR/PR), confirmation is required at least 4 weeks later; treatment continues during the confirmation interval if clinically appropriate [2].
- At progression, permanently discontinue T-DXd and perform end-of-treatment assessments; subsequent anticancer therapy is permitted per investigator discretion outside the study [2].

Actions for intercurrent medical conditions

- Temporarily interrupt dosing for new/worsening medical conditions that may increase the risk of serious toxicity (e.g., febrile neutropenia, active infection, uncontrolled arrhythmia, decompensated pulmonary disease) and evaluate/optimize management. Resume only when retreatment criteria are met and within the 28-day delay limit; otherwise, discontinue [1,3,4].
- For suspected ILD/pneumonitis, interrupt immediately, perform prompt diagnostic evaluation (e.g., chest CT), and manage per protocol; restart only after full resolution of Grade 1 events with risk mitigation, and discontinue for Grade ≥2 [1].

Participant-initiated withdrawal and investigator judgment

Participants may withdraw from treatment and/or the study at any time without penalty and without the need to provide a reason. Investigators retain responsibility to ensure that any decision to continue or stop therapy prioritizes participant safety, protocol compliance, and data integrity in accordance with ICH E6(R3) and the Declaration of Helsinki; when feasible, participants who discontinue therapy are encouraged to complete safety and survival follow-up [4,5].

Post-discontinuation monitoring and follow-up

- Safety follow-up: conduct a visit 40 days (+7) after the last dose to capture adverse events (AEs), serious AEs, and adverse events of special interest (ILD/pneumonitis and LVEF decrease), consistent with IND safety reporting requirements [1,6].
- Long-term follow-up: collect survival status every 12 weeks (±14 days) until study end or withdrawal of consent; record subsequent anticancer therapies and survival outcomes per protocol [2,4].
- Ongoing follow-up for ILD/pneumonitis continues until clinical and radiographic resolution is documented [1].

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8.7 Duration of Follow Up

Overview and objectives of follow-up

Participants will be followed after permanent discontinuation of investigational trastuzumab deruxtecan (T-DXd) to characterize long-term safety, durability of antitumor activity, progression-free survival (PFS), and overall survival (OS). Post-treatment follow-up supports robust interpretation of time-to-event endpoints and late or delayed adverse events (AEs), consistent with oncology trial methodology and Good Clinical Practice [1,2,3,4].

Structure and duration of follow-up

- End-of-treatment (EOT) and safety follow-up: Conduct an EOT visit at discontinuation and a safety follow-up visit 40 days (+7) after the last dose to capture ongoing or new AEs, serious AEs (SAEs), and adverse events of special interest (AESIs: interstitial lung disease [ILD]/pneumonitis and left ventricular ejection fraction [LVEF] decrease). ILD/pneumonitis must be followed until clinical and radiographic resolution, reflecting the potential for delayed onset and protracted recovery with antibody–drug conjugates [2,5,6].
- Disease assessment follow-up after treatment stop without progression or new anticancer therapy: Continue radiologic tumor assessments per the protocol schedule (CT/MRI every 6 weeks [±7 days] in Year 1, then every 12 weeks) until the earliest of objective progression (RECIST v1.1 by independent central review), initiation of non-protocol anticancer therapy, death, withdrawal of consent, or end of study. This approach aligns with RECIST v1.1 conventions for documenting progression and duration of response (DoR) off treatment when feasible [1].
- Survival follow-up: After the safety follow-up visit, ascertain survival status and subsequent anticancer therapies every 12 weeks (±14 days) by clinic visit, telecontact, or review of source records until death, withdrawal of consent, loss to follow-up, or end of study. OS and PFS are key oncology endpoints that require systematic follow-up for unbiased estimation and regulatory interpretability [3,4].
- End of study: Survival follow-up continues until the protocol-defined study end (approximately 12 months after the last participant's first dose), death, withdrawal of consent, or loss to follow-up, whichever occurs first.

Application to early discontinuation scenarios

- Discontinuation for radiographic or unequivocal clinical progression: Stop study treatment and complete EOT and 40-day safety follow-up; discontinue protocol tumor imaging thereafter. Continue survival follow-up every 12 weeks. PFS and DoR will be derived per RECIST v1.1 using assessments obtained up to and including the date of progression [1,3].
- Discontinuation due to unacceptable toxicity (including ILD/pneumonitis Grade ≥2 or LVEF-related events meeting permanent discontinuation thresholds): Perform EOT and 40-day safety follow-up. Continue AE follow-up for unresolved toxicities until resolution or stability at a new baseline; ILD/pneumonitis requires follow-up to resolution. Survival follow-up continues every 12 weeks [2,5,6].
- Start of new anticancer therapy before documented progression: Stop protocol treatment and tumor imaging; collect EOT and 40-day safety follow-up, then survival follow-up every 12 weeks. Per standard time-to-event principles, subsequent therapy is handled as an intercurrent event in the analysis plan (e.g., censoring for PFS at the last adequate assessment before new therapy), consistent with ICH E9(R1) [4].
- Withdrawal of consent for further study procedures: Discontinue all follow-up immediately; participants may optionally allow passive survival status checks if separately consented.

- Loss to follow-up: Make diligent attempts to re-establish contact per site SOPs and document efforts; if unsuccessful, classify as lost to follow-up with date of last contact recorded, per GCP [2].
- Death: Record date and source documentation; no further follow-up.

Criteria defining the endpoint of follow-up for each participant

Follow-up ends at the earliest occurrence of:

- Death from any cause (for OS).
- Participant withdrawal of consent for further data collection.
- Loss to follow-up despite documented reasonable efforts.
- Protocol-defined end of study.

For tumor assessment follow-up specifically, follow-up ends at the earliest of RECIST v1.1 progression, start of new anticancer therapy, death, withdrawal of consent, loss to follow-up, or end of study [1].

Justification of follow-up intervals

- Imaging every 6 weeks in Year 1 then every 12 weeks balances timely detection of progression and confirmation of responses with participant burden, in line with RECIST v1.1 response confirmation and common schedules used in prior T-DXd trials in this setting (e.g., DESTINY-Gastric01) and contemporary second-line gastric cancer studies [1,7]. Off-treatment imaging is maintained when no new therapy has begun to ensure accurate ascertainment of DoR and PFS [1,3].
- A 40-day post-dose safety visit captures AEs occurring after the last administration and accommodates the pharmacology and delayed toxicity profile of antibody–drug conjugates, including ILD/pneumonitis, which can present after treatment interruption; sustained follow-up to resolution is specifically warranted for ILD [2,6].
- Survival status updates every 12 weeks are standard in oncology to ensure timely OS ascertainment while minimizing administrative burden; this frequency is consistent with regulatory expectations for OS as a definitive endpoint and with methodological guidance on time-to-event endpoints [3,4].

Contribution of follow-up to efficacy and safety interpretation

- Efficacy: Continued radiologic follow-up off treatment (when no new therapy has started) enables robust estimation of confirmed ORR, DoR, and PFS under RECIST v1.1. Regular survival ascertainment supports unbiased OS analysis and contextualizes response-based endpoints, consistent with FDA oncology endpoint guidance [1,3].
- Safety: The safety follow-up window and targeted longitudinal tracking of ILD/pneumonitis and cardiac function events support detection of delayed or evolving toxicities relevant to antibody–drug conjugates and inform risk–benefit assessment in regulatory and scientific review [2,6].
- Data integrity and ethics: Follow-up conduct adheres to ICH E6(R3) and the 2024 Declaration of Helsinki, with respect for participants' rights to withdraw and with appropriate documentation of outcomes and intercurrent events per ICH E9(R1) [2,4,8].

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8.8 Criteria for Removal from Study

Circumstances requiring removal from study

Participants must be permanently withdrawn from protocol treatment and removed from further on-treatment study procedures if any of the following occur:

- Objective disease progression per RECIST v1.1 (radiographic by independent central review or unequivocal clinical progression) or initiation of any new anticancer therapy [1].
- Unacceptable toxicity, including:

- Interstitial lung disease (ILD)/pneumonitis of Grade ≥2 (permanent discontinuation and systemic corticosteroids) [4].
- Symptomatic heart failure or left ventricular ejection fraction (LVEF) events meeting protocol-defined permanent discontinuation thresholds [4].
- Life-threatening Grade 4 non-hematologic toxicity (excluding alopecia) or recurrent severe toxicity despite required dose reductions, graded by NCI CTCAE v5.0 [4,5].

- Failure to meet retreatment criteria within the maximum allowable dosing delay (delay of the next planned dose >28 days) [4].
- Intercurrent illness, procedure, or clinical condition that precludes safe continuation or essential monitoring, in the investigator's judgment, in accordance with Good Clinical Practice (GCP) [1].
- Pregnancy or positive confirmatory pregnancy testing during the study [1].
- Noncompliance with essential protocol requirements (e.g., persistent failure to attend critical safety or tumor assessment visits; use of prohibited concomitant therapy; repeated refusal of required evaluations) despite counseling [1].
- Participant-initiated withdrawal of consent for further participation at any time, without penalty or loss of benefits to which the participant is otherwise entitled [2,6].
- Investigator or sponsor decision for safety, regulatory, or administrative reasons under the US IND [1,3,7].

For detailed toxicity management and dose adjustment algorithms, including ILD/pneumonitis and LVEF-related events, see the Adverse events and Medication Administration sections of this protocol [4,5].

Documentation and data handling at withdrawal

- Record the primary reason for removal and all contributory factors in the source documents and electronic case report form (eCRF), using controlled terminology (e.g., "progression," "adverse event—ILD Grade 2," "withdrawal of consent," "noncompliance," "investigator decision—intercurrent illness") [1].
- Document relevant clinical details: signs/symptoms, CTCAE grade, onset/stop dates, diagnostic evaluations (e.g., chest CT for suspected ILD; cardiac imaging for LVEF changes), concomitant medications, and actions taken (dose hold, reduction, discontinuation), with outcomes where available [1,5].

- Ensure adverse events (AEs) and serious adverse events (SAEs) are captured through the date of the end-of-treatment (EOT) visit and the 40-day (+7) safety follow-up, and thereafter until resolution or stability at a new baseline for ongoing toxicities of special interest (e.g., ILD/pneumonitis) [1].
- Retain and analyze data collected up to the time of withdrawal. If a participant withdraws consent for further procedures but allows continued use of previously collected data or passive survival status checks, document the scope of permissions per informed consent regulations and site IRB requirements [1,2,6,7].

Participant discussions and permissions at time of withdrawal

At the time of withdrawal, review with the participant:

- The reason for removal and immediate safety considerations, including symptom monitoring and when to seek urgent care (with emphasis on respiratory symptoms suggestive of ILD and cardiac symptoms) [4].
- Required post-discontinuation procedures: EOT assessments and the 40-day (+7) safety follow-up visit; ongoing follow-up to resolution for ILD/pneumonitis; and survival follow-up every 12 weeks unless consent for further contact is withdrawn [1].
- Options for continued medical care and transition to standard therapies outside the study; provide or arrange referrals as appropriate [1,2].
- Rights regarding participation and data/authorization: the right to withdraw from the study at any time and to clarify any preferences about further contact or use of data already collected, consistent with US human subjects protections and IRB-approved consent language [2,6,7].

Safety notifications and reporting requirements

- Report SAEs to the sponsor (Sample Pharma Co., Ltd.) immediately (within 24 hours of site awareness) per the sponsor's safety reporting procedures; provide follow-up information as it becomes available. The sponsor will determine IND safety reporting obligations under 21 CFR 312.32 (including 7-day reports for unexpected fatal or life-threatening suspected adverse reactions and 15-day reports for other serious and unexpected suspected adverse reactions) [3].
- Sites must comply with IRB reporting requirements for unanticipated problems and SAEs, following 21 CFR Part 56 and local IRB policies. Maintain documentation of all submissions and communications [7].
- Distinguish expedited reporting events from routine AE collection:

- Expedited: all SAEs and all AESIs (ILD/pneumonitis of any grade and LVEF decrease) are reported by the site to the sponsor within 24 hours, regardless of seriousness. IND safety reports to FDA are limited to serious and unexpected suspected adverse reactions under 21 CFR 312.32(c); ILD/pneumonitis, LVEF decrease and infusion-related reactions are expected for T-DXd and are submitted only if more severe or specific than described in the reference safety information, or if aggregate analysis shows a clinically important increase in their rate [3,4].
- Routine: Non-serious AEs and SAEs not meeting expedited criteria are recorded in the eCRF with CTCAE grading and assessed for relatedness; they remain subject to aggregate safety review [3,5].

- Cross-reference for clinical management details and dose modifications: see Adverse events and Medication Administration sections of this protocol [4,5].

Post-withdrawal follow-up and transition of care

- Conduct EOT assessments at discontinuation and a safety follow-up at 40 days (+7) after the last dose to collect ongoing/new AEs, SAEs, and adverse events of special interest (AESIs: ILD/pneumonitis and LVEF decrease). Continue AE follow-up for unresolved toxicities until resolution or stability; ILD/pneumonitis must be followed to clinical and radiographic resolution [1,4,5].
- If treatment stops without documented progression and no new anticancer therapy has started, continue protocol-scheduled tumor imaging until the earliest of progression, start of new therapy, death, withdrawal of consent, or end of study, consistent with RECIST v1.1-based endpoint ascertainment [1].

- Provide transition planning: communicate a clear summary of recent clinical status, key AEs/toxicities, and pending evaluations to the participant and treating clinicians; arrange referrals (e.g., pulmonology for ILD, cardiology for LVEF decrease) and ensure continuity of standard medical care [1].
- Survival follow-up every 12 weeks (±14 days) will continue until death, withdrawal of consent, loss to follow-up, or end of study, unless the participant declines further contact [1].

References

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9 EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

9.1 Anticipated Toxicities

Overview and grading framework

The anticipated toxicity profile of investigational trastuzumab deruxtecan (T-DXd) at 6.4 mg/kg every 3 weeks includes dose-limiting pulmonary, hematologic, gastrointestinal, and cardiac risks, along with infusion-related reactions and laboratory abnormalities. Adverse events (AEs) will be graded per NCI CTCAE v5.0, with management guided by severity, causality, persistence, and reversibility, and by product-specific algorithms for treatment interruption, dose reduction, or permanent discontinuation [1,3]. All serious and unexpected suspected adverse reactions will be expeditiously reported in accordance with 21 CFR 312.32 [4].

Adverse events of special interest

- Interstitial lung disease (ILD)/pneumonitis: ILD/pneumonitis is a serious and potentially fatal risk of T-DXd. Clinical presentations range from asymptomatic radiographic findings to acute dyspnea, cough, hypoxemia, and respiratory failure. In previously treated HER2-positive gastric cancer receiving T-DXd 6.4 mg/kg, ILD/pneumonitis occurred in approximately one in ten patients, with no fatal ILD reported in that cohort (fatal cases have occurred in other T-DXd populations); immediate treatment interruption for any suspicion, prompt diagnostic evaluation, and systemic corticosteroids are required. Permanent discontinuation is mandated for Grade ≥2 ILD/pneumonitis; Grade 1 may allow re-initiation only after complete resolution and risk mitigation [1,2]. Risk is increased in patients with underlying lung disease; such conditions are excluded in this protocol [1].
- Left ventricular ejection fraction (LVEF) decrease/heart failure: HER2-targeted therapy can cause asymptomatic LVEF decline and, rarely, symptomatic heart failure. Monitoring of LVEF

at baseline and periodically during treatment is required; interrupt, reduce dose, or discontinue per product-specific thresholds and clinical status [1]. Report new or worsening dyspnea, edema, or fatigue promptly.
- Infusion-related reactions (IRRs)/hypersensitivity: IRRs (e.g., fever, chills, dyspnea, hypotension, rash) typically occur during or shortly after infusion. Severe hypersensitivity, including anaphylaxis, is uncommon. Manage with infusion interruption, symptomatic therapy, and, if indicated, corticosteroids; permanently discontinue for severe or life-threatening hypersensitivity [1].

Hematologic toxicities and infection risk

- Neutropenia, anemia, and thrombocytopenia are common with T-DXd; Grade ≥3 events can occur and may necessitate dose interruptions, reductions, transfusions, or myeloid growth factors per institutional standards and product-specific guidance [1]. Febrile neutropenia, while less frequent, is a medical emergency requiring immediate evaluation and broad-spectrum antibiotics; resume treatment only after clinical recovery and count recovery per retreatment criteria, with dose modification as indicated [1,3].
- Clinically significant laboratory abnormalities include decreased hemoglobin, neutrophils, lymphocytes, and platelets; monitoring prior to each cycle is required, with more frequent checks during nadirs or when clinically indicated [1].

Gastrointestinal (GI) and mucosal toxicities

- Nausea and vomiting are frequent and can be prolonged; T-DXd should be managed as highly emetogenic for many patients. Prophylactic antiemetics are recommended, with escalation to multi-agent regimens based on prior tolerance; dehydration and electrolyte disturbances should be corrected promptly [1].
- Diarrhea, decreased appetite, weight loss, and stomatitis occur commonly; initiate early antidiarrheals, provide nutritional support, and hold or reduce dose for persistent Grade ≥2–3 symptoms per product guidance and CTCAE grading [1,3].

Hepatic and metabolic laboratory abnormalities

- Elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin have been observed; monitor liver tests at baseline and before each cycle. Interrupt and adjust dose for clinically significant Grade ≥3 elevations or if drug-induced liver injury is suspected [1].
- Electrolyte abnormalities (e.g., hyponatremia, hypokalemia) and hypoalbuminemia may occur secondary to GI losses or disease; replace and correct underlying causes, with treatment holds for severe or symptomatic derangements [1].

Other common reactions

- Fatigue/asthenia, alopecia, cough, constipation, and headache are commonly reported; most are Grade 1–2 and manageable with supportive care. Persistent Grade ≥3 events warrant dose modification per protocol algorithms [1,3].

Rare but important risks and comorbid considerations

- QT interval prolongation risk is not prominent with T-DXd; however, caution is advised when coadministered with other QT-prolonging drugs. Maintain electrolytes in the normal range and obtain ECGs if clinically indicated [1].
- Hemorrhagic events can occur in the setting of thrombocytopenia; assess bleeding risk when using anticoagulants or antiplatelet agents and adjust per clinical status and platelet count [1].

Principles for monitoring, interruption, dose modification, and discontinuation

- Monitoring: Baseline assessments include history/physical, CTCAE-graded symptom review, CBC with differential, comprehensive metabolic panel including liver tests, pregnancy testing

when applicable, LVEF measurement (ECHO or MUGA), and ECG. During treatment, perform clinical review and labs prior to each cycle; LVEF at protocol-specified intervals; additional testing guided by symptoms (e.g., chest CT and oximetry for suspected ILD) [1,3].

- Treatment interruption: Immediately interrupt T-DXd for suspected ILD/pneumonitis, febrile neutropenia, Grade 3–4 non-hematologic toxicity (excluding alopecia and inadequately treated nausea/vomiting), Grade 3–4 neutropenia, or Grade 3–4 thrombocytopenia; initiate diagnostic workup and supportive care [1,3].
- Dose modification: Resume at the same or a reduced dose (to 5.4 mg/kg then 4.4 mg/kg; no re-escalation) after resolution to Grade ≤1 or baseline, following product-specific criteria. Recurrent or persistent severe toxicity despite prior reduction generally necessitates further reduction or discontinuation [1,3].
- Permanent discontinuation: Required for ILD/pneumonitis Grade ≥2, life-threatening non-hematologic toxicity, severe hypersensitivity, inability to meet retreatment criteria within the maximum allowed delay, or protocol-specified LVEF events (e.g., symptomatic heart failure or significant asymptomatic decline meeting discontinuation thresholds) [1,3].
- Expedited reporting: Sites must report all SAEs to the sponsor within 24 hours (21 CFR 312.64(b)); the sponsor assesses expectedness and submits IND safety reports for serious and unexpected suspected adverse reactions per 21 CFR 312.32; all ILD/pneumonitis and LVEF events are adverse events of special interest and must be reported promptly to enable central review and safety surveillance [1,4].

Uncertainty and heterogeneity of risk

Event rates for specific toxicities can vary by dose, prior therapies, comorbidities, and regional practice patterns. Gastric cancer experience at 6.4 mg/kg indicates higher rates of hematologic and GI toxicity and a clinically meaningful risk of ILD; vigilant monitoring and early intervention are essential to mitigate morbidity and mortality in this study population [1,2]. These risks justify focused safety assessments and conservative restart thresholds specified in this protocol [1,3,4].

References

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9.2 Treatment of Overdose

Definition of overdose

For this protocol, an overdose is any administration of investigational trastuzumab deruxtecan (T-DXd) exceeding the protocol-assigned dose or schedule, including:

- A single administered dose greater than 10% above the calculated dose for that infusion (e.g., >7.0 mg/kg when 6.4 mg/kg is prescribed), or an absolute dose based on an incorrect body weight that results in >10% overage.
- Accidental additional or repeated infusion(s) within the same 21-day cycle (duplicate dosing).
- Shortened dosing interval resulting in a subsequent infusion administered earlier than Day 21 (± permitted visit window) without sponsor approval.
- Compounding or infusion errors resulting in higher concentration, faster-than-allowed infusion rate, or total delivered volume exceeding the intended amount.

Clinical management of overdose

- There is no known antidote to T-DXd; management is supportive and directed at emergent toxicities and anticipated adverse reactions based on the pharmacology of an antibody–drug conjugate delivering a topoisomerase I inhibitor payload [1].
- Immediately stop any ongoing infusion when an overdose is recognized. Initiate close clinical observation with frequent vital signs and cardiorespiratory monitoring. Manage infusion reactions/hypersensitivity per institutional standards; provide supplemental oxygen, bronchodilators, antihistamines, corticosteroids, IV fluids, vasopressors, or advanced life support as clinically indicated [1].
- Admit for observation if clinically warranted (e.g., symptoms of respiratory compromise, hemodynamic instability, febrile neutropenia, severe nausea/vomiting with dehydration, or Grade ≥3 laboratory abnormalities) and monitor closely for interstitial lung disease (ILD)/pneumonitis, myelosuppression, severe gastrointestinal toxicity, and cardiac dysfunction, which are toxicities relevant to T-DXd [1,6].

Recommended evaluations and monitoring after overdose

Obtain baseline assessments promptly and repeat at clinically appropriate intervals during the first 72 hours and through the expected toxicity nadir:

- Focused history and physical examination with attention to respiratory status (cough, dyspnea), fever/infection, mucositis, fluid status, and cardiac symptoms [1,6].
- Pulse oximetry; arterial blood gas if hypoxemic.
- 12-lead ECG; telemetry if clinically indicated.
- Laboratory tests: CBC with differential; comprehensive metabolic panel (including AST, ALT, alkaline phosphatase, bilirubin, creatinine, electrolytes, albumin); magnesium and phosphate; pregnancy test when applicable [1].
- Chest imaging (preferably high-resolution CT) if any respiratory symptoms/signs or oxygen desaturation occur; early pulmonology consult and ILD adjudication per protocol for suspected ILD/pneumonitis [1,6].
- LVEF assessment (ECHO or MUGA using the same modality as baseline) for new cardiopulmonary symptoms or signs of heart failure [1].
- Infection work-up (e.g., blood cultures, urinalysis, chest imaging) for fever or neutropenia; treat febrile neutropenia per institutional standards [1].
- Antiemetic optimization, IV hydration, and electrolyte repletion for significant nausea/vomiting or diarrhea; nutritional support as needed [1].
- Hematology support (growth factors, transfusions) for clinically significant cytopenias per institutional practice and CTCAE v5.0 grading [1,4].

Continue monitoring until the participant is clinically stable and acute toxicities have resolved to Grade ≤1 or baseline. Subsequent study dosing must be held; any resumption must follow protocol-specified retreatment criteria and dose-reduction rules, recognizing that an overdose may necessitate further delay or permanent discontinuation depending on resulting toxicity [1].

Prior clinical experience informing risk at higher exposures

In a phase 1 dose-escalation/expansion study of T-DXd (DS-8201a) in HER2-expressing solid tumors, doses up to 8.0 mg/kg every 3 weeks were administered; the maximum tolerated dose was not reached, and recommended doses for further study included 5.4 mg/kg and 6.4 mg/kg. Common treatment-emergent adverse events included nausea, decreased appetite, anemia, and neutropenia; ILD/pneumonitis was observed, including fatal cases in the broader development program, underscoring the need for early detection and corticosteroid management of pulmonary toxicity [5]. In HER2-positive gastric cancer, T-DXd 6.4 mg/kg every 3 weeks demonstrated meaningful antitumor activity but was associated with clinically relevant hematologic and gastrointestinal toxicity and approximately 10% risk of ILD/pneumonitis in that setting, supporting vigilant monitoring after any excess exposure [6].

While a formal overdose threshold for severe toxicity cannot be precisely predicted from available data, higher dose intensity and cumulative exposure to T-DXd have been associated with increased rates of myelosuppression and ILD/pneumonitis across studies; therefore, a conservative monitoring

and supportive care approach is warranted after any overdose [1,5,6].

Reporting requirements and documentation

- Any overdose, regardless of associated symptoms, must be documented in source records and the electronic case report form (eCRF) with date/time, dose intended vs. administered, infusion rate/volume, lot number, and circumstances (e.g., calculation or administration error). Record all related clinical findings and management actions with NCI CTCAE v5.0 grading [4].
- If the overdose results in an adverse event meeting seriousness criteria (death, life-threatening, hospitalization/prolongation, persistent/significant disability, congenital anomaly, or important medical event), report it to the sponsor (Sample Pharma Co., Ltd.) within 24 hours of site awareness as a serious adverse event (SAE). The sponsor will assess for IND expedited safety reporting per 21 CFR 312.32 [2].
- Investigators must provide safety reports to the sponsor as required by 21 CFR 312.64(b), and comply with IRB reporting requirements for unanticipated problems and SAEs under applicable US regulations; maintain copies of all submissions and safety communications [2].
- Overdose events with or without associated AEs remain subject to aggregate safety review by the sponsor's ongoing pharmacovigilance program and may inform protocol amendments or risk mitigation [2,3].

Site procedures upon awareness of an overdose

- Immediately ensure participant safety: stop any ongoing infusion; initiate indicated emergency/supportive measures; engage appropriate specialty consultations (e.g., pulmonology, cardiology, critical care) as needed [1].
- Quarantine and reconcile remaining investigational product; review preparation and administration records to identify root cause; preserve infusion/administration materials per site SOPs to support investigation [3].
- Notify the sponsor medical monitor within 24 hours; submit an initial SAE/overdose report if applicable, followed by detailed follow-up, including relevant laboratory, imaging, and consult results [2,3].
- Determine on-treatment disposition in consultation with the sponsor medical monitor after clinical stabilization. Further dosing must adhere to protocol dose-modification rules and may require delay, reduction, or permanent discontinuation depending on the nature and severity of resulting toxicities [1].

Guidance for participants

- Participants who suspect an overdose (e.g., received an extra infusion, incorrect dose, or experience unexpected severe symptoms after an infusion) should contact the study site immediately using the 24-hour contact information on their study card and seek urgent medical evaluation if severely unwell. They should not skip medical assessment, should bring their study card and any medication diaries, and should not attempt to self-treat beyond previously provided antiemetic or supportive medications unless instructed by the study team [1,3].
- The site will provide instructions regarding observation, testing, and follow-up. Participants should report promptly any new or worsening respiratory symptoms (cough, dyspnea), fever, chest pain, palpitations, severe nausea/vomiting, diarrhea, bleeding, or signs of infection [1,6].

Cross-references within this protocol

- For detailed adverse event documentation and management, including ILD/pneumonitis and LVEF-related events, see Adverse events and Anticipated Toxicities.
- For dose interruption, reduction, and discontinuation criteria after toxicities, see Expected Toxicities and Dosing Delays/Dose Modifications and Medication Administration.
- For timelines and processes for SAE reporting and IND safety reporting, see Adverse events and Criteria for Removal from Study.

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9.3 Dose Modifications / Delays

General Toxicity Monitoring and Management

Adverse events (AEs) will be collected from first administration of investigational trastuzumab deruxtecan (T-DXd) through 40 days (+7) after the last dose, and thereafter until resolution or stabilization at a new baseline for adverse events of special interest (AESIs: interstitial lung disease [ILD]/pneumonitis and left ventricular ejection fraction [LVEF] decrease). AEs will be graded per NCI CTCAE v5.0 and managed with supportive care, temporary treatment interruption, dose reduction, or discontinuation according to severity, causality, and reversibility [1,2]. Immediate interruption is required for suspected ILD/pneumonitis, febrile neutropenia, Grade 3–4 neutropenia, Grade 3–4 thrombocytopenia, Grade ≥3 non-hematologic toxicity (excluding alopecia and inadequately treated nausea/vomiting/diarrhea), severe infusion reactions, and LVEF declines meeting interruption thresholds; institute appropriate diagnostics and supportive measures. Sites must comply with ICH E6(R3) and IND safety reporting per 21 CFR 312.32 for serious and unexpected suspected adverse reactions [3,4].

Dose Modification Rules

T-DXd starting dose is 6.4 mg/kg IV every 3 weeks. Up to two dose reductions are permitted (first to 5.4 mg/kg, then to 4.4 mg/kg). No re-escalation is allowed. If dosing is interrupted for >28 days from the planned date, permanently discontinue study treatment. Resume only when protocol-specified retreatment criteria are met [1].

Toxicity/event	Action (withhold/modify)	Resumption and subsequent dosing
ILD/pneumonitis suspected (any grade)	Immediately withhold; perform prompt evaluation (e.g., high-resolution CT, pulse oximetry) and manage per institutional standards; initiate systemic corticosteroids if clinically indicated	Grade 1: resume only after complete clinical and radiographic resolution; consider dose reduction per overall safety profile. Grade ≥2: permanently discontinue and treat with systemic corticosteroids [1]
Neutropenia (CTCAE)	Grade 3: withhold until Grade ≤2; then resume at same dose. Grade 4: withhold until Grade ≤2; then reduce by one dose	Retreatment requires ANC ≥1.0 × 10^9/L; consider G-CSF per institutional practice [1,2]

	level. Febrile neutropenia: withhold until resolved; then reduce by one dose level [1]	
Thrombocytopenia (CTCAE)	Grade 3: withhold until Grade ≤1; then resume at same dose. Grade 4: withhold until Grade ≤1; then reduce by one dose level [1]	Retreatment requires platelets ≥75 × 10^9/L [1,2]
Other non-hematologic toxicity (excluding alopecia and inadequately treated nausea/vomiting/diarrhea)	Grade 3: withhold until Grade ≤1 or baseline; then reduce by one dose level. Grade 4 or life-threatening: permanently discontinue [1,2]	Resume per above; no re-escalation [1]
Infusion-related reactions (IRRs)/hypersensitivity	Interrupt infusion and treat symptoms; for severe/life-threatening hypersensitivity, permanently discontinue [1]	If resumed after non-severe IRR, consider slower rate and premedication [1]
LVEF decrease (ECHO/MUGA, same modality)	LVEF >45% with 10–20% absolute drop from baseline: continue. LVEF 40–45% with <10% drop: continue and repeat within 3 weeks. LVEF 40–45% with 10–20% drop: interrupt and repeat within 3 weeks; resume at same dose if LVEF returns to within 10% of baseline; otherwise discontinue. LVEF <40% or >20% absolute drop from baseline: interrupt, repeat within 3 weeks; if confirmed, discontinue. Symptomatic heart failure: permanently discontinue [1]	Cardiology evaluation as indicated; manage per heart failure standards; resume only if criteria above are met [1]

Withholding criteria (applies at any time during a cycle): suspected ILD/pneumonitis, febrile neutropenia, Grade 3–4 neutropenia, Grade 3–4 thrombocytopenia, Grade ≥3 non-hematologic toxicity (excluding alopecia and inadequately treated nausea/vomiting/diarrhea), severe IRR/hypersensitivity, and LVEF events meeting interruption thresholds [1,2].

Resumption criteria (prior to each subsequent dose): toxicities resolved to required grades per the table; ANC ≥1.0 × 10^9/L; platelets ≥75 × 10^9/L; afebrile and hemodynamically stable after febrile neutropenia; non-hematologic toxicities recovered to Grade ≤1 or baseline; ILD/pneumonitis Grade 1 fully resolved; LVEF meets restart thresholds above. If recovery does not occur within 28 days of the planned dose date, permanently discontinue [1,2].

Dose reduction limits and discontinuation triggers: maximum of two dose reductions (6.4 → 5.4 → 4.4 mg/kg). Permanently discontinue for ILD/pneumonitis Grade ≥2; recurrent or persistent severe toxicity despite two reductions; LVEF events requiring discontinuation; life-threatening non-hematologic toxicity; inability to meet retreatment criteria within 28 days [1,2].

Hepatic Impairment Management

Baseline hepatic function: No initial dose adjustment is recommended for mild hepatic impairment; limited data suggest no clinically meaningful impact on exposure in mild impairment. For moderate hepatic impairment, initiate at the assigned dose with close monitoring; exposure may be increased—monitor for toxicity and adjust per events [1].

On-study hepatic events:

- ALT or AST >5 × ULN or total bilirubin >3 × ULN (Grade ≥3): withhold T-DXd; evaluate for drug-induced liver injury; resume at the next lower dose level after recovery to Grade ≤1 and when clinically stable; permanently discontinue for recurrent Grade ≥3 events or if Hy's law criteria are met [1,2].
- Any signs of severe hepatic dysfunction (e.g., jaundice with transaminase elevation, hepatic failure): permanently discontinue and provide appropriate care [1].

Severe baseline hepatic impairment has not been adequately studied; enrollment requires adequate organ function per protocol. If severe hepatic impairment develops on study, withhold and reassess risk–benefit; permanent discontinuation is generally warranted in the setting of Grade ≥3 hepatic

dysfunction or inability to safely resume within 28 days [1].

Peri-operative Management

For major surgical procedures requiring suturing or stapling, interrupt T-DXd prior to surgery and resume only after adequate wound healing and hematologic recovery. Given the approximately 6-day terminal half-life and myelosuppressive potential, an interruption spanning at least one dosing interval before surgery (about 3 weeks) and a minimum of 2 weeks postoperatively until wounds are healed and counts meet retreatment criteria is a common practice approach; individualize based on surgical risk, healing, and recovery of ANC and platelets [1,2]. For minor procedures (e.g., diagnostic endoscopy without extensive biopsy, simple line placement, paracentesis, thoracentesis), T-DXd may be interrupted for a shorter period (e.g., omit the dose immediately preceding the procedure) or continued if bleeding risk is minimal and counts are adequate; ensure hemostasis and resume once clinically appropriate and laboratory criteria for retreatment are met [2,3].

Renal Function Considerations and Additional Dose Adjustments

Baseline renal function: No initial dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance ≥30 mL/min by Cockcroft–Gault); limited data are available in severe renal impairment (CrCl <30 mL/min), for which close monitoring is advised [1].

On-study renal events:

- Creatinine increase to Grade ≥2 or acute kidney injury: withhold T-DXd; correct reversible causes (e.g., dehydration, nephrotoxic concomitants); resume at the same or next lower dose after recovery to Grade ≤1 or baseline and stabilization of renal function. Consider dose reduction if recurrent [1,2].
- Retreatment requirements include stabilization of renal parameters at Grade ≤1 (e.g., creatinine ≤1.5 × ULN or return to baseline if baseline was abnormal), adequate urine output, and absence of ongoing nephrotoxic insults. Hematologic criteria (ANC ≥1.0 × 10^9/L, platelets ≥75 × 10^9/L) must also be met [1,2].

Persistent renal dysfunction that precludes meeting retreatment criteria within 28 days requires permanent discontinuation [1].

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9.4 Study Discontinuation

Overview and authority to discontinue the study

The study may be suspended or terminated before planned completion by the Investigator or by the Sponsor (Sample Pharma Co., Ltd.) to protect participants, ensure scientific integrity, or comply with regulatory and ethical requirements. Under ICH E6(R3), investigators and sponsors must continuously assess risks, ensure rights, safety, and well-being of participants, and act when new information indicates that the risk–benefit is no longer favorable or the trial cannot be conducted per the protocol and Good Clinical Practice (GCP) [1]. US IND regulations authorize the FDA to impose or maintain a clinical hold, and require sponsors to monitor, evaluate safety, and discontinue investigators or studies when risks are unacceptable or compliance is deficient [2]. Ethical principles

mandate prompt communication of significant changes affecting participants, arrangements for appropriate medical care after discontinuation, and transparency with oversight bodies [3].

Investigator-initiated discontinuation (site-level early closure)

The Investigator may suspend enrollment or discontinue the study at the site when, in their judgment:

- New or emerging safety concerns (e.g., serious or unexpected adverse events, a pattern of ILD/pneumonitis or LVEF decline) materially increase risk to participants [1,2].
- Protocol-required procedures, monitoring, or IP accountability cannot be performed with acceptable quality (e.g., loss of imaging capacity for RECIST assessments; pharmacy or infusion constraints; staffing or facility interruptions) [1].
- Regulatory, IRB, or institutional noncompliance or restrictions preclude continued conduct per GCP, the protocol, or applicable regulations [1,2].
- Operational feasibility is compromised (e.g., persistent insufficient participant follow-up, repeated missed critical safety assessments) such that participant safety or data integrity is at risk [1].

Investigator obligations in the event of site-level discontinuation:

- Immediately implement measures to protect participants, including medical management of ongoing adverse events and ensuring continuity of clinical care and appropriate referrals outside the trial (e.g., pulmonology for suspected ILD, cardiology for LVEF changes) [1,3].
- Promptly notify the Sponsor in writing of the decision, effective date, and detailed rationale; provide supporting documentation and safety data to enable centralized risk assessment and regulatory determinations under the IND [1,2].
- Notify and obtain guidance from the site IRB without delay; submit a report describing reasons for early closure, actions taken to protect participants, and plans for follow-up and data handling, consistent with 21 CFR Part 56 and institutional policies [4].
- Inform active participants in clear, timely language about the discontinuation, reasons, implications for their care, alternatives to participation, and plans for safety follow-up; obtain any required consent addenda when transitioning to non-study care [3,4].
- Complete end-of-treatment and safety follow-up assessments as clinically feasible; continue safety surveillance and report all SAEs to the Sponsor within 24 hours (21 CFR 312.64(b)) for assessment under 21 CFR 312.32 [1,2].
- Secure, complete, and reconcile essential documents, source data, and eCRFs; ensure investigational product (IP) accountability, return, or destruction per Sponsor instructions; retain records per 21 CFR 312.62 and GCP [1,2].

Sponsor-initiated suspension or termination

The Sponsor may suspend enrollment, halt dosing, close individual sites, or terminate the study for reasons including:

- Participant safety concerns based on ongoing pharmacovigilance, aggregate safety review, external data, or regulatory communications (e.g., increased frequency/severity of ILD/pneumonitis or cardiac events) [1,2].
- Insufficient enrollment or failure to meet predefined operational milestones rendering the study scientifically or operationally nonviable [1].
- Emerging scientific or clinical information (e.g., new evidence that continuation is futile or exposes participants to undue risk) or strategic considerations affecting feasibility [1].
- Persistent protocol noncompliance, data integrity issues, serious GCP deviations, or IP mismanagement by an Investigator/site; under 21 CFR 312.56, the Sponsor must discontinue noncompliant investigators and notify FDA and IRBs as appropriate [2].
- Regulatory actions (e.g., FDA clinical hold under 21 CFR 312.42) or discovery that the Investigator/site is no longer eligible per institutional or regulatory determinations [2].

Sponsor obligations when initiating early termination or suspension:

- Take prompt action to protect participants, including immediate notification to all Investigators and instruction on participant management, follow-up, and IP disposition; communicate safety rationale and any protocol amendments or holds under the IND [1,2].
- Notify FDA as required (e.g., safety findings per 21 CFR 312.32; discontinuation of investigators per 21 CFR 312.56; withdrawal or inactive status of the IND per 21 CFR 312.38 and 312.45, as applicable) and provide follow-up analyses supporting the decision [2].

- Ensure Investigators notify their IRBs and that participants are informed of the change in study status, reasons, and next steps for medical care and safety follow-up [1,4].
- Update the ClinicalTrials.gov record to reflect recruitment status, study closure, and final disposition in accordance with US registration regulations, with timely updates to minimize public misinformation [5].
- Oversee site close-out activities, essential document consolidation, data capture/lock plans, and final IP reconciliation; ensure records are retained per regulatory and GCP requirements [1,2].

Procedures and expectations for early closure

Upon decision to discontinue (by Investigator or Sponsor), the following procedures apply:

- Suspend further enrollment immediately; interrupt dosing unless the Sponsor authorizes limited continuation solely to mitigate immediate medical risks during transition of care [1,2].
- Conduct a risk-adapted safety evaluation for each active participant, including completion of end-of-treatment and 40-day (+7) safety follow-up assessments where feasible; continue AE follow-up for unresolved toxicities until resolution or stability, consistent with GCP and ethical obligations [1,3].
- Maintain expedited reporting of serious and unexpected suspected adverse reactions per 21 CFR 312.32 until all participants complete safety follow-up; maintain IRB reporting of unanticipated problems per institutional policy [2,4].
- Deactivate central procedures dependent on active conduct (e.g., central imaging reads after last scheduled assessments; independent ILD adjudication continues for any pending or new suspected ILD cases identified during safety follow-up) and archive oversight committee materials per Sponsor SOPs [1].
- Manage IP: quarantine, reconcile, and return or destroy unused T-DXd per Sponsor instructions; document final accountability and disposition [1].
- Finalize data handling: complete and verify eCRFs, resolve queries, and document protocol deviations arising from early closure; preserve audit trails and source documentation to enable regulatory inspection and reliable reporting [1,2].
- Communicate study status and participant guidance using IRB-approved materials; offer referrals and ensure a safe transition to non-study care, in alignment with the Declaration of Helsinki [3,4].

Documentation, oversight, and ethical safeguards

Rationales and processes related to early discontinuation are aligned with protocol sections addressing safety oversight, monitoring, risk management, adverse event reporting, and ILD/cardiac safety procedures. ICH E6(R3) requires proportionate, ongoing safety evaluation, transparent communication of significant new findings, and documentation sufficient for reconstruction and verification of the trial, including after premature termination [1]. US IND regulations assign Sponsors explicit responsibility for safety evaluation, investigator compliance oversight, FDA/IRB notifications, and appropriate disposition of the IND and study records; FDA may impose a clinical hold if participant safety is at risk [2,4]. The Declaration of Helsinki requires that researchers prioritize participant welfare, inform participants of new information relevant to their continued participation, and make provisions for appropriate medical care and follow-up after trial termination [3]. Clinical trial registration records must be updated to reflect early termination to maintain public transparency [5].

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10 STUDY DRUGS FORMULATION AND ADMINISTRATION

10.1 STUDY DRUGS FORMULATION

Investigational Product — Mechanism and Use

Trastuzumab deruxtecan (T-DXd) is an antibody–drug conjugate (ADC) composed of a humanized anti-HER2 IgG1 antibody linked via a cleavable tetrapeptide linker to a potent topoisomerase I inhibitor payload (DXd). Following HER2 binding and internalization, lysosomal enzymes cleave the linker to release DXd intracellularly, inducing DNA damage and apoptosis; membrane-permeable DXd can confer a bystander effect in HER2-heterogeneous tumors. DXd is the principal active catabolite contributing to antitumor activity; systemic exposure to unconjugated DXd remains a relevant pharmacologic consideration in safety and efficacy assessments [1,3]. In phase 2 gastric cancer studies, T-DXd has been administered at 6.4 mg/kg IV every 3 weeks with meaningful antitumor activity in previously treated HER2-positive disease, informing the regimen used in this protocol [2,3]. Preparation and administration in clinical studies follow weight-based dosing, aseptic reconstitution, dilution in 5% dextrose, in-line filtration, and controlled infusion rates as detailed below [1–3].

Additional Background Therapy — Mechanism and Use

No additional antineoplastic background therapy is planned in this single-agent study. Supportive medications (e.g., antiemetics, antidiarrheals, antipyretics, growth factors, and transfusional support) may be used per institutional practice to prevent or manage adverse events commonly associated with ADCs and as recommended in the T-DXd product information (see Premedication and Infusion Reactions) [1].

General Properties and Preparation

- Supplied presentation: Single-dose vial containing 100 mg lyophilized powder for reconstitution [1].
- Storage (unreconstituted): Refrigerate at 2–8°C in the original carton to protect from light. Do not freeze or shake [1].
- Reconstitution: Using aseptic technique, add 5 mL of Sterile Water for Injection to yield 20 mg/mL. Gently swirl; do not shake. Inspect for particulate matter or discoloration; do not use if unacceptable [1].
- Dilution: Withdraw the calculated volume and dilute in an infusion bag containing 5% Dextrose Injection (D5W). Do not use sodium chloride solutions. Prepare to a final concentration consistent with institutional compounding practices within the range described in the product information [1].
- Filtration: Administer via an IV set with a sterile, non-pyrogenic 0.20 or 0.22 µm in-line polyethersulfone (PES) or polysulfone (PS) filter, using an infusion set made of polyolefin or polybutadiene [1].
- Stability after preparation: Use immediately after dilution when feasible. If not used immediately, follow label stability instructions; reconstituted vials and diluted infusion solutions may be stored refrigerated (2–8°C) for limited durations per the product information. Do not freeze; protect from light during storage and infusion setup [1].

Dosing and Protocol Considerations

- Starting dose and schedule: 6.4 mg/kg IV every 3 weeks (21-day cycles). Dose is calculated by body weight on the day of dosing and rounded per institutional SOPs; no re-escalation after reduction [1–3].

- Infusion administration: First infusion over at least 90 minutes; if well tolerated, subsequent infusions may be administered over at least 30 minutes. Flush the line with D5W after infusion; avoid saline flushes [1].
- Cycle-to-cycle practice: Continue on Day 1 of each 21-day cycle if retreatment criteria are met per protocol. Up to two dose reductions (to 5.4 mg/kg, then 4.4 mg/kg) may be used for toxicity management; permanent discontinuation is required for protocol-specified events (cross-referenced in the Dose Modifications/Delays section) [1–3].

Premedication and Infusion Reactions

- Antiemetics: Prophylactic antiemetics are recommended because nausea and vomiting are common with T-DXd; multi-agent regimens may be used based on prior tolerance and institutional standards [1].
- IRR/hypersensitivity mitigation: Routine premedication for hypersensitivity is not mandated but may be used per clinical judgment. Have emergency medications immediately available (e.g., oxygen, bronchodilators, H1/H2 antihistamines, corticosteroids, epinephrine, IV fluids, vasopressors) [1].
- Infusion procedures: Begin the first infusion at a controlled rate sufficient to meet the minimum 90-minute duration; if tolerated, subsequent infusions may use a faster rate consistent with a ≥30-minute duration. Monitor during and after infusion for fever, chills, dyspnea, hypotension, rash, or other IRR symptoms [1].
- Management of reactions: For suspected IRR, interrupt infusion and institute symptomatic care. Upon resolution of Grade 1–2 symptoms, resume at a slower rate with or without additional premedication. For severe or life-threatening hypersensitivity, permanently discontinue and treat per emergency standards of care [1].

Adjustments

- Divided administration: Splitting the first dose over multiple days is not standard for T-DXd and is not recommended; mitigation of first-dose intolerance should rely on slower infusion rates, temporary interruption, and symptomatic management rather than day-to-day fractionation [1].
- Early-cycle adjustments: If clinically indicated after an infusion interruption (e.g., IRR), resume the same total dose within the cycle at a slower rate once symptoms resolve; if intolerance recurs or significant toxicity emerges, implement protocol-specified dose reductions for subsequent cycles [1].
- General considerations: Adjust dosing per protocol for hematologic and non-hematologic toxicities, cardiac events, or suspected interstitial lung disease/pneumonitis. Hold treatment for events meeting interruption criteria and resume only after recovery thresholds are met; permanently discontinue when criteria are met (see Dose Modifications/Delays) [1–3].

Logistical and Regulatory Considerations

- Supply and labeling: The investigational product will be manufactured and supplied by Sample Pharma Co., Ltd. for use under a US IND. Packaging and labeling will comply with 21 CFR Part 312, including investigational use statements, and site pharmacies will maintain temperature control and light protection as specified [4,5].
- Storage and accountability: Sites will store vials refrigerated at 2–8°C in secured, access-controlled conditions, with continuous temperature monitoring, excursion documentation, and quarantine procedures. Drug accountability logs will record receipt, lot numbers, preparation, dispensing, returns, and destruction per ICH E6(R3) and sponsor SOPs [4,5].
- Pharmacy preparation: Compounding will occur in a USP <797>/<800>-compliant cleanroom environment using aseptic technique, D5W-only dilution, and in-line filtration, with beyond-use dating per the product information and institutional policy. Sodium chloride must not be used at any step [1].
- Investigational context: T-DXd is investigational in the target US population and setting of this protocol. Its evaluation at 6.4 mg/kg every 3 weeks as monotherapy is supported by prior phase 1–2 experience in HER2-expressing or HER2-positive solid tumors, including gastric

cancer, while this study will define antitumor activity and safety in US centers under standardized preparation and administration procedures outlined above [2,3].

References

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10.2 STUDY DRUGS ADMINISTRATION

Dose and Administration

Trastuzumab deruxtecan (T-DXd) will be administered as investigational monotherapy at 6.4 mg/kg by intravenous (IV) infusion on Day 1 of each 21-day cycle until discontinuation criteria are met. The first infusion will be administered over at least 90 minutes; if well tolerated, subsequent infusions may be administered over at least 30 minutes. Use 5% Dextrose Injection (D5W) for dilution and line flush; do not use sodium chloride solutions. Administer through a sterile, non-pyrogenic 0.20–0.22 µm in-line filter. Vital signs and clinical status will be monitored during and after infusion; infusion reactions will be managed per institutional standards and the study treatment plan [1].

For missed or delayed dosing, infuse the dose as soon as the participant meets retreatment criteria within the allowable delay window (up to 28 days from the planned date per protocol), then resume the 3-weekly schedule from the new administration date. If a participant does not meet retreatment criteria within 28 days of the planned dose, discontinue treatment per protocol. Doses must not be “made up” with additional infusions within a cycle. Duplicate dosing and shortened intervals are not permitted [1].

No specific food or beverage restrictions are required for IV T-DXd. Clinically meaningful drug–drug interactions are not expected based on available data; however, concomitant medications should be reviewed routinely for overlapping toxicities and supportive care optimized to mitigate nausea and vomiting, which are common with T-DXd [1]. Live vaccines should generally be avoided during cytotoxic therapy per institutional policy.

The standard treatment cycle length is 21 days. The initial cycle differs operationally by requiring a longer minimum infusion time (≥90 minutes) and closer on-site observation for infusion reactions; in subsequent cycles, infusion duration may be reduced (≥30 minutes) if prior tolerance is established. Laboratory and safety assessments will be performed at baseline and at protocol-specified intervals, with additional assessments in Cycle 1 as clinically indicated to establish individual tolerability [1].

Dose modifications will follow protocol rules aligned with the current US product information: up to two reductions are permitted (to 5.4 mg/kg, then to 4.4 mg/kg); re-escalation is not allowed. Withhold for suspected interstitial lung disease (ILD)/pneumonitis pending evaluation; permanently discontinue for Grade ≥2 ILD/pneumonitis. Withhold and resume/reduce as specified for hematologic and

non-hematologic toxicities, infusion reactions, and left ventricular ejection fraction (LVEF) decreases [1].

[References]

1. US Food and Drug Administration. Enhertu (fam-trastuzumab deruxtecan-nxki) prescribing information. Silver Spring (MD): FDA; 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s030lbl.pdf

Formulation and Packaging

Investigational T-DXd will be supplied as a single-dose vial containing 100 mg lyophilized powder for reconstitution. Vials will be provided in tamper-evident secondary packaging that protects from light and supports cold-chain storage. Labels will include protocol-specific identifiers (protocol number SP-TDXD-GC-201), batch/lot number, storage conditions, preparation and administration instructions, and required investigational use statements in accordance with 21 CFR 312.6. Site pharmacies must maintain segregation of investigational product (IP) with access-controlled storage and chain-of-custody documentation from receipt through final disposition consistent with ICH E6(R3) [1,2,3].

[References]

2. US Food and Drug Administration. Enhertu (fam-trastuzumab deruxtecan-nxki) prescribing information. Silver Spring (MD): FDA; 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s030lbl.pdf
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4. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf

Storage, Stability, and Handling

Unreconstituted vials must be stored refrigerated at 2–8°C in the original carton to protect from light. Do not freeze or shake. Reconstitute with Sterile Water for Injection to 20 mg/mL using aseptic technique; gently swirl to dissolve. Dilute only in D5W to the final infusion concentration per institutional compounding standards. If not administered immediately, follow labeled stability limits for reconstituted vials and diluted infusion bags under refrigeration (2–8°C); do not freeze; protect from light during storage and setup [1].

T-DXd is an antineoplastic hazardous drug; pharmacy staff and handlers must use appropriate personal protective equipment (PPE) and engineering controls (e.g., certified biological safety cabinet, closed-system transfer device if available) to avoid skin, eye, or mucosal contact, and to minimize aerosolization and spills, consistent with NIOSH hazardous drug handling guidance and institutional SOPs. At minimum, double chemotherapy gloves tested to ASTM standards, protective gown, and eye/face protection for splash risk are recommended during compounding and administration setup, with spill kits readily available [4].

After dispensing, the site pharmacy retains responsibility for ensuring proper storage and chain of custody until administration. If accidental exposure occurs:

- Skin contact: immediately remove contaminated clothing and wash the affected area with soap and water for at least 15 minutes; seek medical evaluation.
- Eye/mucosal contact: rinse with copious amounts of water or isotonic eyewash for at least 15 minutes; seek urgent ophthalmologic/medical evaluation.
- Inhalation/ingestion: move to fresh air; do not induce vomiting; seek immediate medical attention.

All incidents must be managed per institutional hazardous exposure procedures and reported to the Sponsor and IRB as required [1,4].

[References]

5. US Food and Drug Administration. Enhertu (fam-trastuzumab deruxtecan-nxki) prescribing information. Silver Spring (MD): FDA; 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s030lbl.pdf
6. National Institute for Occupational Safety and Health (NIOSH). NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings. 2023. Cincinnati (OH): CDC/NIOSH; 2023. Available from: https://www.cdc.gov/niosh/docs/2023-130/

Drug Accountability and Return

Investigators and site pharmacies will maintain complete, contemporaneous IP accountability records, including IP receipt, lot numbers, quantities, storage conditions, preparation logs, dispensing to participants (with participant identifiers and dates), returns, reconciliations, and final disposition. Records will be sufficient to reconstruct the IP lifecycle and will be retained per ICH E6(R3) and 21 CFR 312.62 [2,3,5].

Participants will be instructed to return any ancillary study materials (e.g., medication cards/diaries) at each visit. As T-DXd is administered on site by infusion, no IP will be dispensed for home use. Any partially used vials or prepared infusion solutions not administered must be quarantined and destroyed per institutional hazardous waste procedures and Sponsor instructions; returned or unused IP will not be reissued to another participant. Destruction will be documented with certificates of destruction and prior Sponsor authorization when required; alternatively, IP may be returned to the Sponsor or designee per shipping instructions. All reconciliation and discrepancies will be resolved and documented before site close-out [2,3,5].

[References]

7. US Food and Drug Administration. Investigational new drug application. 21 CFR Part 312 (including §312.62). Silver Spring (MD): FDA; 2024. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312
8. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
9. US Food and Drug Administration. Investigational new drug application. 21 CFR Part 312 (including §312.57 and §312.59). Silver Spring (MD): FDA; 2024. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312

Overdose and Safety

In this study, overdose is defined operationally as administration exceeding the protocol-assigned dose or schedule (e.g., >10% above the calculated dose, duplicate dosing within a cycle, or administering earlier than permitted). There is no known antidote to T-DXd; management is supportive with close monitoring for toxicities associated with higher exposure, including ILD/pneumonitis, myelosuppression (e.g., neutropenia, anemia, thrombocytopenia), gastrointestinal toxicity (nausea, vomiting, diarrhea), and cardiac dysfunction. Immediate actions include stopping the infusion (if ongoing), evaluating vital signs, obtaining targeted labs and imaging as indicated, and instituting supportive care (e.g., antiemetics, IV fluids, growth factors, infection work-up for febrile neutropenia). Expedite reporting to the Sponsor within 24 hours for overdose events meeting seriousness criteria under 21 CFR 312.32 and document per CTCAE v5.0 [1,6,7,8].

[References]

10. US Food and Drug Administration. Enhertu (fam-trastuzumab deruxtecan-nxki) prescribing information. Silver Spring (MD): FDA; 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s030lbl.pdf
11. US Food and Drug Administration. Investigational new drug application. 21 CFR Part 312 (including §312.32). Silver Spring (MD): FDA; 2024. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312
12. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Bethesda (MD): NCI; 2017. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

13. Shitara K, Bang Y-J, Iwasa S, Sugimoto N, Ryu M-H, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382(25):2419–30. doi:10.1056/NEJMoa2004413. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2004413

Distribution, Ordering, and Availability

T-DXd will be supplied by Sample Pharma Co., Ltd. as investigational product for this protocol under a US IND. Sites will order IP through the Sponsor's designated clinical supply portal or ordering form. Shipments will use qualified cold-chain logistics with continuous temperature monitoring to maintain 2–8°C and protection from light; sites must inspect and document integrity, temperature data, lot numbers, and quantities upon receipt, and quarantine shipments if excursions or damage are suspected pending Sponsor instructions. Inventory control, reorders, and stock rotation will be managed by the site pharmacy to ensure adequate on-hand supply while minimizing expiry risk. Transfers between sites require prior Sponsor authorization and full documentation of chain of custody [2,3].

[References]

14. US Food and Drug Administration. Investigational new drug application. 21 CFR Part 312. Silver Spring (MD): FDA; 2024. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312
15. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf

Self-Administration and Compliance

T-DXd is administered exclusively at the study site by qualified healthcare professionals; there is no self-administration. Participants will be asked to maintain a brief diary or study card to document:

- Date and time of each infusion.
- Occurrence and timing of nausea, vomiting, diarrhea, fever, dyspnea, cough, chest pain, or other symptoms within 72 hours and throughout the cycle.
- Use of supportive medications (e.g., antiemetics, antidiarrheals), new concomitant medications, or changes to existing therapies.
- Any emergency room visits, hospitalizations, or unscheduled medical contacts.
- Missed or rescheduled infusion appointments and the reason.

Deviations (e.g., missed visits, vomiting soon after infusion, new respiratory symptoms) must be reported to the study team promptly and recorded in source documents and the eCRF. Participants should keep infusion appointments as scheduled to maintain consistent exposure and inform the site immediately if delays are anticipated so that rebooking within the permitted window can be arranged [1,3].

[References]

16. US Food and Drug Administration. Enhertu (fam-trastuzumab deruxtecan-nxki) prescribing information. Silver Spring (MD): FDA; 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s030lbl.pdf
17. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf

11 CORRELATIVE/SPECIAL STUDIES

11.1 Pharmacokinetic Studies

Not applicable. No pharmacokinetic sampling is planned in this study.

11.2 Pharmacodynamic Studies

Not applicable. No pharmacodynamic, genomic or other biomarker assessments are planned in this study.

12 STUDY CALENDAR

Overview and Scheduling Principles

All protocol-specified assessments must be completed and reviewed before each investigational treatment administration on the scheduled day to confirm ongoing eligibility for dosing and participant safety. Scheduling and documentation will follow ICH E6(R3) and applicable US IND regulations; any deviations must be prospectively minimized, justified, and documented in source records and the eCRF, with prompt safety reporting as required [1,2]. Tumor response assessments will be performed per RECIST v1.1 with confirmation of objective responses on a subsequent scan at least 4 weeks later; adverse events will be graded per NCI CTCAE v5.0 [3,4].

Baseline Evaluations and Eligibility Confirmation

Baseline evaluations will be completed within 28 days prior to the first dose (Cycle 1 Day 1, C1D1), unless otherwise specified below. Eligibility, including central confirmation of HER2 positivity on a new post-progression biopsy, must be fully verified no later than the day of first dosing. If clinical status changes (e.g., intercurrent illness, decline in performance status), key clinical and laboratory eligibility parameters must be repeated to ensure data remain current and representative of the participant's condition before initiating treatment [1].

- Core baseline assessments (≤28 days before C1D1): full medical history, physical examination, ECOG performance status, vital signs, height/weight, targeted symptom review (with emphasis on pulmonary symptoms), LVEF by echocardiogram or MUGA using a single consistent modality thereafter, CT/MRI for disease assessment, and documentation of measurable disease per RECIST v1.1 [1,3].
- Laboratory assessments (preferably within 7 days of C1D1; repeated if clinically indicated before dosing): CBC with differential; serum chemistries including electrolytes, renal function, and hepatic panel. Thresholds for adequate organ function (see Section 7.1) are absolute neutrophil count ≥1.5 × 10^9/L; platelets ≥100 × 10^9/L; hemoglobin ≥9 g/dL (transfusion permitted per protocol); total bilirubin ≤1.5 × ULN (≤3 × ULN with Gilbert syndrome); AST and ALT ≤2.5 × ULN (≤5 × ULN with liver metastases); creatinine clearance ≥50 mL/min (Cockcroft–Gault or institutional standard) [1].
- Cardiac and pregnancy testing (≤28 days before C1D1): triplicate 12-lead ECG at screening; serum or urine pregnancy test for women of childbearing potential within 72 hours before first dose [1,2].
- Maximum interval between enrollment and start of therapy: 28 days. All inclusion and exclusion criteria must be met and documented no later than C1D1 [1,2].

Treatment-Phase Visits, Windows, and Administration Rules

Treatment is administered at 6.4 mg/kg IV every 3 weeks (21-day cycles). Day 1 visits in all cycles have a ±3-day window to accommodate operational needs while maintaining safety and data integrity; all pre-dose assessments must be completed before dosing on the administration day [1].

- First infusion: at least 90 minutes; subsequent infusions may be ≥30 minutes if previously tolerated [1].
- Safety labs prior to each dose: obtained within 72 hours before dosing; abnormal or clinically changed findings require confirmation and clinical review before infusion [1].
- ECG: 12-lead ECG at screening (triplicate) and during treatment as part of routine safety surveillance; perform at Day 1 of a cycle or as clinically indicated for new cardiac symptoms or QT-relevant concomitant medications [1].

- LVEF: echocardiogram or MUGA at screening, on Cycle 5 Day 1, and every 4 cycles thereafter (e.g., C9D1, C13D1), using the same modality throughout; complete before dosing at the corresponding visit [1].
- ILD/pneumonitis surveillance: targeted pulmonary symptom review and pulse oximetry at every on-treatment visit, with prompt imaging as indicated for suspected events; withhold dosing for suspected ILD pending evaluation and manage per protocol [1].
- Dose delays and allowable windows: if retreatment criteria are not met on the planned Day 1, dosing may be delayed up to 28 days from the planned date; beyond 28 days, permanently discontinue treatment per protocol. Doses must not be “made up” within a cycle or administered at shortened intervals [1].
- Imaging during treatment: CT/MRI of disease sites every 6 weeks (±7 days) during the first year from C1D1, then every 12 weeks (±7 days) thereafter, irrespective of treatment holds, to allow consistent efficacy evaluation and timely response confirmation per RECIST v1.1 [3].

Post-Treatment and Long-Term Follow-up Windows

Participants who discontinue investigational treatment will continue protocol-mandated follow-up to ensure comprehensive safety and outcome collection consistent with GCP and IND requirements [1,2]:

- End-of-Treatment (EOT) visit: performed at treatment discontinuation or as soon as feasible thereafter to capture final on-treatment safety and disease status; if EOT coincides with a scheduled imaging timepoint, imaging within the visit window should be obtained [1,3].
- Safety follow-up: 40 days (+7 days) after the last dose to capture late-onset and evolving adverse events, including ILD/pneumonitis and cardiac events; additional follow-up continues until resolution or stabilization of any ongoing adverse events of special interest [1,2].
- Disease assessments after treatment discontinuation: continue CT/MRI per the protocol’s efficacy schedule (every 6 weeks ±7 days in Year 1, then every 12 weeks ±7 days thereafter) until objective radiographic disease progression, initiation of new anticancer therapy, withdrawal of consent, or end of study, whichever occurs first [3].
- Survival follow-up: every 12 weeks (±14 days) by site contact or permissible records review until death, loss to follow-up, withdrawal of consent, or end of study [2].

Visit-Window Rationale and Handling of Deviations

- Treatment-phase windows (±3 days for Day 1 visits) enable operational flexibility while preserving the timing of safety evaluations relative to dosing and maintaining a consistent pharmacodynamic observation interval; all pre-dose assessments must occur before infusion to satisfy retreatment criteria [1].
- Efficacy-assessment windows (±7 days) balance feasibility with the need to confirm responses at least 4 weeks apart under RECIST v1.1 and to estimate PFS with minimal temporal bias [3].
- Post-treatment windows (+7 days for the 40-day safety visit; ±14 days for survival follow-up) facilitate ongoing safety and outcome ascertainment in line with GCP and IND oversight while accommodating participant circumstances [1,2].
- Deviations outside the defined windows should be minimized; when unavoidable, they must be documented with rationale, assessed for impact on participant safety and endpoint integrity, and reported per regulatory and sponsor requirements [1,2].

Study Calendar Table

Study period	Visit	Target timing	Window	Key assessments to be completed before dosing or per schedule
Screening	Pre-treatment	Days −28 to −1	Not applicable	Informed consent; eligibility review; medical history; PE; ECOG; vitals; height/weight; triplicate ECG; labs (CBC, chemistries, hepatic/renal); pregnancy test (≤72 h pre-dose); LVEF (ECHO/MUGA); baseline CT/MRI;

				central HER2 on new biopsy; documentation of measurable disease [1–3]
Treatment	Cycle 1 Day 1	Day 1	±3 days	Interval history; AEs/SAEs; vitals; targeted PE; ECOG; concomitant meds; safety labs (≤72 h pre-dose); pulse oximetry; ECG as indicated; administer T-DXd (≥90 min) [1,4]
Treatment	Cycle n Day 1 (n ≥2)	Every 21 days	±3 days	Interval history; AEs/SAEs; vitals; targeted PE; ECOG; concomitant meds; safety labs (≤72 h pre-dose); pulse oximetry; ECG as indicated; administer T-DXd (≥30 min if prior tolerance) [1,4]
Cardiac monitoring	C5D1 and every 4 cycles thereafter (e.g., C9D1, C13D1)	Per cycle schedule	±3 days	LVEF by same modality before dosing; review for cardiac AEs and LVEF decline [1]
Imaging efficacy	Disease assessment	Every 6 weeks in Year 1; then every 12 weeks thereafter	±7 days	CT/MRI per RECIST v1.1; confirm responses ≥4 weeks after first documentation on repeat imaging [3]
End of Treatment	Discontinuation visit	At treatment stop	As soon as feasible	Final on-treatment safety and disease status; arrange 40-day safety follow-up; continued imaging schedule if no progression/new therapy [1–3]
Post-treatment safety	Safety follow-up	Day 40 after last dose	+7 days	Targeted PE; vitals; AEs/SAEs; concomitant meds; directed tests for unresolved AEs/ESIs (e.g., ILD, cardiac) [1,2]
Long-term efficacy	Disease follow-up	Per protocol schedule	±7 days	Continue CT/MRI schedule until progression, new therapy, withdrawal, or study end [3]
Survival	Follow-up contact	Every 12 weeks	±14 days	Survival status and subsequent anticancer therapies (no imaging mandated) [2]

[References]

18. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
19. US Food and Drug Administration. Investigational new drug application. 21 CFR Part 312 (including §§312.50–312.62). Silver Spring (MD): FDA; 2024. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312
20. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47. doi:10.1016/j.ejca.2008.10.026. Available from: https://pubmed.ncbi.nlm.nih.gov/19097774/
21. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Bethesda (MD): NCI; 2017. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

12.1 Pre-Treatment Evaluations

Scope and Timing

Pre-treatment evaluations are required to verify eligibility, establish baseline status, characterize disease burden, and ensure safe initiation of investigational trastuzumab deruxtecan (T-DXd). Unless otherwise specified below, complete all assessments within 28 days prior to Cycle 1 Day 1 (C1D1). Key safety laboratories for dosing should be performed preferably within 7 days and no later than 72 hours before C1D1, and a pregnancy test for women of childbearing potential within 72 hours prior to first dose. All results relevant to eligibility and safety must be reviewed and deemed acceptable before infusion on C1D1 in accordance with ICH E6(R3) and US IND requirements [1,2,3].

Informed Consent and Regulatory Prerequisites

- Written informed consent obtained prior to any study-specific procedures, under IRB approval and in compliance with 21 CFR Parts 50 and 56 and ICH E6(R3) [1,2,4,5].
- Documentation of eligibility, including central HER2 status on a new post-progression biopsy (IHC 3+ or IHC 2+/ISH+ using ASCO/CAP criteria), recognizing potential HER2 loss following trastuzumab exposure [6].

Medical History, Physical Examination, and Baseline Status

- Complete medical history, including prior anticancer therapies (confirm no systemic anticancer therapy after first-line trastuzumab-containing regimen), comorbidities, and risk factors for interstitial lung disease (ILD)/pneumonitis and cardiac dysfunction [7].
- Focused concomitant medication review to identify agents with overlapping toxicities (e.g., myelosuppressive, cardiotoxic, or pulmonary) [7].
- Physical examination and vital signs, including resting pulse oximetry, with targeted pulmonary symptom review (cough, dyspnea, fever, chest pain) given the risk of ILD/pneumonitis with T-DXd [7].
- ECOG performance status assessment (0–1 required) recorded at screening [1].

Laboratory Tests

Obtain the following within 7 days (and no later than 72 hours) before first dosing unless otherwise noted; repeat any out-of-range or clinically changed results before C1D1 to confirm eligibility and safety [1,7]:

- Hematology: complete blood count with differential and platelets. Baseline thresholds: absolute neutrophil count ≥1.5 × 10^9/L; platelets ≥100 × 10^9/L; hemoglobin ≥9 g/dL (transfusion permitted per protocol) [7].
- Serum chemistry: electrolytes; renal function (creatinine, blood urea nitrogen; creatinine clearance ≥50 mL/min by Cockcroft–Gault or institutional standard); hepatic panel (AST and ALT ≤2.5 × ULN or ≤5 × ULN with liver metastases; total bilirubin ≤1.5 × ULN, or ≤3 × ULN with Gilbert syndrome) [7].
- Pregnancy testing: serum or urine human chorionic gonadotropin for women of childbearing potential within 72 hours before C1D1 due to embryo-fetal toxicity risk; counsel on effective contraception per protocol [7].
- Additional tests as clinically indicated to clarify eligibility or safety (e.g., inflammatory markers, microbiology, coagulation) should be obtained based on history, exam, and site standards; broad viral screening is not mandated by protocol [1].

Cardiac Evaluations

- 12-lead ECG: triplicate at screening; repeat if clinically indicated for new symptoms or QT-relevant medications [1].
- Left ventricular ejection fraction (LVEF): transthoracic echocardiogram or multigated acquisition (MUGA) scan at screening to confirm LVEF ≥50%; use the same modality for all subsequent on-study assessments. Baseline and periodic LVEF monitoring are recommended due to risk of cardiac dysfunction with HER2-directed agents, including T-DXd [7].

Imaging and Disease Characterization

- Baseline tumor imaging: contrast-enhanced CT or MRI of chest, abdomen, and pelvis within 28 days prior to C1D1 to document measurable disease per RECIST v1.1; include additional sites as clinically indicated. Baseline images must be of sufficient quality to support independent central review and subsequent response confirmation at least 4 weeks after first documentation of response [8].
- Central HER2 confirmation: submit tissue from a new biopsy obtained after progression on first-line trastuzumab for central IHC and ISH per ASCO/CAP gastroesophageal adenocarcinoma criteria; document assay methodology and scoring to ensure standardized classification (IHC 3+ or IHC 2+/ISH+) [6].
- Brain imaging: MRI (preferred) or CT only if clinically indicated (e.g., neurologic symptoms) or to document stability of previously treated brain metastases; untreated or symptomatic brain metastases are excluded [1].

Pulmonary Assessment and ILD/Pneumonitis Risk Mitigation

- Baseline evaluation for ILD/pneumonitis: targeted pulmonary history and exam, resting pulse oximetry, and review of baseline thoracic imaging from staging scans to identify pre-existing interstitial changes. Participants with a history of non-infectious ILD/pneumonitis requiring steroids or current/suspected ILD are excluded [7].
- Educate participants on early symptom reporting (new or worsening cough, dyspnea, fever); establish a low threshold for prompt evaluation and imaging if symptoms arise during screening or prior to first dose. Suspected ILD warrants treatment hold pending evaluation per protocol [7].

Contraception and Reproductive Safety

- Verify and document reproductive status. For women of childbearing potential, a negative pregnancy test within 72 hours before C1D1 is required. Provide contraception counseling consistent with the embryo-fetal risk of T-DXd and applicable regulations; collect baseline contraceptive method in source documents and eCRF [7].

Documentation Standards

- Source documentation must support all eligibility criteria and baseline measures prior to dosing, maintained per ICH E6(R3) and 21 CFR Part 312. Baseline assessments should be completed and reviewed before infusion on C1D1; any clinically significant abnormalities must be resolved, deemed not clinically significant by the investigator, or otherwise addressed per protocol prior to dosing [1,2,3].

References

1. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
2. US Food and Drug Administration. Investigational new drug application. 21 CFR Part 312. Silver Spring (MD): FDA; 2024. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312
3. US Food and Drug Administration. Protection of human subjects. 21 CFR Part 50. Silver Spring (MD): FDA; 2024. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50
4. US Food and Drug Administration. Institutional review boards. 21 CFR Part 56. Silver Spring (MD): FDA; 2024. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-56
5. US Food and Drug Administration. Clinical trials registration and results information submission. 42 CFR Part 11. Washington (DC): HHS; 2024. Available from: https://www.ecfr.gov/current/title-42/chapter-I/subchapter-L/part-11
6. Bartley AN, Washington MK, Colasacco C, Ventura CB, Ismaila N, Benson AB, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: Guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. Arch Pathol Lab Med. 2016;140(12):1345–63. doi:10.5858/arpa.2016-0331-CP. Available

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7. US Food and Drug Administration. Enhertu (fam-trastuzumab deruxtecan-nxki) prescribing information. Silver Spring (MD): FDA; 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s030lbl.pdf
8. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47. doi:10.1016/j.ejca.2008.10.026. Available from: https://pubmed.ncbi.nlm.nih.gov/19097774/

12.2 Evaluations During Treatment

Overview

During each 21-day cycle, participants will undergo protocol-specified safety and disease evaluations timed to ensure fitness for dosing, consistent efficacy ascertainment, and timely detection of adverse events of special interest (AESIs: interstitial lung disease [ILD]/pneumonitis and left ventricular ejection fraction [LVEF] decrease). All pre-dose assessments must be reviewed on the day of administration before infusion. Adverse events (AEs) are graded per NCI CTCAE v5.0 and managed per protocol and the investigational product labeling; serious and unexpected events are reported in accordance with 21 CFR Part 312.32. Response assessments follow RECIST v1.1 with confirmation of objective responses on a subsequent scan at least 4 weeks later. Ongoing conduct adheres to ICH E6(R3) Good Clinical Practice (GCP) and applicable US IND requirements [1,2,3,4,5].

Cycle Day 1 Pre-Dose Assessments (Each Cycle, ±3 Days)

- Interval history and targeted physical examination with weight, vital signs (including temperature, heart rate, blood pressure, respiratory rate), and resting pulse oximetry; focused review of pulmonary symptoms (new/worsening cough, dyspnea, fever, chest pain) given ILD risk [1,3].
- ECOG performance status; concomitant medications and supportive care review (capture start/stop dates and indications) [1].
- Safety laboratories obtained within 72 hours before dosing: complete blood count with differential and platelets; comprehensive serum chemistry including electrolytes, renal function (creatinine, blood urea nitrogen), and hepatic panel (AST, ALT, alkaline phosphatase, total bilirubin). Abnormal or clinically changed results must be verified and reviewed to confirm retreatment criteria are met; dose delays or modifications follow protocol rules [1,3].
- 12-lead ECG if clinically indicated (e.g., new cardiac symptoms, initiation of QT-prolonging drugs); otherwise per routine surveillance at Day 1 as operationally feasible [1].
- Pregnancy test before dosing at each cycle for women of childbearing potential (negative result required), in addition to the mandatory baseline test [1,3].

Cardiac Monitoring

- LVEF assessment by transthoracic echocardiogram or MUGA at screening, on Cycle 5 Day 1, and every 4 cycles thereafter (e.g., C9D1, C13D1), using the same modality for each participant throughout the study. Review LVEF results before dosing at the corresponding visit; manage declines per protocol and investigational product guidance [1,3].
- ECG during treatment as described above; obtain additional ECGs for cardiac-related symptoms or as directed by concomitant medications [1].

Pulmonary/ILD Surveillance

- At every on-treatment visit, perform a targeted respiratory symptom assessment and resting pulse oximetry. For any suspicion of ILD/pneumonitis, withhold dosing immediately, obtain high-resolution CT of the chest (without contrast unless otherwise indicated), exclude alternative causes (e.g., infection), and initiate management per protocol and label, including corticosteroids as appropriate. Grade 2 or higher ILD/pneumonitis requires permanent discontinuation; Grade 1 permits re-initiation only after complete resolution and risk–benefit reassessment [3].

- All potential ILD cases are submitted to the independent ILD adjudication committee with standardized source materials (clinical narrative, imaging, oximetry, and relevant laboratory/microbiology results). Sites must cooperate with adjudication requests and document final outcomes and dates of resolution in the eCRF [1,3].

Imaging for Efficacy and Response Confirmation

- CT/MRI of disease sites every 6 weeks (±7 days) during the first year from Cycle 1 Day 1, then every 12 weeks (±7 days) thereafter, irrespective of treatment holds, until radiographic progression, new anticancer therapy, withdrawal of consent, or study end. Use consistent imaging modalities, acquisition parameters, and measurement techniques across time points and within participants. Confirm complete or partial responses on a subsequent scan at least 4 weeks after first documentation, per RECIST v1.1, for the primary endpoint by independent central review [4].

Infusion-Day Monitoring and Exposure Documentation

- Administer trastuzumab deruxtecan at 6.4 mg/kg IV every 3 weeks (first infusion ≥90 minutes; subsequent infusions ≥30 minutes if previously tolerated). Record actual dose (mg and mg/kg), lot number, infusion start/stop times, interruptions, and infusion-related reactions (IRRs). Monitor participants during infusion and as clinically indicated afterward for IRRs; manage per institutional standards and product guidance [3].
- Document dose modifications, delays (up to 28 days), and reasons. No re-escalation after dose reduction; no “make-up” doses or shortened intervals within a cycle [1,3].

Adverse Event Ascertainment and Reporting

- At each visit, assess and document all treatment-emergent AEs, SAEs, and AESIs from the last visit to the current assessment, with CTCAE v5.0 grading, onset/stop dates, seriousness, causality, action taken with study drug, and outcome. Capture supportive diagnostics (e.g., imaging for ILD, cardiac testing for LVEF events) [2,5].
- Between visits, participants must promptly report new or worsening symptoms, especially respiratory or cardiac. Sites will provide 24-hour contact instructions and document all unsolicited reports in source and eCRF. Investigators will notify the sponsor immediately of any SAE to enable IND safety reporting in accordance with 21 CFR 312.32; the sponsor will conduct ongoing aggregate safety review throughout the study [2].

Laboratory and Measurement Consistency

- Use the same laboratory (or harmonized methods) per site whenever feasible; apply the same reference ranges for longitudinal interpretation. For LVEF, maintain the same modality and, if possible, the same laboratory/reader for each participant. For imaging, maintain the same scanner and technique across time points when possible, and measure the same target lesions at each assessment per RECIST v1.1 [1,4].

Contraception and Reproductive Precautions During Treatment

- Reinforce embryo-fetal risk counseling at each cycle visit. Continue protocol-required contraception during treatment and for the post-treatment period defined in the protocol; document ongoing adherence in source and eCRF [3].

Documentation and Data Quality

- All evaluations and their timing relative to dosing must be contemporaneously documented in source records and transcribed to the eCRF. Deviations from scheduled assessments and windows must be minimized; when they occur, record the rationale, assess safety/endpoint impact, and report per GCP and IND requirements [1,2].

References

1. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
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12.3 Evaluations after Treatment

End-of-Treatment (EOT) Assessments

At permanent discontinuation of investigational treatment, perform the EOT visit as soon as feasible to capture final on-treatment safety, disease status, and disposition. Complete the following and document in source and eCRF [1,2]:

- Interval history, targeted physical examination, vital signs, weight, ECOG status, and review of concomitant medications.
- Adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs: interstitial lung disease [ILD]/pneumonitis; left ventricular ejection fraction [LVEF] decrease) with CTCAE v5.0 grading, onset/stop dates, seriousness, causality, action taken, and outcome; submit suspected ILD cases for independent adjudication per protocol [2,3,5].
- Safety labs (CBC with differential; comprehensive chemistry including hepatic and renal panels) as clinically indicated to characterize ongoing or new toxicities [1,2].
- Pregnancy test for women of childbearing potential (WOCBP) and contraceptive counseling for the protocol-defined post-treatment period [3].
- Cardiac assessments due at EOT per schedule: LVEF by the participant's assigned modality (ECHO or MUGA) if an on-treatment LVEF assessment is due or clinically indicated; 12-lead ECG if clinically indicated [1,3].
- Disease assessment: obtain CT/MRI if EOT coincides with a scheduled imaging time point within the protocol window to maintain consistency of efficacy endpoints; otherwise, continue per post-treatment disease follow-up schedule [4].
- Disposition: reason for discontinuation; plans for subsequent anticancer therapy or procedures; consent status for continued follow-up; preferred contacts for follow-up.

Safety Follow-up After Last Dose

A targeted safety assessment will occur 40 days (+7 days) after the last dose to capture delayed or evolving toxicities, with emphasis on ILD/pneumonitis and cardiac events [1–3]:

- Targeted physical exam; vital signs; interval medical history; review of concomitant medications; AE/SAE ascertainment with CTCAE v5.0 grading and outcomes [2,5].
- Directed tests guided by ongoing or new AEs/AESIs (e.g., high-resolution chest CT and oximetry for suspected ILD; LVEF and ECG for cardiac events; pertinent labs) until resolution or stabilization to baseline/chronic status. ILD/pneumonitis must be followed to complete resolution; Grade 2 or higher ILD requires permanent discontinuation and systemic corticosteroids per protocol and label [1–3].
- Pregnancy follow-up for any exposure during or within the protocol-specified post-treatment window, documenting outcomes per IND safety requirements [2,3].

Participants with unresolved Grade ≥3 AEs or any ongoing AESI will remain in active safety follow-up beyond Day 40 at intervals appropriate to the event until resolution or stabilization, with continued IND safety reporting as applicable [2].

Post-Treatment Disease Assessments

Participants who discontinue treatment without objective radiographic progression will continue protocol-mandated imaging to ensure unbiased assessment of antitumor activity and time-to-event endpoints [1,4]:

- CT/MRI every 6 weeks (±7 days) during the first year from Cycle 1 Day 1, then every 12 weeks (±7 days) thereafter, until objective progression by independent central review, start of new anticancer therapy, withdrawal of consent, loss to follow-up, or end of study, whichever occurs first [4].
- Use consistent imaging modalities and target lesion measurements across time points; confirm responses on a subsequent scan at least 4 weeks after first documentation per RECIST v1.1 [4].
- Record any subsequent anticancer therapy (start/stop dates, modality, and intent) at or after progression or EOT to support interpretation of overall survival (OS) and downstream outcomes [1,2].

Survival Follow-up

After completion of safety follow-up, ascertain survival status every 12 weeks (±14 days) by direct site contact (participant, caregiver) or permissible review of medical records and public sources, in accordance with GCP and IND requirements, until death, withdrawal of consent, loss to follow-up, or end of study [1,2]. At each contact:

- Update vital status and date last known alive.
- Document new anticancer therapies and significant procedures since the prior contact.
- Record intercurrent events relevant to interpretation of OS (e.g., non-cancer deaths) when available.

Management of Missed or Incomplete Post-Treatment Assessments

- Minimize missing data through proactive scheduling within visit windows and multiple documented contact attempts (e.g., calls, electronic messages, certified mail) using site SOPs consistent with ICH E6(R3) [1].
- When a post-treatment assessment is missed, document the reason, date of discovery, and corrective actions; obtain the assessment as soon as feasible within the allowable window. Out-of-window assessments should still be performed and recorded, with the deviation documented and impact assessed for safety and endpoint integrity per IND requirements [1,2].
- For participants lost to follow-up, document all reasonable efforts to re-establish contact and permissible records searches; record the date last known alive and status at that time [1,2].
- All incomplete assessments must be clearly flagged in source and eCRF; no retrospective data fabrication is permitted. Analytic handling of missing data will follow the Statistical Methods section; site teams must ensure timely, accurate documentation to support auditability and independent review [1,2].

Data Flow, Quality, and Ongoing Safety Review

- Transmit post-treatment imaging to the central review per charter timelines to maintain independence and response confirmation rules; ensure consistent acquisition parameters and lesion tracking [4].
- Continue expedited reporting of any post-treatment SAEs that meet IND criteria, including events related to prior investigational exposure such as ILD/pneumonitis, until the end of participant follow-up, per 21 CFR 312.32 [2].
- The sponsor will conduct ongoing aggregate safety review across treatment and post-treatment periods to identify potential safety signals and implement risk mitigation as needed in accordance with GCP and IND obligations [1,2].

References

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12.4 Participant Retention and Complete Follow-up

Purpose of Retention and Complete Follow-up

Participant retention and complete follow-up are essential to protect participant safety, ensure comprehensive ascertainment of the primary endpoint (confirmed ORR by independent central review) and secondary outcomes (including PFS, OS, duration of response, and safety), and to maintain the validity and interpretability of interim operational checks and final analyses in this Phase II single-arm study of investigational trastuzumab deruxtecan (T-DXd) in HER2-positive gastric/GEJ adenocarcinoma [1,2]. Retention activities will be conducted ethically and without coercion, consistent with Good Clinical Practice (GCP) and US regulations on informed consent, which affirm that participants may withdraw at any time without penalty or loss of benefits to which they are otherwise entitled [1,3].

Participant Retention Strategy

To promote retention across screening, treatment, safety follow-up, and long-term follow-up, sites will implement participant-centred operational practices in alignment with GCP and IND obligations [1,2]:

- Provide clear, comprehensible communication of study expectations during informed consent, including the visit schedule, disease assessments every 6 weeks in Year 1 then every 12 weeks, and the importance of continued follow-up even after treatment discontinuation [1,3].
- Offer participant-friendly scheduling within defined visit windows (±3 days for Day 1 treatment visits; ±7 days for imaging; +7 days for Day 40 safety follow-up; ±14 days for 12-week survival contacts), with flexible appointment times and coordination with routine oncology care to reduce travel and time burden [1].
- Use documented reminder systems (calls, texts, emails, calendars) and provide visit summaries to support adherence to upcoming assessments [1].
- Reimburse reasonable, IRB-approved, study-related expenses (e.g., transportation, lodging, meals, parking) where permitted, without creating undue influence, and consistent with site policies and local regulations [1,3].
- Maintain proactive communication between visits to address symptoms, adverse events of special interest (ILD/pneumonitis; LVEF decrease), concomitant medications, and supportive care, facilitating timely management and minimizing unplanned interruptions [1,2].
- Reinforce the value of continued outcome collection during interim assessment periods, treatment holds, after permanent treatment discontinuation, and throughout survival follow-up to support accurate estimation of ORR, PFS, OS, and safety outcomes [1,4,5].

Follow-up After Treatment Discontinuation

Participants who permanently discontinue investigational treatment should be encouraged to continue all protocol-specified follow-up and outcome assessments unless they withdraw consent for further data collection [1,3]. Continued follow-up after treatment stop supports intention-to-treat analyses, characterization of safety after exposure, assessment of durability of antitumor effect, and reduction of bias from informative missingness [1,4,5]:

- Conduct the End-of-Treatment (EOT) visit as soon as feasible to capture final on-treatment safety and disease status.
- Perform the safety follow-up visit 40 days (+7) after the last dose to collect adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs), with continued follow-up of unresolved or evolving AEs/AESIs until resolution or stabilization [2].
- Continue radiologic disease assessments per protocol (every 6 weeks in Year 1, then every 12 weeks) until objective progression, start of new anticancer therapy, withdrawal of consent, loss to follow-up, or study end.
- Ascertain survival status every 12 weeks (±14 days), including documentation of subsequent anticancer therapies, until death, withdrawal of consent, loss to follow-up, or study end [1,2].

Follow-up After Protocol Deviations or Intercurrent Events

For participants with protocol deviations or intercurrent events (e.g., missed visits, temporary treatment interruptions, noncompliance, prohibited medications, initiation of rescue or subsequent therapy, early permanent discontinuation, pregnancy, disease progression, unacceptable toxicity), sites should, unless precluded by safety concerns or withdrawal of consent, continue protocol-specified follow-up for clinically relevant outcomes and document the event and its timing [1,5]. Handling of intercurrent events, missing data, censoring, and analysis populations will align with the Statistical Methods section and the ICH E9(R1) estimands framework to preserve interpretability of ORR, PFS, and OS [5].

Follow-up After Withdrawal From the Study

- Withdrawal from study treatment only: If a participant stops T-DXd but agrees to ongoing participation, continue all protocol-specified safety, efficacy, and survival follow-up described above [1,2].
- Withdrawal from study assessments or follow-up: If a participant declines further visits but permits limited contact, collect allowable data through remote or records-based methods as described below, consistent with consent and regulations [1,3].
- Withdrawal of consent for further contact and/or data collection: Document the scope of withdrawal (contact, new data, medical record access, use of previously collected data) and adhere to the informed consent form (ICF), IRB approval, and applicable regulations. Previously collected data up to the point of withdrawal may generally be retained and used to preserve scientific integrity, unless the participant explicitly requests otherwise and applicable law permits removal; all determinations must be documented [1,3,6].

Lost to Follow-up Procedures

A participant will be considered lost to follow-up when the site is unable to establish contact or ascertain outcome data after completing reasonable, protocol-defined and documented contact attempts within and beyond visit windows, consistent with GCP and institutional policies [1].

- Perform and document multiple attempts using different modalities (e.g., phone calls on different days/times, secure electronic messages, letters/certified mail) and, if permitted by consent and regulation, outreach to approved alternative contacts or treating physicians, and review of available medical records or permissible public/institutional records to determine status [1,2,3].
- Record all attempts (dates, methods, outcomes, and responsible personnel) in source documents and study logs. Do not classify a participant as lost to follow-up until the defined attempts are exhausted and documented [1,2].

Outcome Data to Be Collected for Participants Who Discontinue or Deviate From the Protocol

The following data should continue to be collected according to the Outcomes and Endpoint Definitions, Schedule of Events, and Statistical Methods sections, unless the participant withdraws consent for further data collection [1,2,5]:

- Primary endpoint data: confirmed ORR by independent central review per RECIST v1.1.
- Key secondary endpoint data: PFS by independent central review; OS.
- Additional secondary outcomes: duration of response; safety outcomes (TEAEs, SAEs, AESIs: ILD/pneumonitis and LVEF decrease) with CTCAE v5.0 grading; concomitant medications; hospitalizations and major clinical events.
- Disease status: radiologic assessments per schedule until progression or new anticancer therapy; date of progression; date and reason for new therapy.
- Survival status and dates (including date last known alive).
- Subsequent anticancer/rescue therapies: type, start/stop dates, and intent.
- Pregnancy outcomes, if applicable.
- Reason for discontinuation, deviation, or incomplete follow-up.
- Note: No patient-reported outcomes or other exploratory biomarkers are planned in this protocol.

Minimization of Missing Data

Consistent with GCP and best practices for preventing missing data, the study will implement operational controls to minimize missingness that can compromise trial validity and introduce bias [1,4,5]:

- Real-time visit tracking with automated reminders; prompt site outreach after any missed or rescheduled visit to rebook within windows and to capture critical data as soon as feasible.
- Rapid, documented follow-up on incomplete assessments; acceptance of out-of-window assessments when necessary, with impact assessment and documentation per GCP [1].
- Investigator review of incomplete or inconsistent data at each visit; timely resolution of data queries.
- Central monitoring of missingness patterns (e.g., missed imaging, missed safety labs, lost-to-follow-up rate), with operational support and corrective/preventive actions for sites exhibiting concerning trends [1].

Remote or Alternative Follow-up Methods

Where permitted by the protocol, IRB approval, participant consent, and local regulations, the following alternative methods may be used to obtain essential outcomes and safety data while preserving data quality, confidentiality, and endpoint definitions [1,2]:

- Telephone or telemedicine visits for interval history, AE/SAE updates, and concomitant medications review.
- Electronic or phone-administered questionnaires for limited administrative information (no PRO endpoints are planned).
- Local laboratory testing and review of external medical records or imaging reports when participants cannot return to the site; imaging source data should still be transferred for independent central review when feasible to maintain consistency with RECIST v1.1 requirements.
- Contact with treating physicians and access to institutional or public records, as allowed by consent and regulation, to ascertain key outcomes (progression dates, survival status, subsequent therapies) [1,2].

All remote collections must be documented as source data with verification of identity, date, method, and responsible personnel, and transcribed to the eCRF consistent with endpoint definitions and chartered central review processes [1].

Participant Burden and Ethical Considerations

Retention procedures will minimize participant burden by leveraging visit windows, coordinated scheduling with standard care, reasonable reimbursement, and accommodations for accessibility and language needs where feasible, while strictly avoiding coercion or undue influence [1,3]. The right to withdraw at any time is preserved, and discussions about continued participation will be informational, not persuasive, in keeping with ethical principles and US regulations [1,3].

Documentation of Retention and Follow-up

Sites will contemporaneously document all retention and follow-up activities in source documents and study records consistent with GCP and IND recordkeeping [1,2]:

- Visit attendance, cancellations, rescheduling, and reminders sent.
- Participant communication preferences and updates.
- Reasons for missed assessments, discontinuation of treatment, discontinuation of assessments, withdrawal from follow-up, and withdrawal of consent (including scope).
- Post-discontinuation follow-up data collected and methods used (in-person, remote, records-based).
- Lost-to-follow-up attempts and outcomes.
- Protocol deviations related to incomplete follow-up and corrective actions.

These data will be captured in source documents, eCRFs, screening/enrolment logs, follow-up logs, monitoring reports, and the trial master file as applicable [1,2].

Monitoring of Retention and Follow-up Completeness

The sponsor and sites will monitor retention and follow-up completeness throughout the study via central and on-site review, including [1,2,4]:

- Retention rate; missed visit rate; treatment discontinuation rate; withdrawal rate; lost-to-follow-up rate.
- Completeness of primary endpoint data (central RECIST assessments and confirmation scans) and key secondary outcomes (PFS, OS).
- Completeness and timeliness of safety follow-up, particularly for AESIs (ILD/pneumonitis and LVEF decrease).
- Site-level patterns of missing data and delays in imaging or safety assessments.

Concerning patterns will trigger targeted site communication, retraining, corrective and preventive actions, enhanced monitoring, or additional operational support, as appropriate, to safeguard participant safety and data integrity [1,2].

Summary

The above retention and complete follow-up procedures operationalize GCP and US IND requirements to protect participants, respect autonomy, and ensure comprehensive capture of efficacy and safety outcomes. By promoting continued participation after treatment discontinuation, supporting alternative follow-up methods when appropriate, and systematically minimizing and accounting for missing data and intercurrent events, the study seeks to reduce bias, preserve the interpretability of ORR, PFS, and OS, and meet regulatory and scientific expectations for a Phase II evaluation of investigational T-DXd in HER2-positive gastric/GEJ adenocarcinoma [1,2,4,5].

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policy/guidance/guidance-on-withdrawal-of-subjects/index.html

13 ASSESSMENT OF TREATMENT EFFECT AND CLINICAL OUTCOMES

13.1 Definitions

Analysis Populations

- Full Analysis Set (FAS): all participants who receive any amount of investigational trastuzumab deruxtecan (T-DXd). The FAS is the primary efficacy analysis set for confirmed objective response rate (ORR) by independent central review (ICR) and for all time-to-event outcomes, consistent with an intention-to-treat principle for treated participants under a single-arm design [1,2].
- Safety Analysis Set (SAS): all participants who receive any amount of T-DXd. Safety will be summarized for treatment-emergent adverse events (TEAEs) collected from first dose through the protocol-specified safety observation period (40 days after last dose), with continued follow-up of ongoing or serious events per regulatory requirements [3–5].
- Response-Evaluable Set (RES): supportive analysis subset of the FAS comprising participants with measurable disease at baseline per RECIST v1.1 and at least one post-baseline ICR tumor assessment, or documented progression or death before the first post-baseline tumor assessment. The RES is used for sensitivity analyses of ORR and duration of response (DoR) [1,2].
- Per-Protocol Set (PPS): supportive analysis subset excluding participants with major protocol deviations expected to meaningfully affect efficacy evaluation (e.g., key eligibility violations, prohibited anticancer therapy before first tumor assessment, or grossly noncompliant imaging intervals precluding confirmation). PPS is used for sensitivity analyses only, not for primary inference [2].

Endpoint and Evaluable-Case Definitions

- Confirmed ORR (primary endpoint): proportion of participants with a confirmed complete response (CR) or partial response (PR) as best overall response per RECIST v1.1 by ICR, requiring confirmation of CR/PR on a subsequent scan at least 4 weeks after initial documentation and before unequivocal progression or initiation of new anticancer therapy [1,6].
- Progression-free survival (PFS, key secondary): time from first dose to radiographic progression per RECIST v1.1 by ICR or death from any cause, whichever occurs first. If no event occurs, participants are right-censored at the latest date of an adequate ICR tumor assessment without progression, applying prespecified censoring rules below [1,6,7].
- Duration of response (DoR, secondary): time from first documentation of CR or PR (that is subsequently confirmed) to progression per RECIST v1.1 by ICR or death, whichever occurs first. Responders without an event are right-censored at the date of the last adequate ICR tumor assessment showing no progression; initiations of new anticancer therapy without prior progression lead to censoring at the last adequate assessment before that therapy [1,6,7].
- Overall survival (OS, secondary): time from first dose to death from any cause; participants not known to have died are censored at the last date known alive [7].
- Safety (secondary): TEAEs, serious adverse events (SAEs), and adverse events of special interest (AESIs: interstitial lung disease [ILD]/pneumonitis and left ventricular ejection fraction [LVEF] decrease) collected and graded per NCI CTCAE v5.0; relatedness and reportability follow ICH-GCP and 21 CFR requirements [3–5,8].

Intercurrent Events and Estimand Strategies

- New anticancer therapy before response confirmation: counted as a non-responder for ORR (composite strategy); for PFS and DoR, if no prior progression, data are right-censored at the last adequate ICR assessment before starting new therapy (hypothetical strategy regarding the effect had new therapy not started) [1,2,6,7].

- New anticancer therapy after confirmed response: participant remains a responder for ORR; DoR is censored at the last adequate ICR assessment before new therapy in the absence of prior progression; PFS is censored similarly if no prior event [1,6,7].
- Treatment discontinuation without progression: continue protocol-mandated tumor assessments to avoid informative missingness; if no adequate post-baseline assessment occurs, ORR = non-responder, PFS censored at baseline (date of first dose) or last adequate baseline disease assessment per prespecified rules; OS continues until death or censoring [1,2,6,7].
- Death from any cause prior to response assessment: ORR = non-responder (composite strategy); PFS event at date of death; OS event at date of death [1,2,7].
- Missing or unevaluable tumor assessments: for ORR, absence of confirmation or missing assessments needed to establish response leads to non-response; for time-to-event endpoints, apply right-censoring at the last adequate ICR assessment without progression according to RECIST-compatible conventions and FDA guidance [1,6,7].
- Prohibited or confounding concomitant medications: if initiated before first on-study tumor assessment, participants remain in the FAS with ORR = non-responder; PPS sensitivity analyses may exclude such cases. Post-baseline corticosteroids or supportive care allowed per protocol do not themselves define events unless they meet RECIST progression criteria (e.g., unequivocal clinical progression) [1,2,6].
- Non-cancer deaths and unrelated clinical events: handled per endpoint definition (event for PFS/OS; non-response for ORR if before confirmation), consistent with a conservative, clinically oriented estimand aligned to decision-making in this setting [2,7].

Safety Definitions and Observation Periods

- Treatment-emergent adverse event (TEAE): any untoward medical occurrence emerging or worsening from first T-DXd dose through 40 days after the last dose (the protocol-specified safety observation period), irrespective of causality. Events ongoing at Day 40 are followed to resolution or stabilization; SAEs related to prior exposure are reportable per 21 CFR 312.32 beyond Day 40 as required [3–5].
- Serious adverse event (SAE): any event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event per regulatory definitions; expedited reporting follows 21 CFR 312.32 [4,5].
- Adverse events of special interest (AESIs):

- ILD/pneumonitis: suspected cases trigger immediate dose interruption, diagnostic work-up, and independent adjudication; grade per CTCAE v5.0 and manage per protocol with mandated permanent discontinuation for Grade ≥2; all ILD/pneumonitis cases are followed to complete resolution (not censored at Day 40 for follow-up) [3,8].
- LVEF decrease: assessed by ECHO or MUGA per schedule; grade cardiac dysfunction per CTCAE v5.0; management per protocol [3,8].

Time Origins, Assessment Adequacy, and Censoring Rules

- Time origin: the date of first T-DXd dose (Cycle 1 Day 1) is time zero for PFS, DoR (measured from first response date), and OS [6,7].
- Adequate tumor assessment: an ICR-reviewed imaging time point that meets RECIST v1.1 technical adequacy for lesion measurement and overall response assignment [1].
- Censoring rules (ICR-based):

- PFS: censor at the latest adequate ICR tumor assessment without progression if no event; censor at last adequate assessment before starting new anticancer therapy in the absence of prior progression; if no post-baseline adequate assessment and no death, censor at first dose date [1,6,7].
- DoR: for responders only, event is progression or death; if neither occurs, censor at the date of the last adequate ICR assessment showing no progression; initiation of new therapy without prior progression leads to censoring at the last adequate assessment before that therapy [1,6,7].
- OS: censor at last known alive date if death not documented [7].
- Confirmation window for ORR: ≥4 weeks after first documentation of CR/PR; the confirmatory scan must occur before unequivocal progression or new anticancer therapy to count as confirmed response [1,6].

Handling of Early Discontinuation and Missing Data

- Early discontinuation for reasons other than progression or death: participants remain in FAS/SAS; ORR = non-responder if response not confirmed; time-to-event endpoints are censored per rules above. Continued post-treatment imaging and survival follow-up are pursued per protocol to minimize bias, consistent with ICH E6(R3) and ICH E9(R1) principles on missing data prevention and estimands [1,2].
- Missed assessments and out-of-window imaging: late assessments are included if technically adequate and temporally interpretable by ICR; dates are analyzed as occurred, with censoring and confirmation requirements applied per RECIST and FDA guidance [1,6,7].
- Rescue treatment or subsequent therapy: handled as intercurrent events per strategies above; documentation of type and dates is required to inform censoring and sensitivity analyses [2,7].

Role of Independent Central Review

- The primary efficacy endpoints (confirmed ORR, PFS, DoR) are determined by an ICR blinded to site assessments and clinical data except for imaging and essential dates, to reduce assessment bias in a single-arm study. Local assessments guide clinical management but are not used for primary efficacy analyses [1,6,7].

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13.2 Methods for Evaluation of Clinical Outcomes and Disease/Condition Status

Overview and General Principles

Clinical outcomes and disease status will be evaluated using standardized, prespecified procedures aligned with RECIST v1.1 for antitumor activity, with independent central review (ICR) of imaging for

the primary and key secondary efficacy endpoints. Safety will be assessed systematically using NCI CTCAE v5.0. Methods emphasize consistency of timing, modality, equipment, operator/assessor training, and source documentation across visits and sites, with chartered processes for ICR and for independent adjudication of suspected ILD/pneumonitis to mitigate bias in this single-arm study [1–5,9,10].

Confirmation of Disease and HER2 Status

- Histopathologic confirmation of unresectable or metastatic gastric/GEJ adenocarcinoma is required prior to enrollment.
- HER2 positivity must be centrally confirmed on a new tumor biopsy obtained after progression on first-line trastuzumab-containing therapy, using ASCO-CAP criteria: IHC 3+ (uniform intense membrane staining in ≥10% of tumor cells) or IHC 2+ with HER2 gene amplification by ISH per validated assay and scoring protocols. The central laboratory will employ validated platforms, positive/negative controls, and dual-reader verification with discrepancy reconciliation to ensure analytic validity and reproducibility [6].
- The requirement for a post-progression biopsy reflects recognized intra-tumoral heterogeneity and potential loss of HER2 positivity after prior anti-HER2 exposure; central retesting reduces misclassification risk and supports interpretability of HER2-directed treatment effects [6].

Baseline and On-Study Tumor Imaging and Response Evaluation

- Imaging modalities and schedule:

- Contrast-enhanced CT of chest/abdomen/pelvis is the default modality; MRI is permitted when clinically indicated (e.g., contrast contraindication, superior lesion characterization). The same modality and acquisition parameters should be used longitudinally for each participant and lesion set [1–3].
- Imaging frequency: every 6 weeks (±7 days) in Year 1 from Cycle 1 Day 1, then every 12 weeks (±7 days) thereafter until radiographic progression, initiation of new anticancer therapy, withdrawal of consent, loss to follow-up, or end of study. Out-of-window scans should still be performed and submitted; ICR will apply RECIST-compatible rules for adequacy and timing [1–3].

- Lesion selection and measurement:

- Baseline measurable disease is required per RECIST v1.1. Target lesions (up to 5 total, maximum 2 per organ) will be selected at baseline by site radiology following RECIST v1.1 technical criteria; the same target lesions must be tracked at each time point unless unequivocally non-measurable or resected/ablated, in which case RECIST rules for replacement apply [1,2].
- Unidimensional measurements will be recorded to the nearest millimeter; non-nodal lesions require longest diameter; lymph nodes require short-axis measurement. Non-target disease and new lesions will be assessed qualitatively per RECIST v1.1 [1,2].

- Independent central review:

- All baseline and on-study imaging will be transferred to the ICR per an imaging charter specifying acquisition parameters, de-identification, transfer timelines, blinding procedures, quality control, adjudication of discordant reads, and response confirmation rules. The ICR will be blinded to local clinical assessments and outcomes except for dates required to establish assessment windows [2,3].
- Primary endpoint (confirmed ORR), key secondary (PFS), and DoR will be determined exclusively by ICR per RECIST v1.1, with confirmation of CR/PR on a subsequent adequate scan at least 4 weeks after initial documentation and before unequivocal progression or new anticancer therapy [1,2].

- Imaging quality assurance:

- Sites will use calibrated scanners, harmonized protocols (slice thickness ≤5 mm for body CT; consistent contrast timing), and standard positioning. Each site will designate a radiology lead responsible for training, adherence to the charter, and prompt remediation of image quality deficiencies identified by central QC [2,3].

Clinical Examinations and Performance Status

- At screening and each on-treatment visit, conduct interval medical history, targeted physical examination, weight, and vital signs including blood pressure, heart rate, respiratory rate, temperature, and resting pulse oximetry, with specific queries for pulmonary symptoms (cough, dyspnea, fever, chest pain) given ILD risk [4,5].

- ECOG Performance Status will be assessed by trained staff using standard definitions to ensure inter-rater reliability; the same assessor category (physician/qualified clinician) should be maintained longitudinally when feasible [4].

Cardiac Function and ECG Assessments

- LVEF measurement by transthoracic echocardiography (ECHO) or multigated acquisition (MUGA) at screening, on Cycle 5 Day 1, and every 4 cycles thereafter, using the same modality for each participant throughout. ECHO should use biplane Simpson's method with standardized endocardial border definition and image acquisition per ASE recommendations; LVEF will be reported as a percentage with laboratory-specific reference ranges. MUGA, when used, should follow radionuclide blood pool imaging standards for count statistics, region-of-interest placement, and background subtraction [5,7,8].
- A 12-lead ECG (triplicate at screening) will be obtained using calibrated equipment with standardized lead placement; additional ECGs will be performed during treatment if clinically indicated (e.g., new cardiac symptoms, QT-prolonging concomitants). All tracings must include date/time stamps and be archived as source [4,5].

Pulmonary/ILD Surveillance and Adjudication

- At every visit, assess respiratory symptoms and resting pulse oximetry. For any suspicion of ILD/pneumonitis, immediately interrupt dosing, obtain high-resolution chest CT (non-contrast unless otherwise indicated), and perform a directed work-up to exclude alternative etiologies (e.g., infection, heart failure, pulmonary embolism). Management follows protocol-specified actions aligned with the T-DXd product information: permanent discontinuation and systemic corticosteroids for Grade ≥2; Grade 1 may allow re-initiation only after complete resolution and careful risk-benefit assessment [5].
- All potential ILD cases will be submitted to an independent ILD adjudication committee per a prespecified charter defining case package content (clinical narrative, imaging, oximetry, laboratory/microbiology), review timelines, and outcome categories. Sites must provide required source materials and document final adjudication outcomes in the eCRF [5].

Laboratory and Other Safety Evaluations

- Safety laboratories at screening and pre-dose each cycle within 72 hours:

- Hematology: complete blood count with differential and platelets.
- Serum chemistry: electrolytes; renal function (creatinine, blood urea nitrogen); hepatic panel (AST, ALT, alkaline phosphatase, total and direct bilirubin); albumin; glucose.
- Additional tests as clinically indicated for adverse event evaluation (e.g., troponin/BNP for suspected cardiotoxicity; inflammatory markers if infection suspected) [4,5,10].

- Pregnancy testing:

- For women of childbearing potential, serum or urine pregnancy test at screening and prior to each dose; results must be negative before administration. Continue testing through the defined post-treatment period per protocol [5].

- Organ function thresholds at screening (as in Section 7.1):

- Absolute neutrophil count ≥1.5 × 10^9/L; platelets ≥100 × 10^9/L; hemoglobin ≥9.0 g/dL (transfusion permitted per protocol).
- Total bilirubin ≤1.5 × ULN (≤3 × ULN if Gilbert syndrome is documented); AST and ALT ≤3 × ULN (≤5 × ULN with liver metastases).
- Creatinine clearance ≥50 mL/min calculated by Cockcroft–Gault; electrolytes within normal limits or clinically acceptable per investigator with correction prior to dosing.
- LVEF ≥50% by ECHO or MUGA at screening, using site-consistent modality thereafter [5,9,11].

Assessment Timing, Visit Windows, and Handling of Missed/Out-of-Window Assessments

- Apply protocol-specified windows: Day 1 pre-dose assessments each 21-day cycle (±3 days); imaging every 6 weeks (±7 days) in Year 1 then every 12 weeks (±7 days); LVEF at screening, Cycle 5 Day 1, then every 4 cycles; safety follow-up 40 days (+7) after last dose; survival follow-up every 12 weeks (±14 days). Missed or delayed assessments should be

performed as soon as feasible and documented; technically adequate out-of-window imaging will be included in ICR per RECIST-compatible rules [1–5,10].

Assessor Training, Standardization, and Quality Control

- Site investigators, radiologists, cardiologists/echocardiographers, nuclear medicine physicians/technologists, and study coordinators will be trained on:

- RECIST v1.1 measurement rules; imaging acquisition per charter; image transfer and de-identification procedures.
- CTCAE v5.0 grading; AESI recognition and reporting; ILD evaluation algorithms and adjudication submissions.
- ECHO/MUGA LVEF measurement standards; ECG acquisition; laboratory collection and reporting; pregnancy testing procedures.

Training completion and competency will be documented; refreshers will be provided following monitoring findings or charter updates [1–5,7,8,10].

- Central processes:

- Imaging core lab will conduct incoming quality checks (DICOM header review, slice thickness, contrast timing, motion artifacts), manage blinded dual reads with adjudication, and issue corrective feedback to sites per the imaging charter [2,3].
- The ILD adjudication committee will operate under a written charter independent from site management decisions; adjudication outcomes will not delay urgent clinical care [5].

- Equipment calibration and method consistency:

- Maintain the same imaging modality and scanner model when feasible; for LVEF, use the same modality and, ideally, the same laboratory/reader longitudinally. Calibrate ECG machines and ensure consistent lead placement; laboratories should use harmonized methods and stable reference ranges over time [2,3,7,8,10].

Event Ascertainment and Documentation

- Efficacy events:

- Objective responses require ICR-confirmed CR or PR with a confirmatory scan ≥4 weeks after first documentation. PFS events are ICR-determined radiographic progression per RECIST v1.1 or death, whichever occurs first. DoR is measured from first confirmed response to ICR progression or death. All imaging dates, lesion measurements, and response assignments will be captured in source and eCRF, with linkage to imaging file identifiers [1,2].

- Safety events:

- TEAEs, SAEs, and AESIs will be collected from first dose through 40 days after last dose and graded per CTCAE v5.0, with seriousness, relatedness, action taken, and outcome; expedited reporting follows 21 CFR 312.32. Suspected ILD/pneumonitis and clinically significant LVEF decreases trigger protocol-specified evaluations and management, with follow-up to resolution or stabilization beyond Day 40 as needed [4,5,9].

Data Sources and Traceability

- Source documentation will include original radiology reports, imaging DICOM files, ECHO/MUGA raw data and final reports, ECG printouts, laboratory reports with collection times, clinic notes, vital sign flowsheets, and pregnancy test results. All entries will be contemporaneous, dated, signed, and attributable per ICH E6(R3). Data transcription to the eCRF will preserve dates/times to enable accurate time-to-event analyses and audit trails [10].

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13.3 Outcome and Response Criteria

Efficacy Outcome Classifications and Response Adjudication

- Assessment framework: Efficacy outcomes will be classified per RECIST v1.1, determined by independent central review (ICR) of contrast-enhanced CT/MRI. The same imaging modality and lesion set must be used longitudinally. Imaging occurs every 6 weeks (±7 days) in Year 1, then every 12 weeks (±7 days), until objective progression, start of new anticancer therapy, withdrawal of consent, loss to follow-up, or study end [1–3].
- Measurable disease at baseline: At least one RECIST-measurable lesion is required. Up to 5 target lesions (maximum 2 per organ) will be selected and measured unidimensionally (non-nodal: longest diameter; lymph nodes: short axis). Non-target disease and new lesions are assessed qualitatively per RECIST v1.1 [1,2].
- Objective response categories (per ICR, RECIST v1.1) [1,2]:

- Complete Response (CR): Disappearance of all target lesions; any pathological lymph nodes must have a short axis <10 mm; no new lesions; non-target disease resolves.
- Partial Response (PR): At least a 30% decrease from baseline in the sum of diameters of target lesions, no unequivocal progression of non-target disease, and no new lesions.
- Stable Disease (SD): Neither sufficient shrinkage for PR nor sufficient increase for PD, with no new lesions and no unequivocal progression of non-target disease, assessed at least once after baseline at ≥6 weeks to be considered disease control in summary outputs.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions (minimum absolute increase of 5 mm) from nadir, or unequivocal progression of non-target disease, or appearance of one or more new lesions (including unequivocal new bone lesions with soft-tissue component) [1,2].

- Best overall response (BOR): The best category (CR, PR, SD, PD, or Not Evaluable [NE]) recorded from baseline until first objective progression or start of new anticancer therapy, inclusive of required confirmation rules. SD requires a minimum interval of ≥6 weeks from first dose to the first assessment showing SD. NE is used when no adequate post-baseline assessment is available or when assessments are technically inadequate [1,2].

- Confirmation of response for the primary endpoint: CR/PR must be confirmed on a subsequent adequate scan at least 4 weeks after first documentation and before unequivocal progression or initiation of new anticancer therapy to be counted in confirmed ORR. Unconfirmed CR/PR will not count toward the primary endpoint but may inform BOR narratives [1,2].
- New lesion handling and equivocal results: New lesions must be unequivocal on ICR; when findings are equivocal (e.g., likely artifact, inflammatory change), classification should favor non-progression with mandated repeat imaging at the next scheduled time point or earlier if clinically indicated. If technical inadequacy or motion/artifact precludes assessment, the time point is NE and not used to define progression or response; subsequent adequate imaging will determine status [1–3].
- Clinical progression: Clear, objective, and substantial clinical deterioration attributable to disease may be classified as progression by ICR if supported by imaging or unequivocal clinical evidence consistent with RECIST v1.1 guidance; such events and documentation requirements are specified in the imaging charter [1,3].

Primary Endpoint Responder Definition

- Confirmed ORR: Proportion of participants with ICR-determined confirmed CR or confirmed PR as BOR per RECIST v1.1, requiring confirmation ≥4 weeks after first documentation and before new anticancer therapy or unequivocal progression. Participants without any post-baseline adequate assessment, with missing confirmation, or with death before confirmation are counted as non-responders for ORR [1,2,4].

Time-to-Event Endpoint Event Definitions and Censoring Rules

- Progression-free survival (PFS; key secondary): Time from first dose to ICR-determined radiographic progression per RECIST v1.1 or death from any cause, whichever occurs first. If neither occurs, censor at the date of the last adequate ICR tumor assessment showing no progression. If new anticancer therapy starts without prior progression, censor at the last adequate assessment before that therapy. If no post-baseline adequate assessment and no death, censor at first dose date [1,2,4,5].
- Duration of response (DoR; secondary): For responders (confirmed CR/PR) only, time from first documentation of the response (that is subsequently confirmed) to ICR progression or death, whichever occurs first. If neither occurs, censor at the last adequate ICR assessment showing no progression; if new anticancer therapy starts before progression, censor at the last adequate assessment before that therapy [1,2,5].
- Overall survival (OS; secondary): Time from first dose to death from any cause; otherwise censor at the last date known alive. Non-cancer deaths are events for OS and PFS. Time origins and censoring follow consensus good-practice conventions for oncology trials [4,5].

Safety Outcome Classifications

- Safety observation window: Treatment-emergent adverse events (TEAEs) are collected from first dose through 40 days after the last dose; events ongoing at Day 40 are followed until resolution or stabilization. Serious adverse events (SAEs) that are related to prior investigational exposure remain reportable per 21 CFR 312.32 beyond Day 40 as required [6].
- Adverse event grading and attribution: TEAEs, SAEs, and adverse events of special interest (AESIs) are graded per NCI CTCAE v5.0; investigators will assign seriousness, severity, causality, action taken, and outcomes. Incidence will be summarized by maximum grade, relationship, and outcome [6,7].
- AESIs and specific criteria:

- Interstitial lung disease (ILD)/pneumonitis: Any suspected ILD/pneumonitis leads to immediate dose interruption, standardized diagnostic work-up, and independent adjudication. Outcomes are classified by CTCAE grade and adjudication category; Grade ≥2 requires permanent discontinuation and systemic corticosteroids. All ILD/pneumonitis cases are followed to complete resolution; recurrence upon rechallenge after Grade 1 will be recorded as an event of special interest [7].
- Left ventricular ejection fraction (LVEF) decrease: LVEF is assessed by echocardiography or

MUGA using a consistent modality per participant. Decreases are graded per CTCAE v5.0; clinically significant decreases (e.g., symptomatic heart failure or LVEF below lower limit of normal with ≥10% absolute drop from baseline) are recorded as AESIs. Management and re-assessment follow protocol guidance; events are captured through Day 40 and followed thereafter if unresolved [7].

Assessment Timing, Confirmation, and Assessor Qualifications

- Timing and windows: Tumor imaging every 6 weeks (±7 days) in Year 1, then every 12 weeks (±7 days) thereafter. Confirmatory scans for CR/PR must occur ≥4 weeks after first documentation. Post-treatment disease assessments continue per schedule until objective progression or start of new anticancer therapy to ensure unbiased PFS and DoR estimation [1–3].
- Assessor qualifications and blinding: ICR will be conducted by board-certified radiologists trained in RECIST v1.1, operating under a written imaging charter with blinded dual reads and adjudication of discordances. Site radiologists and investigators use RECIST v1.1 for clinical management but local reads do not determine primary/secondary efficacy outcomes [2,3].
- Consistency and quality: Sites must maintain consistent imaging modalities, acquisition parameters, and lesion selection across time points. Equivocal or technically inadequate assessments are minimized through chartered quality controls; when they occur, they are classified as NE and not used to define response or progression [2,3].

Handling of Intercurrent Events, Missing or Out-of-Window Assessments

- New anticancer therapy before confirmation or progression: Counts as non-response for ORR; for PFS/DoR, censor at the last adequate ICR assessment before new therapy if no prior event [1,4,5].
- Death prior to first post-baseline assessment: Non-responder for ORR; event for PFS and OS at the date of death [4,5].
- Missing/unevaluable tumor assessments: Missing confirmation or inadequate scans preclude confirmed responses and contribute to non-response for ORR; time-to-event endpoints are right-censored at the last adequate ICR assessment without progression per predefined rules. Out-of-window but technically adequate scans are included with dates as performed; RECIST-compatible timing and confirmation rules are applied by ICR [1,2,4,5].

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14 ADVERSE EVENT REPORTING REQUIREMENTS

14.1 Definitions

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a participant administered an investigational product, which does not necessarily have a causal relationship with the treatment. AEs include any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product, whether or not related to it [1,3]. Disease progression itself is not an AE; however, clinically significant signs, symptoms, complications, or laboratory abnormalities that arise in association with disease progression must be recorded as AEs when medically relevant (e.g., new or worsening pain requiring intervention, obstructive complications, pathologic fracture, tumor-related bleeding) [1,4].

AEs encompass:

- New symptoms or clinically meaningful worsening of pre-existing conditions beyond expected disease fluctuation, as judged by the investigator [1].
- Abnormal laboratory values, vital signs, imaging, or other test results that are clinically significant, require evaluation, or prompt medical intervention or therapy modification [1,3].
- Treatment-emergent complications (e.g., infusion reactions, hypersensitivity), protocol-required procedure complications (e.g., biopsy-related bleeding, pneumothorax), and events related to study assessments (e.g., contrast reactions) [1].
- Events occurring after the first dose through the prespecified safety observation period, irrespective of causality; events ongoing beyond that window are followed to resolution or stabilization per protocol and applicable regulations [1,2,5].

Events Not Considered AEs

The following are not considered AEs unless they are associated with a complication or a clinically significant change in condition:

- Pre-existing conditions that remain stable or unchanged in severity, frequency, or clinical significance during the study [1].
- Elective or pre-planned procedures or hospitalizations (e.g., scheduled port placement, planned surgery) that are not due to a worsening condition; however, any complications of these procedures must be reported as AEs/SAEs as appropriate [1,4].
- Routine diagnostic or monitoring procedures performed per protocol (e.g., imaging, biopsies) in the absence of complications; only procedure-related complications or clinically significant findings are reportable as AEs/SAEs [1,4].

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above. “Life-threatening” refers to an event in which the participant was at immediate risk of death at the time of the event; it does not include hypothetical risk had the event been more severe [2–4]. Events judged serious by either the investigator or the sponsor must be classified as SAEs, even if they do not strictly meet the above outcomes, when they are medically important or require intervention to prevent a serious outcome [2–4].

Examples of important medical events that may be SAEs include intensive treatment for severe allergic bronchospasm, blood dyscrasias requiring urgent intervention, or seizures not resulting in hospitalization but requiring acute management [3,4].

Expectedness

Expectedness is assessed against the current, approved reference safety information for the investigational product, typically the Investigator's Brochure (IB) for an unapproved use. An expected adverse event is one that is consistent in nature, severity, specificity, or frequency with the information described in the IB or other authoritative product information available to investigators. An unexpected adverse event is one for which the nature, severity, specificity, or frequency is not consistent with the applicable reference safety information; unexpectedness is a criterion for expedited reporting when combined with seriousness and a reasonable possibility of a causal relationship (i.e., a SUSAR under ICH) [2–4].

Attribution

Causality assessment is the investigator's primary responsibility, with the sponsor providing additional evaluation as needed. The standard for regulatory reporting is whether there is a "reasonable possibility" that the investigational product caused the event, meaning there is evidence to suggest a causal relationship [1,2,4]. For protocol reporting and analysis, attribution will use the following categories:

- Not Related: No reasonable possibility of association with the investigational product; the event is clearly and solely attributable to alternative causes (e.g., underlying disease, concomitant illness, or medications) and lacks temporal or biological plausibility [1,2].
- Unlikely: A causal relationship is improbable based on timing, dose/exposure, lack of biologic plausibility, or the presence of more plausible alternative explanations; evidence does not suggest a causal link [1,2,4].
- Possibly Related: A reasonable potential relationship exists; timing is compatible and a causal role cannot be excluded, though alternative causes may be present and evidence may be limited [1,2,4].
- Related: The temporal association, dechallenge/rechallenge information (if available), known pharmacology or class effects, and clinical context support a clear causal association with the investigational product [1,2,4].

Severity (graded per NCI CTCAE v5.0) is distinct from seriousness and causality; all three dimensions (severity grade, seriousness, and attribution) must be assessed and documented for each event [5].

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14.2 Procedures for AE and SAE Recording and Reporting

Recording and Reporting Responsibilities

Investigators will actively assess participants for adverse events (AEs) at every study visit from the time informed consent is obtained until completion of protocol-specified follow-up. AE/SAE identification may arise from multiple sources, including participant self-report, caregiver observations, physical examinations, clinical assessments, laboratory abnormalities, imaging, hospital or emergency department records, or communications from other healthcare providers. All identified AEs

and SAEs must be documented in the source records and transcribed into the case report form (CRF)/electronic data capture (EDC) and any sponsor-mandated safety tools with complete, contemporaneous, and attributable entries, in accordance with ICH E6(R3) Good Clinical Practice [1].

For operational consistency, the treatment-emergent AE (TEAE) collection window is from first dose of investigational trastuzumab deruxtecan (T-DXd) through 40 days after the last dose, irrespective of causality; events ongoing at Day 40 are followed to resolution or stabilization. Pre-treatment medical conditions and symptoms identified after consent but before first dose should be recorded as baseline medical history unless they result from protocol procedures, in which case they are recorded as AEs. SAEs that are related to prior investigational exposure remain reportable beyond Day 40 as required under the IND regulations [1,2,4].

Investigators are responsible for prompt, accurate, and complete reporting of all SAEs to the sponsor, Sample Pharma Co., Ltd., within 24 hours of awareness, including all required data elements (diagnosis or sign/symptom term, onset/stop dates and times, seriousness criteria, severity grade, causality, action taken with T-DXd, medical management, outcome, and relevant diagnostic results). Investigators must provide follow-up information and requested source documents, including narratives for SAEs, until the event resolves, stabilizes, or the participant is lost to follow-up. Investigators will also report unanticipated problems involving risks to subjects or others to their IRB(s) according to 21 CFR Part 56 and local IRB requirements [1,2,7].

The sponsor will conduct ongoing safety review throughout the study and will determine expectedness against the current Investigator's Brochure (reference safety information) and whether there is a reasonable possibility of a causal relationship to T-DXd, consistent with ICH E2A and FDA IND safety reporting requirements (21 CFR 312.32). The sponsor will submit expedited IND safety reports to FDA for any SUSARs within the required timelines (7 calendar days for unexpected fatal or life-threatening suspected adverse reactions; 15 calendar days for other reportable serious and unexpected suspected adverse reactions) and will inform all investigators per regulation [2–4]. Investigators will comply with any sponsor or regulatory requests for additional information to support timely safety evaluation and reporting.

Given the known risk profile of HER2-directed antibody-drug conjugates, any suspected interstitial lung disease (ILD)/pneumonitis must trigger immediate dose interruption, expedited notification to the sponsor within 24 hours regardless of perceived seriousness, and protocol-specified diagnostic evaluation, with independent adjudication per charter. All ILD/pneumonitis events will be followed to complete resolution; Grade ≥2 requires permanent discontinuation and systemic corticosteroids as clinically indicated [1,6].

Severity Grading and Use of CTCAE

AE severity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0, which defines a standardized scale from Grade 1 (mild) to Grade 5 (death related to AE). Investigators must assign a single CTCAE grade at each assessment for each AE, document the maximum grade, and update grades over time as the clinical course evolves. When a specific AE term is present in CTCAE, the corresponding grading criteria must be applied. When a specific AE is not listed, investigators will determine the grade using the CTCAE generic rubric, considering the degree of functional impairment, need for medical or procedural intervention, and clinical significance to ensure consistent classification across participants and sites [5].

Severity grading is independent of seriousness and causality; investigators must assess and record all three attributes (severity, seriousness, causality) for each AE. For AESIs in this study (ILD/pneumonitis and decreases in left ventricular ejection fraction [LVEF]), investigators must apply the relevant CTCAE v5.0 terms and grading criteria (e.g., pneumonitis, dyspnea, hypoxia; cardiac failure, LVEF decrease) and follow protocol-mandated management and reporting procedures, including expedited reporting when seriousness and unexpectedness criteria are met under 21 CFR 312.32 [2,5,6].

Custom AE Grading System (for Non-CTCAE Events)

For AEs that are not represented in CTCAE v5.0, the following study-specific grading framework will be used solely to ensure continuity and uniformity of severity assessment:

- Grade 1 (mild): Transient or mild symptoms; minimal or no interference with activities of daily living (ADLs); no intervention indicated.
- Grade 2 (moderate): Limitation of instrumental ADLs; local or noninvasive intervention indicated; no major therapeutic intervention required.
- Grade 3 (severe): Medically significant but not immediately life-threatening; significant limitation of self-care ADLs; hospitalization or prolongation of hospitalization indicated; invasive or intensive therapeutic intervention often required.
- Grade 4 (life-threatening): Life-threatening consequences; urgent intervention required to prevent death or severe permanent harm.
- Grade 5 (death): Death related to the AE.

These custom definitions apply only when no CTCAE term adequately captures the event. If a CTCAE term becomes applicable as additional clinical information emerges, the event should be re-mapped and graded per CTCAE v5.0. Regardless of grading framework, investigators must continue to determine seriousness per regulatory definitions and report SAEs to the sponsor within 24 hours; the sponsor will fulfill expedited reporting obligations under 21 CFR 312.32 and ICH E2A as applicable [2–5].

References

1. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
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14.3 Reporting to the Institutional Review Board (IRB)

Overview and Scope

Each investigative site must report serious adverse events (SAEs) and other unanticipated problems involving risks to subjects or others to its Institutional Review Board (IRB) promptly, using the IRB's required submission mechanism and timelines, and in a manner that is consistent with the study's safety reporting framework and applicable US regulations and Good Clinical Practice (GCP) [1–3]. Under 21 CFR Part 56, IRBs must have written procedures for ensuring prompt reporting, and investigators are required to adhere to those procedures. Unanticipated problems are those that are unexpected, related or possibly related to participation, and suggest that the research places subjects or others at a greater risk of harm than previously known or recognized [2,4].

Events Requiring IRB Submission

Sites must submit to the IRB:

- Any SAE that, in the investigator's judgment, meets the IRB's definition of an unanticipated problem involving risks to subjects or others (UPIRTSO), including deaths and life-threatening events with a reasonable possibility of relation to the investigational product or study procedures [2,4].
- Any important new safety information from the sponsor's IND safety reports that represents an unanticipated problem and may affect participants' willingness to continue (submit with the investigator's assessment of relevance to the local study population; do not forward routine external reports lacking local relevance) [3,4].
- Any protocol change implemented to eliminate an apparent immediate hazard to participants (report promptly after implementation) [1].
- Any other safety information the IRB specifically requires per its policies (e.g., trending of related Grade 3–4 AEs, hospitalizations related to study procedures) [1,2].

Reporting Timelines

- Initial report: Investigators must notify the IRB as soon as possible and within the IRB's specified deadline for prompt reporting of unanticipated problems; IRB policies typically include accelerated timelines for deaths or life-threatening events. Sites must follow their IRB's written procedures without exception [1,2,4].
- Follow-up report(s): Submit updated or clarifying information to the IRB as it becomes available until the event is resolved or stabilized, including final outcome and any changes to risk/benefit or study conduct [2,3].

These IRB submissions occur in parallel with, and do not replace, expedited safety reporting to the sponsor and FDA under the IND (21 CFR 312.32) [3].

Required Content and Documentation

Each IRB submission must use the IRB's forms/portal and include, at minimum:

- Study identifiers: protocol number SP-TDXD-GC-201; sponsor Sample Pharma Co., Ltd.; IND number if required by the IRB; site and IRB protocol numbers; subject ID (coded) [1,2].
- Event information: diagnosis (or primary signs/symptoms if not yet diagnosed); onset and resolution dates; CTCAE v5.0 severity grade; seriousness criterion; outcome (including death date, if applicable); action taken with investigational trastuzumab deruxtecan (T-DXd); relevant concomitant medications and medical history; pertinent tests, imaging, and hospitalization details [2].
- Attribution and expectedness: investigator's causality assessment (reasonable possibility related to T-DXd and/or study procedures) and expectedness versus the current Investigator's Brochure/reference safety information; rationale supporting the assessment [2–4].
- Narrative: concise clinical course, diagnostic evaluation, management, and justification for why the event constitutes (or does not constitute) an unanticipated problem involving risks to subjects or others [2,4].
- Supporting documents: de-identified source records as required by the IRB (e.g., hospitalization discharge summary, imaging reports), and any relevant sponsor safety communications (e.g., applicable IND safety report) [1–4].

Ongoing Updates and Risk Communication

- Provide timely follow-up updates to the IRB until the event is resolved or stabilized, including results of additional evaluations, adjudication outcomes for suspected interstitial lung disease (ILD)/pneumonitis, and any changes to the study risk mitigation or consent materials [2,3].
- Submit proposed revised consent forms or participant information if new information may affect willingness to continue, and implement consent changes per IRB approval requirements; urgent changes necessary to eliminate immediate hazards may be implemented before IRB approval but must be reported promptly thereafter [1,2].

Alignment With Study Safety Framework

- IRB reporting must remain aligned with the protocol's AE/SAE reporting requirements, CTCAE v5.0 grading, and the IND expedited reporting framework. The sponsor will provide investigators with IND safety reports; investigators must review these and submit to the IRB only those that represent unanticipated problems with local relevance, accompanied by the investigator's assessment as required by IRB policy [2–4].
- For suspected ILD/pneumonitis and clinically significant LVEF decreases (adverse events of special interest), ensure expedited sponsor notification per protocol and submit to the IRB when events meet the IRB's criteria for unanticipated problems; include the ILD adjudication outcome in follow-up reports when available [2,3].

Submission Procedures and Recordkeeping

- Use the site IRB's designated submission pathway (e.g., electronic portal or forms) and retain acknowledgments, determinations, and all submitted materials in the site regulatory file. Maintain a log of all IRB safety submissions with dates of initial and follow-up reports to ensure traceability for monitoring and audit [1,2].
- Summarize AEs/SAEs and unanticipated problems in continuing review or annual progress reports as required by the IRB, ensuring consistency with the sponsor's safety data and the study's cumulative risk assessment [1,2].

References

1. US Food and Drug Administration. Institutional Review Boards. 21 CFR Part 56. Silver Spring (MD): FDA; 2024. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-56
2. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
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4. Office for Human Research Protections (OHRP). Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events. Rockville (MD): HHS; 2007 (updated). Available from: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

14.4 Reporting to the Food and Drug Administration (FDA) and Other Applicable Authorities

IND holder responsibilities and scope

Sample Pharma Co., Ltd. is the IND holder and is responsible for identifying, evaluating, and expeditiously communicating to FDA and all investigators any safety information that meets the criteria for IND safety reporting under 21 CFR 312.32. Reportable events are serious, unexpected suspected adverse reactions for which there is a reasonable possibility that investigational trastuzumab deruxtecan (T-DXd) caused the event, as well as other safety findings that suggest a significant risk to participants, including findings from aggregate analyses or new nonclinical data that indicate a risk in humans [1–3]. Expectedness is assessed against the current Investigator's Brochure (reference safety information); "reasonable possibility" means evidence to suggest a causal relationship [1–3].

Events that trigger expedited IND safety reports

The sponsor will submit expedited reports to FDA and notify all investigators when any of the following are identified during the study or from any other source relevant to the investigational product [1–3]:

- Any suspected adverse reaction that is serious and unexpected (i.e., a SUSAR), including:
  - Any unexpected fatal or life-threatening suspected adverse reaction [1–3].
  - Any other serious and unexpected suspected adverse reaction [1–3].

- Aggregate finding: A clinically important increased rate of a serious suspected adverse reaction compared with the rate listed in the Investigator's Brochure, suggesting a significant risk in humans [1–3].
- Findings from animal or in vitro testing that suggest a significant risk to humans exposed to the investigational product (e.g., mutagenicity, teratogenicity, or carcinogenicity) [1].
- A clinically significant hazard associated with the investigational product or protocol (e.g., safety-related dosing errors) that suggests risk to participants [2,3].

For this protocol, suspected interstitial lung disease (ILD)/pneumonitis and clinically significant decreases in left ventricular ejection fraction (LVEF) are adverse events of special interest. If such events are serious, unexpected, and there is a reasonable possibility of relation to T-DXd, they meet criteria for expedited reporting. Unexpected fatal or life-threatening presentations (e.g., acute, severe pneumonitis with respiratory failure) trigger the 7-day reporting timeline below [1–3].

Reporting timelines and follow-up

- Unexpected fatal or life-threatening suspected adverse reactions: as soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information; additional relevant information will be submitted as a follow-up report within 15 calendar days [1–3].
- All other reportable serious and unexpected suspected adverse reactions and other qualifying significant risk findings: as soon as possible but no later than 15 calendar days after the sponsor's initial receipt of the information [1–3].
- Follow-up information that materially impacts the assessment of a reportable event (e.g., new outcome, diagnostic clarification, causality reassessment) will be submitted promptly, generally within 15 calendar days of receipt, clearly identifying the submission as a follow-up to the original safety report [1–3].

Reportable safety information	Criteria	Timeline to FDA
Unexpected fatal or life-threatening suspected adverse reaction	Serious + unexpected + reasonable possibility related	≤7 calendar days, with 15-day follow-up [1–3]
Other serious and unexpected suspected adverse reaction	Serious + unexpected + reasonable possibility related	≤15 calendar days [1–3]
Aggregate analysis suggests significant risk	Clinically important increased rate of a serious suspected adverse reaction	≤15 calendar days [1–3]
Nonclinical finding indicates significant human risk	Animal/in vitro data suggesting significant risk	≤15 calendar days [1]

Content, format, and submission mechanism

- Each IND safety report will include a concise narrative, an analysis of the significance of the reportable information, relevant clinical and diagnostic data, and the sponsor's assessment of causality and expectedness. When multiple similar events suggest a safety signal, analyses across the clinical program will be included, consistent with FDA guidance and ICH E2A [2,3].
- Submissions to FDA will be made to the active IND via the Electronic Submissions Gateway using eCTD format, with appropriate Module 1 placement for IND safety reports and follow-ups, and an accompanying Form FDA 1571 as required for the submission package. The sponsor will follow the current eCTD Technical Conformance Guide for file formats, structure, and regional metadata, and will ensure that the submission is clearly identified as an IND safety report or follow-up [4].
- The sponsor will provide written IND safety reports (or written notification directing investigators to the report) to all investigators participating in the study within the same timelines used for FDA reporting, enabling investigators to meet their obligations to notify their IRBs of unanticipated problems as applicable [1,2].

Ongoing safety surveillance and coordination

- Sample Pharma Co., Ltd. will conduct ongoing, systematic review of all serious adverse events, adverse events of special interest (ILD/pneumonitis; LVEF decrease), and any new safety information from all sources to determine if expedited reporting criteria are met.

Decisions reflect an integrated assessment of seriousness, expectedness relative to the IB, and reasonable possibility of causality, including evaluation of aggregate data across sites and studies when applicable [1–3].

- These FDA submissions operate in parallel with site-level SAE reporting to the sponsor and IRB reporting requirements described elsewhere in the protocol. Safety communications to FDA will be coordinated with updates to investigators, protocol amendments implemented to eliminate immediate hazards (submitted per 21 CFR 312.30), and revisions to the Investigator's Brochure and informed consent documents when new safety information affects the risk/benefit profile [1,2].
- The sponsor will include cumulative safety information in the IND annual report (submitted within 60 days of the IND anniversary date) per 21 CFR 312.33, including a summary of adverse events, IND safety reports, and any significant preclinical findings, maintaining alignment with the protocol's broader safety oversight framework [1].

Other applicable authorities

- This multicenter study is conducted exclusively at U.S. sites under a U.S. IND; all expedited safety reporting will comply with U.S. requirements. If additional non-FDA authorities become applicable (e.g., state requirements or other national authorities in the event of site additions), the sponsor will comply with their safety reporting regulations and formats in parallel with FDA submissions, without delaying required U.S. reporting [1–3].

References

1. US Food and Drug Administration. Investigational new drug application. 21 CFR Part 312 (including §§312.30–312.33). Silver Spring (MD): FDA; 2024. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312
2. US Food and Drug Administration. Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies. Final guidance. Silver Spring (MD): FDA; 2025. Available from: https://www.fda.gov/media/150356/download
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4. US Food and Drug Administration. eCTD Technical Conformance Guide. Revision, February 2024. Silver Spring (MD): FDA; 2024. Available from: https://www.fda.gov/media/136174/download

14.5 Reporting requirements and Sponsor notification

Reporting Requirements

All adverse events (AEs) and serious adverse events (SAEs) observed or reported from the time of first dose of investigational trastuzumab deruxtecan (T-DXd) through 40 days after the last dose must be documented in source records and captured in the case report form/electronic data capture (CRF/EDC), graded per NCI CTCAE v5.0, and assessed for seriousness and causality by the investigator, consistent with ICH E6(R3) and ICH E2A [1–3,5]. SAEs considered related to prior investigational exposure remain reportable beyond Day 40, in accordance with 21 CFR 312.32 and FDA guidance on sponsor safety reporting; all SAEs ongoing at Day 40 must be followed to resolution or stabilization [2,4].

Investigators are responsible for prompt notification of all SAEs to the sponsor (Sample Pharma Co., Ltd.) within 24 hours of awareness, irrespective of expectedness, with subsequent follow-up information provided as it becomes available until the event is resolved, stabilized, or otherwise explained [1–4]. The sponsor will determine expectedness against the current Investigator's Brochure and evaluate whether there is a reasonable possibility of a causal relationship to T-DXd for regulatory reporting under 21 CFR 312.32 and ICH E2A [2–4].

Serious Adverse Event (SAE) Reporting Timelines and Attribution

- Initial SAE notification to the sponsor: within 24 hours of site awareness, regardless of attribution or expectedness [1–4].
- Follow-up information: submit promptly as additional data become available until outcome is known or the event stabilizes [1–4].
- Attribution: Investigators must assign causality using protocol categories (Not Related, Unlikely, Possibly Related, Related). For expedited reporting to regulators, the sponsor determines whether a “reasonable possibility” exists that T-DXd caused the event, per ICH E2A and 21 CFR 312.32 [2–4]. Attribution categories do not alter the obligation to report SAEs within 24 hours; all SAEs require 24-hour notification. Grade 2 or Grade 3 AEs that meet seriousness criteria (e.g., hospitalization) must be reported within 24 hours regardless of attribution category [2–4].

Expedited Reporting Procedures

- Sites affiliated with the primary research institution: submit SAEs via the sponsor-designated safety reporting channel and the study EDC SAE module, as specified in the site regulatory binder; telephone or email notification to the sponsor’s 24-hour safety contact listed in the binder must occur within 24 hours of awareness, followed by the completed sponsor SAE form and supporting source documents per sponsor instructions [1–4].
- External or affiliate sites: follow the same 24-hour notification requirement using the sponsor-designated safety contact and EDC SAE module; if EDC is unavailable, transmit the completed sponsor SAE form and required source documentation using the secure submission pathway provided in the regulatory binder, with subsequent EDC reconciliation when access is restored [1–4].
- Adverse events of special interest (AESIs): suspected interstitial lung disease (ILD)/pneumonitis and clinically significant decreases in left ventricular ejection fraction (LVEF) require expedited notification to the sponsor within 24 hours of suspicion, with immediate treatment interruption and protocol-required evaluation for ILD/pneumonitis; these events are followed to complete resolution and managed per protocol and current safety information [2,5,6].

Follow-up of Unresolved Serious Adverse Events

Investigators must provide timely follow-up reports to the sponsor until each SAE is resolved, returns to baseline, or is judged to be chronic/stable without further expected change. Follow-up must include updated diagnoses (superseding signs/symptoms), key test results, interventions, outcome, and any change in causality or seriousness. Follow-up is considered complete when: the final diagnosis is established (or a differential diagnosis with supporting rationale is documented), the clinical course and outcome are known, and no additional clinically meaningful information is expected. Deaths require submission of cause of death (if known) and relevant documentation (e.g., death certificate, autopsy summary, hospital discharge summary) [1–4].

Protocol-Specific Reporting Exclusions

The following do not require expedited reporting unless a complication meets SAE criteria; they must still be documented as AEs when clinically meaningful per protocol and ICH definitions:

- Disease/condition progression itself (without complications) is not an AE; however, clinically significant signs/symptoms or complications of progression are AEs and, if serious, must be reported within 24 hours [1].
- Elective or pre-planned procedures/hospitalizations not due to a worsening condition; report any complications as AEs/SAEs, as applicable [1–3].
- Routine protocol-mandated assessments in the absence of complications; report complications (e.g., biopsy-related pneumothorax) as AEs/SAEs [1–3].

Special Safety Reporting Situations

The following must be reported to the sponsor within 24 hours, even if standard SAE criteria are not yet met, with continued follow-up until final outcome:

- Suspected ILD/pneumonitis and clinically significant LVEF decreases (AESIs): expedited notification upon suspicion; ILD/pneumonitis requires immediate treatment interruption and diagnostic workup with independent adjudication per charter; Grade ≥2 ILD/pneumonitis mandates permanent discontinuation and systemic corticosteroids as clinically indicated [2,5,6].
- Overdose, medication error, or accidental/occupational exposure involving T-DXd: report within 24 hours; if associated with an SAE, follow SAE procedures; the sponsor will evaluate for IND safety reporting per FDA guidance [2,4].
- Product quality complaint with potential to cause harm (e.g., suspected contamination): report within 24 hours and retain the product as feasible for investigation; associated AEs/SAEs must be reported per standard timelines [1–4].
- Major bleeding: define per International Society on Thrombosis and Haemostasis (ISTH) as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, and/or bleeding causing a fall in hemoglobin of ≥2 g/dL or leading to transfusion of ≥2 units of whole blood or red cells; major bleeding that meets SAE criteria must be reported within 24 hours [3,7].
- Pregnancy: any pregnancy in a study participant or partner of a male participant following exposure to T-DXd must be reported to the sponsor within 24 hours of awareness and followed to outcome; pregnancy complications, elective or spontaneous abortion, fetal death, and congenital anomalies/birth defects are SAEs and must be reported within 24 hours with follow-up to outcome, consistent with ICH-GCP and ICH E2A (congenital anomaly as a seriousness criterion) [1,3].

Other Specific Reportable Events

- Newly diagnosed malignancy during or after study treatment: record as an AE; if it meets seriousness criteria or is judged an important medical event, report as an SAE within 24 hours. Expedited IND reporting by the sponsor applies if the event is a serious, unexpected suspected adverse reaction (SUSAR) per 21 CFR 312.32 [2–4].

Non-Serious Adverse Event Reporting

- Collection and timing: all non-serious AEs are collected from first dose through 40 days after the last dose and recorded in the CRF/EDC with CTCAE v5.0 grading, seriousness assessment, causality, action taken with T-DXd, and outcome [1–3,5].
- Beyond the standard window: after Day 40, only SAEs judged related to prior investigational exposure must be reported to the sponsor without delay; other non-serious AEs are not routinely collected after Day 40 unless required to clarify an ongoing SAE or AESI outcome [2,4].

Documentation, Grading, and Terminology

- Grading: use NCI CTCAE v5.0 for severity; when no exact CTCAE term applies, use the protocol's predefined severity rubric while continuing to classify seriousness per regulatory criteria [5].
- Disease progression: not an AE by itself; associated clinically significant signs/symptoms or complications must be recorded as AEs and, if serious, reported within 24 hours [1].
- Diagnosis versus signs/symptoms: when possible, report a single unifying diagnosis rather than multiple signs/symptoms; if a diagnosis is not yet established, report the primary sign/symptom and update to a diagnosis when confirmed [1–3,5].

- Source documentation for all AEs/SAEs must include: event term/diagnosis (or key sign/symptom), onset and resolution dates (and times if available), CTCAE grade, seriousness criterion, outcome, action taken with T-DXd, relevant tests/procedures, medical management, and investigator's causality assessment with rationale [1–3,5].
- Causality: the principal investigator or qualified sub-investigator is responsible for initial causality assessment; the sponsor may further evaluate expectedness and "reasonable possibility" of causation to fulfill regulatory obligations under 21 CFR 312.32 and ICH E2A [2–4].

Reporting to the Study Sponsor

- Point of contact and methods: investigators must notify Sample Pharma Co., Ltd. of all SAEs and special safety reporting situations within 24 hours of awareness, using the sponsor's 24-hour safety contact and the sponsor-designated SAE reporting form/module described in the site regulatory binder. Required minimum information includes an identifiable subject, an identifiable reporter, a suspect product (T-DXd), and a reportable event, with follow-up to provide a complete narrative and supporting documentation [1–4].
- Sponsor actions: the sponsor will assess seriousness, expectedness relative to the current Investigator's Brochure, and reasonable possibility of causation, and will submit expedited IND safety reports to FDA and inform all investigators per 21 CFR 312.32 and ICH E2A timelines (7-day for unexpected fatal or life-threatening suspected adverse reactions; 15-day for other serious and unexpected suspected adverse reactions) [2–4]. The sponsor will conduct ongoing safety review throughout the study and may request additional information or source documents to support regulatory reporting [2,4].
- Parallel obligations: site reporting to the sponsor does not replace investigators' responsibilities to notify their IRBs of unanticipated problems per 21 CFR Part 56 and institutional policies; these processes occur in parallel and without delaying sponsor notification or regulatory reporting timelines [1,2].

References

1. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
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15 DATA AND SAFETY MONITORING

Data capture, reporting, and ongoing data quality

Investigative sites must maintain complete, contemporaneous, and attributable source records for all study procedures from the time informed consent is obtained through the end of follow-up, and ensure accurate, timely transcription to the study electronic data capture (EDC) system in accordance with ICH-GCP E6(R3) and applicable US regulations [1,2]. Sites will:

- Enter visit-related data (including assessments supporting endpoints, dose administration, concomitant medications, vital signs, ECGs, echocardiogram/MUGA, laboratory results, and adverse events) into the EDC within 5 business days of each study visit; serious adverse events (SAEs) and adverse events of special interest (AESIs) must be reported to the sponsor within 24 hours per protocol, with EDC entry and reconciliation to follow without delay [1,2].
- Resolve data queries and address data inconsistencies within 5 business days of notification, and implement corrective and preventive actions when systemic issues are identified, consistent with risk-based quality management principles under ICH E6(R3) [1,3].
- Maintain an up-to-date investigator site file/essential documents, including current approvals, training records, protocol and amendment versions, delegation logs, monitoring correspondence, and all EDC audit trails and data clarification forms, to support traceability and verification [1].
- Ensure source data are accurate, legible, original, attributable, contemporaneous, and verifiable; when electronic source is used, comply with FDA guidance on electronic source data (e.g., validated systems, role-based access, audit trails, data backup and security) and Part 11 where applicable [1,4].
- Retain study records for the period required by 21 CFR 312.62(c) (at least 2 years after the date a marketing application is approved for the drug for the indication for which it was investigated, or, if no application is to be filed or if the application is not approved, until 2 years after the investigation is discontinued and FDA is notified) and longer if required by institutional policy or the clinical trial agreement [2].

All protocol-specified forms and documentation (e.g., imaging transfer forms, independent central review submissions, ILD adjudication packages, investigational product accountability, end-of-treatment and safety follow-up forms) must be completed and submitted per the schedule and technical specifications provided in the study manuals. Imaging and cardiology assessments must use consistent methods across visits, and source documentation must support all endpoint determinations and safety evaluations [1,2].

Safety oversight structure

Safety oversight is continuous and multi-layered:

- Investigator responsibilities: Investigators are responsible for the ongoing clinical evaluation of each participant, prompt detection and management of adverse events, assessment of seriousness and causality, and timely reporting as required by the protocol and 21 CFR Part 312 [1,2].
- Sponsor medical and safety review: The sponsor (Sample Pharma Co., Ltd.) conducts ongoing aggregate and case-level safety surveillance across sites, including review of SAEs, AESIs (suspected interstitial lung disease [ILD]/pneumonitis; decreases in left ventricular ejection fraction [LVEF]), and any new safety information, and fulfills IND safety reporting obligations under 21 CFR 312.32 [2].
- Independent components: All suspected ILD/pneumonitis cases undergo review by an independent ILD adjudication committee per a separate charter; sites must provide requested de-identified source documents and imaging promptly to facilitate adjudication [1,2].

No independent Data and Safety Monitoring Committee (DSMC) is planned for this single-arm, open-label Phase II study. Sponsor medical oversight, risk-based centralized and on-site monitoring, independent central tumor assessment, and independent ILD adjudication comprise the safety monitoring framework. The sponsor may request additional participant-specific information or source documentation at any time to support safety evaluation and regulatory reporting [1–3].

Monitoring by the sponsor

Monitoring will follow a risk-based approach combining centralized data review and targeted on-site or remote visits to verify the rights, safety, and well-being of participants; the reliability and integrity of trial data; and compliance with the protocol, ICH-GCP, and applicable regulations [1,3].

- Scope and timing: Monitoring begins once informed consent is obtained and continues through database lock and closeout. Visits typically include site initiation, periodic monitoring during enrollment and treatment, and closeout; frequency and intensity are tailored based on enrollment rate, data quality, protocol compliance, and risk indicators identified through centralized monitoring [1,3].
- Key verification areas:

- Informed consent process and documentation before any study-specific procedures.
- Eligibility criteria and protocol adherence, including prohibited therapies and dose modification rules.
- Accurate, complete, and timely AE/SAE capture, CTCAE v5.0 grading, causality and seriousness assessments, and adherence to 24-hour SAE reporting.
- AESI management (ILD/pneumonitis and LVEF decrease), including required interruptions, evaluations, adjudication submissions, and follow-up to resolution.
- Endpoint-critical data (e.g., imaging dates, modalities, measurable disease per RECIST v1.1, response confirmations, PFS events, survival status), and concordance between source and EDC.
- Investigational product accountability, storage conditions, temperature logs, and drug disposition.
- Data governance and system controls for electronic records, audit trails, and user access [1–4].

Monitoring findings will be documented in written reports to the sponsor and site, with required corrective and preventive actions tracked to resolution. The sponsor will oversee the adequacy of monitoring and take prompt action for significant noncompliance, consistent with 21 CFR 312.56 [2,3].

Audits and regulatory inspections

- Sponsor audits: Independent of routine monitoring, the sponsor's quality assurance unit may conduct audits of investigators, sites, vendors (e.g., central imaging), and trial-level processes to assess compliance with the protocol, ICH-GCP, and regulatory requirements. Audit scheduling is risk-based and may occur at any time during or after the trial; sites must provide direct access to all requested records, systems, and personnel [1,3].
- Regulatory inspections: FDA may inspect clinical trial records and facilities under 21 CFR 312.68. Investigators must permit authorized FDA personnel to access, copy, and verify all records, including electronic records, that are required to be maintained for the investigation. The sponsor will support sites in preparing for and responding to inspections. Findings requiring action will be addressed with documented corrective and preventive actions; where serious or persistent noncompliance is identified, the sponsor will take appropriate measures consistent with 21 CFR 312.56 and other applicable provisions of Part 312 [2].
- Point of data subject to review: All participant data and records from the time of informed consent—including screening logs, eligibility documentation, protocol-mandated assessments, source documents, EDC entries and audit trails, investigational product accountability, safety reports, and correspondence—are subject to monitoring, audit, and inspection [1,2,4].

Integration with overall safety monitoring

This data and safety monitoring framework aligns with ICH-GCP E6(R3) and FDA guidance on risk-based oversight, ensuring timely identification, evaluation, and reporting of safety information, protection of participants, and high-quality, verifiable data. In the absence of a DSMC, routine sponsor safety surveillance, independent central review of tumor response, and independent ILD adjudication provide complementary safeguards. Sites must cooperate fully with all oversight activities and maintain readiness for audits and inspections throughout the study lifecycle [1–3].

References

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16 REGULATORY CONSIDERATIONS

Protocol Review and Amendments

Before site initiation, each participating site must obtain written approval or a favorable determination from its Institutional Review Board (IRB) for the protocol SP-TDXD-GC-201, the informed consent form (ICF) and any participant-facing materials, recruitment materials, HIPAA authorization (if separate), and all other site-specific documents required by institutional policy and 21 CFR Parts 50 and 56 [1,2]. Under the IND regulations, investigators must also ensure that the IRB is responsible for the continuing review of the study at intervals appropriate to the degree of risk and not less than once per year, per IRB policies [2].

Protocol amendments, revised ICFs, and any changes to participant materials must receive prospective IRB approval before implementation, except when necessary to eliminate an apparent immediate hazard to participants; changes implemented to eliminate an immediate hazard must be reported promptly to the IRB and the sponsor, and submitted for IRB approval as soon as possible [2,3]. IRB determinations (approvals, disapprovals, requests for modification, acknowledgments) must be communicated in writing and retained in the site regulatory file [2]. Where required by clinical trial agreements or the sponsor’s policies, sites must obtain sponsor authorization before submitting amendments to the IRB and must distribute IRB-approved amendments and updated documents to all local study personnel before use [3].

Informed Consent

Written informed consent must be obtained and documented from each participant before performing any protocol-specific procedure, including screening assessments that are not part of routine care, in compliance with 21 CFR Part 50 and ICH E6(R3) [1,4]. The ICF must be signed and dated by the participant or legally authorized representative and by the person obtaining consent; the original signed ICF must be filed in the investigator site file (or medical record per institutional policy), with a copy provided to the participant. If required by the institution, a HIPAA authorization for research use/disclosure of protected health information must also be executed and documented; a copy must be provided to the participant and the original filed with the ICF [1,4,5]. Participants will receive a copy of all materials provided at consent (e.g., ICF, HIPAA authorization if separate, study information sheet, and contact information for the study team and IRB) [1,4,5].

Ethics and Good Clinical Practice

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH E6(R3) Good Clinical Practice (GCP), applicable U.S. regulations governing clinical investigations under an IND (21 CFR Parts 50, 56, and 312), and institutional policies [1–4,6]. Trastuzumab deruxtecan (T-DXd) is investigational in this setting; all participants will be treated under a U.S. IND, with IRB oversight and written informed consent [2–4]. Protocol deviations are permissible only when necessary to eliminate an apparent immediate hazard

to a participant; such deviations must be documented, reported promptly to the IRB, and communicated to the sponsor, with corrective and preventive actions implemented as appropriate [1–3]. All other deviations must be minimized through training and oversight, documented in source and regulatory files, and addressed per site CAPA processes [1,3].

Study Documentation

Investigators must maintain adequate and accurate participant case histories and essential documents to permit evaluation of the conduct of the trial and the quality of the data produced, including source documents that substantiate all case report form (CRF)/electronic data capture (EDC) entries, in alignment with ICH E6(R3) and 21 CFR 312.62 [1,3]. Source documentation may include, but is not limited to:

- Medical records/electronic health records, clinic notes, consultation reports, and specialty notes.
- Laboratory reports, ECGs, echocardiogram/MUGA outputs, pulmonary evaluations, imaging reports and images, and central review submissions.
- Medication administration records, investigational product (IP) accountability logs, temperature logs, and pharmacy records.
- Participant diaries or questionnaires (if used), visit worksheets, and procedure reports.
- IRB approvals and correspondence, delegation of authority logs, training records, monitoring reports/letters, and safety communications [1,3].

All data must be attributable, legible, contemporaneous, original, accurate, and complete, with audit trails for electronic records and timely reconciliation of queries and corrections per GCP [1].

Records Retention

Investigators must retain study records, including source documents, CRFs/EDC records, consent/HIPAA documents, IRB approvals and correspondence, IP accountability, and all other essential documents, for at least 2 years after the date a marketing application is approved for T-DXd for the indication under investigation, or, if no application is to be filed or if the application is not approved for this indication, for 2 years after the investigation is discontinued and FDA is notified, or longer if required by institutional policy or agreement [3]. Records must be accessible for monitoring, audit, and FDA inspection upon request [3].

Multi-Center Guidelines

To ensure consistent monitoring and data integrity across participating U.S. sites:

- Site activation and investigational product: Sites may order or receive T-DXd only after written IRB approval, completion of all regulatory and administrative prerequisites (e.g., fully executed clinical trial agreement, Form FDA 1572, financial disclosure per 21 CFR Part 54, current CVs/licenses, GCP training, delegation of authority log, pharmacy qualification and storage verification, and site initiation), and sponsor confirmation of activation. Shipment and use must comply with site pharmacy SOPs and accountability requirements [1,3,7].
- Coordinating oversight: The Coordinating Investigator or designated central site will, in collaboration with the sponsor, distribute safety reports and other regulatory communications to participating investigators and ensure that any protocol amendments and updates to the Investigator's Brochure or ICF are disseminated and implemented uniformly across sites following IRB approval [1–3].
- Monitoring and data quality: Sponsor-directed risk-based monitoring, including centralized review and targeted on-site/remote assessments, will be applied consistently to verify informed consent, eligibility, protocol adherence, endpoint-critical data, adverse event capture and reporting, and investigational product accountability, in accordance with FDA guidance and ICH-GCP [1,8]. Sites must maintain readiness for audits and FDA inspections and provide direct access to all requested records and systems [1,3].
- Operational systems: Each site must maintain an investigator site file/regulatory binder, EDC access with role-based permissions, procedures for timely data entry and query resolution, systems for IP receipt, storage, dispensing, and temperature monitoring, and processes to

manage and report protocol deviations and safety events per this protocol and applicable regulations [1–3,8].

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17 Data Monitoring Committee and Independent Interim Oversight

Need for a Data Monitoring Committee

No independent Data Monitoring Committee (DMC) is planned. This single-arm, open-label, multicentre Phase II study enrolls approximately 80 participants at U.S. sites, has no planned interim efficacy or futility analyses, and does not involve randomization, blinding, or adaptive modifications. Under FDA guidance, DMCs are typically indicated for large, multicenter randomized trials, blinded trials, or studies with major morbidity/mortality endpoints or pre-specified interim analyses where unblinded comparative data are reviewed; for early-phase, single-arm studies without formal interim analyses, independent DMC oversight is generally not required if proportional alternative safety oversight is in place [1]. In line with ICH E6(R3) principles of proportionate, risk-based trial oversight, independent components (central imaging review for efficacy endpoints; independent adjudication for suspected interstitial lung disease [ILD]/pneumonitis) and robust sponsor safety surveillance under the U.S. IND provide appropriate protections for participants and trial integrity [2–5].

Alternative Independent Oversight and Safety Monitoring Framework

In lieu of a DMC:

- Sponsor medical safety surveillance will continuously review accumulating safety data, fulfill IND safety reporting obligations (21 CFR 312.32), and take prompt action for significant risks (21 CFR 312.56) [3].
- All potential ILD/pneumonitis cases undergo review by an independent ILD adjudication committee operating under a written charter; outcomes inform sponsor safety assessment and participant management [2–5].

- Confirmed objective response and time-to-event endpoints are determined by an independent central imaging review per RECIST v1.1, operating under a charter separate from site investigators and sponsor operations [2,5].
- Site- and trial-level oversight includes IRB review and continuing oversight per 21 CFR Part 56, and risk-based monitoring consistent with FDA guidance and ICH-GCP E6(R3) [2,4,5].

This layered oversight aligns with the Declaration of Helsinki and maintains participant protection and scientific validity without a DMC [6].

DMC Composition

Not applicable; a DMC will not be established for this trial. If regulators or ethics bodies subsequently request a DMC, members will be independent of the sponsor and investigators and include at minimum one disease-area clinician, one biostatistician with interim monitoring expertise, and one pharmacovigilance/safety physician, with additional expertise (e.g., pulmonology, cardiology, ethics) as warranted by the investigational product's risk profile, selected and qualified per FDA guidance and ICH-GCP [1,2].

Independence of the Independent Components

- ILD adjudication committee members and the independent central imaging review organization are contractually independent of the sponsor's operational team, investigators, and participating sites; conflicts are disclosed and managed prior to accessing case materials [1,2].
- Operational separation is maintained between blinded independent reviewers and sponsor/site personnel; access to case materials follows role-based controls and confidentiality agreements, with documentation retained in the trial master file (TMF) [2,5].

Roles and Responsibilities

- Sponsor medical/safety team: continuous review of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs: ILD/pneumonitis; left-ventricular ejection fraction [LVEF] decrease), and benefit–risk; implementation of risk mitigation; expedited and annual reporting under the IND; consideration of enrollment hold or study termination if risks become unreasonable (21 CFR 312.56) [2,3].
- Independent ILD adjudication committee: case-level adjudication of suspected ILD/pneumonitis using pre-specified clinical, imaging, and diagnostic criteria; recommendation of case classification and clinical urgency to inform protocol-specified management and sponsor safety assessment [2,5].
- Independent central imaging review: determination of confirmed objective response and progression per RECIST v1.1; reporting of endpoint-critical data to the sponsor per charter timelines [2,5].

Recommendations from independent components are advisory; the sponsor has final authority for operational decisions, protocol amendments, and regulatory communications [2–4].

Reporting Structure and Communication Pathways

- Independent committees transmit written adjudication/assessment outputs to the sponsor via secure, role-restricted channels. Summary conclusions are shared with investigators only as needed for participant safety or endpoint confirmation, without disclosing confidential materials beyond necessity [1,2,5].
- Sponsor communicates safety actions to investigators and, when applicable, to FDA under 21 CFR 312.32 and to IRBs per 21 CFR Part 56 and institutional policies, preserving confidentiality of any sensitive materials [3,4].

Charters and Governance Documents

- The ILD adjudication committee and the independent central imaging review each operate under a written charter defining purpose, membership/qualifications, independence, conflict-of-interest procedures, data flows, meeting procedures, review timelines, documentation, and communication pathways [1,2,5].
- Charters and version histories are maintained in the TMF and made available to regulators and IRBs as required; they are not appended to this protocol [2].

Meetings and Operating Procedures

- ILD adjudication: rolling review with prompt ad hoc meetings for urgent safety concerns; quorum and voting procedures prespecified in the charter; minutes and outcomes archived in the TMF with restricted access [1,2,5].
- Independent central imaging review: periodic batched reads aligned to the imaging schedule (every 6 weeks in Year 1, then every 12 weeks), with quality control processes, read reconciliation rules, and audit trails as defined in the imaging charter [2,5].
- Sponsor safety review: scheduled aggregate safety reviews and ad hoc reviews triggered by safety signals; documentation of deliberations and actions retained per ICH-GCP and 21 CFR Part 312 [2,3].

Access to Interim Data

- Only the sponsor’s designated safety/pharmacovigilance personnel and statisticians responsible for safety surveillance, the independent ILD adjudication committee, and the independent imaging reviewers will access accumulating data as required for their roles. Investigators, site personnel, and other blinded independent assessors will not receive confidential interim safety packages beyond what is necessary for patient management or endpoint verification [1–3,5].
- Access is controlled by role-based permissions, secure data transfer, confidentiality agreements, and auditable systems; unblinded comparative analyses are not generated because the study is single-arm [2,5].

Interim Analyses and Stopping Guidelines

- No formal interim efficacy or futility analyses, adaptive modifications, or statistical stopping boundaries are planned. Any decision to pause enrollment, modify risk mitigations, or terminate will be driven by emerging safety information, regulatory obligations (21 CFR 312.56, 312.32), and ethics oversight, documented in the TMF and communicated per regulatory and IRB requirements [2–4].

Safety Oversight

- Continuous review will include SAEs, deaths, AESIs (suspected ILD/pneumonitis; LVEF decrease), clinically significant laboratory abnormalities, treatment interruptions/discontinuations due to AEs, and safety trends over time. The ILD adjudication committee may request additional diagnostic data or analyses and recommend urgent actions for suspected ILD [2,3,5].

- The sponsor may implement enhanced monitoring, protocol modifications, temporary enrollment holds, or treatment suspension if warranted, and will submit IND safety reports to FDA and notify investigators per 21 CFR 312.32 [3].

Trial Conduct Oversight

- Oversight of recruitment, retention, completeness of follow-up, protocol deviations affecting safety, eligibility violations, treatment compliance, data quality, and event accrual is conducted through risk-based centralized monitoring and targeted on-site/remote visits, consistent with FDA monitoring guidance and ICH-GCP E6(R3) [2,5].

Confidentiality and Blinding Protections

- Although the study is open-label, confidentiality of interim safety packages, adjudication materials, and central imaging outputs is preserved through operational separation, need-to-know access, labeled open/closed materials where applicable, and secure, auditable systems, to prevent inappropriate disclosure and preserve trial integrity [1,2,5].

Conflict-of-Interest Disclosure and Management

- Members of the ILD adjudication committee and independent imaging review must disclose financial, professional, institutional, and personal interests before appointment and periodically thereafter; identified conflicts are documented and managed (e.g., recusal, replacement) before access to case materials, in accordance with the relevant charters and ICH-GCP [1,2].

Documentation and Archiving

- The TMF will retain: committee charters; membership qualifications; conflict-of-interest and confidentiality records; meeting agendas; adjudication data packages; read outputs; minutes; recommendation letters or adjudication determinations; sponsor responses and implementation records; and related correspondence. Access to confidential/unblinded materials is restricted and auditable, consistent with ICH-GCP and 21 CFR Part 312 [2,3].

Relationship With Regulatory Authorities and Ethics Committees

- Safety actions and urgent concerns affecting participant risk, dosing, or study continuation will be communicated to FDA under 21 CFR 312.32/312.56 and to IRBs per 21 CFR Part 56 and institutional requirements. Protocol amendments follow 21 CFR 312.30 and are implemented after IRB approval unless required to eliminate immediate hazards [3,4].

Training and Preparedness

- Before activation, independent reviewers receive orientation on the protocol, relevant risk mitigation (ILD and LVEF assessments), charters, confidentiality and conflict-of-interest policies, and communication pathways, emphasizing the distinction between independent oversight functions and trial operations per ICH-GCP E6(R3) [2].

Summary

In this single-arm, open-label Phase II study without interim efficacy analyses, a DMC is not planned per FDA guidance; proportional independent oversight is ensured through continuous sponsor safety surveillance under the U.S. IND, independent ILD adjudication, and independent central imaging review. This framework supports participant safety, ethical conduct, regulatory accountability, and scientific validity while preserving confidentiality and operational integrity [1–6].

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18 Ancillary and Post-Trial Care

Overview of Ancillary and Post-Trial Care

Ancillary care comprises medical care needs identified during study participation that extend beyond protocol-required procedures, including management of clinically significant incidental findings, complications from protocol-mandated assessments, and coordination with participants' usual healthcare providers. Post-trial care encompasses medical follow-up, treatment transition, and any access to study treatment after a participant completes study treatment, discontinues early, withdraws, or if the trial terminates early. These provisions are implemented under investigator medical judgment, IRB oversight, and applicable U.S. regulations and ICH-GCP to protect participant welfare and ensure continuity of care [1–4].

Ancillary Care During the Trial

- Trial-related adverse events and complications: Participants will receive appropriate medical evaluation and treatment for adverse events (AEs), serious adverse events (SAEs), and complications of protocol-required procedures (e.g., infusion reactions, biopsy-related events), managed by the site or through specialist referral (e.g., pulmonology for suspected interstitial lung disease [ILD]/pneumonitis; cardiology for left-ventricular ejection fraction [LVEF] decrease), with continued follow-up per protocol and clinical judgment [1–3].
- Clinically significant incidental findings: Abnormal laboratory values, imaging findings, vital signs, ECG findings, or other results discovered during study assessments that require medical attention will be reviewed by the investigator, discussed with the participant,

documented in source records, and addressed through on-site management or referral to the participant's usual treating clinician as appropriate [1,2].

- Coordination with usual care: Investigators will coordinate with participants' non-study clinicians to avoid duplication of testing and ensure consistent management of comorbidities and concomitant medications [1,2].
- Costs: Protocol-required procedures and study drug are provided per the clinical trial agreement; ancillary care that is not study-mandated (e.g., management of comorbid conditions, non-study diagnostics) will generally be billed to insurance or the participant per local practice unless covered by sponsor policy or clinical trial insurance for study-related injury, consistent with IRB-approved consent language and applicable regulations [2–4].

Management of Clinically Significant Findings

- Identification and review: Clinically significant abnormalities identified in protocol-required tests (e.g., chemistry/hematology, ECGs, echocardiogram/MUGA, chest imaging, pregnancy tests) will be reviewed by the investigator, documented in source records and CRFs, communicated to the participant when appropriate, and followed until resolution, stabilization, or explanation, in accordance with ICH-GCP and site standards [1–3].
- Referrals: When findings are not directly related to the investigational product or protocol procedures but merit clinical action, participants will be referred to their usual care providers or appropriate specialists for further evaluation and treatment, with relevant medical information shared as permitted by consent and privacy regulations [1,2].
- Ongoing safety assessments: Suspected ILD/pneumonitis triggers immediate treatment interruption, diagnostic workup, and independent adjudication; Grade ≥2 ILD/pneumonitis requires permanent discontinuation and systemic corticosteroids as clinically indicated. Clinically significant LVEF decrease will be managed per cardiology standards and protocol guidance, including treatment interruption/discontinuation and follow-up imaging [1–3].

Care for Trial-Related Harm

Participants who experience harm related to study participation (including harm from investigational trastuzumab deruxtecan [T-DXd], protocol-mandated procedures, or study conduct) will receive prompt medical evaluation, treatment, and follow-up at the site or via referral, consistent with investigator judgment, protocol requirements, sponsor pharmacovigilance procedures, and applicable regulatory and ethical requirements. Events will be assessed for seriousness and causality, documented, and reported per regulatory timelines, with follow-up until resolution or stabilization, as required by ICH-GCP and 21 CFR Part 312 [1–3].

Compensation for Trial-Related Harm

Compensation and/or coverage of medical costs for injury reasonably related to study participation will follow applicable laws and regulations, IRB requirements, sponsor policy, and the clinical trial insurance/indemnity arrangements described in the IRB-approved informed consent. If local policy requires, participants may be directed first to their usual payers; study-related injuries will be handled per the insurance and indemnity provisions in effect for this protocol [2,4]. Sample Pharma Co., Ltd. maintains clinical trial insurance for this study; details of coverage for study-related injury are provided in the informed consent form.

Post-Trial Access to Study Treatment

Post-trial access to investigational T-DXd is planned for eligible participants who, at end of study treatment or study closure, are receiving clinical benefit without unacceptable toxicity and lack a comparable or satisfactory alternative therapy, provided that the anticipated benefit justifies the potential risks and continued access is permitted by regulation and IRB approval. Access will be implemented through a sponsor-supported continued access or expanded access mechanism under 21 CFR 312 Subpart I (e.g., individual patient or intermediate-size expanded access), subject to FDA

and IRB authorization, adequate drug supply, and feasibility of appropriate monitoring and reporting [2,5,6]. Post-trial access will continue until one of the following occurs: disease progression, unacceptable toxicity, withdrawal of consent, physician decision that risks outweigh benefits, drug becomes commercially available and accessible to the participant, or regulatory/ethical conditions for access are no longer met [2,5,6]. This plan will not delay standard transition to locally available therapies when clinically indicated.

Transition to Standard Clinical Care

At end of treatment (EOT) or early discontinuation, the site will:

- Provide the participant and treating physician a summary of treatment received, disease status, ongoing AEs/AESIs (e.g., ILD/pneumonitis; LVEF decrease), concomitant medications, and recommended follow-up, including pending test results.
- Document and communicate any unresolved or new clinically significant findings and required monitoring or referrals (e.g., pulmonology, cardiology) [1–3].
- Coordinate initiation of appropriate next-line standard therapy per local practice, independent of the post-trial access determinations; if post-trial access is pursued, obtain required authorizations and consent and transition oversight accordingly [2,5,6].

Post-Trial Follow-up

- Safety follow-up: A safety visit will occur 40 days (+7) after the last dose to assess AEs, SAEs, and concomitant medications; all unresolved AEs/AESIs will be followed to resolution, baseline, or stabilization, consistent with ICH-GCP and IND obligations [1–3].
- Survival follow-up: Survival status will be collected every 12 weeks until study end or loss to follow-up, using minimal-risk methods (e.g., phone contact, medical records) [1–3].
- Special situations: Pregnancies in participants or partners following exposure will be followed to outcome; ILD/pneumonitis and clinically significant cardiac events will be followed until resolution or stabilization per protocol and clinical judgment [1–3].

Care After Early Termination or Trial Suspension

If the study is terminated early or suspended, investigators will:

- Inform participants promptly, discontinue study drug safely, and perform an early EOT visit with appropriate safety assessments [1–4].
- Ensure continued medical follow-up of ongoing AEs/SAEs/AESIs until resolution or stabilization, report per applicable timelines, and transition participants to standard-of-care therapy or post-trial access if permitted and appropriate [1–3,5,6].
- Communicate pertinent medical information to treating physicians and document actions taken, consistent with IRB guidance and regulatory obligations [2–4].

Responsibilities for Ancillary and Post-Trial Care

- Investigators and sites: Identify ancillary care needs; manage or refer clinically significant findings; provide medical care for trial-related harm; ensure timely AE/SAE reporting and follow-up; coordinate transitions to standard care or expanded access; and document all actions in source records and CRFs, in accordance with ICH-GCP and 21 CFR Part 312 [1–3].
- Sponsor (Sample Pharma Co., Ltd.): Maintain pharmacovigilance systems; assess safety reports; fulfill IND safety reporting; arrange and administer post-trial access programs where applicable; ensure adequate insurance/indemnity; and support sites in early termination scenarios and transitions [2,5,6].

- Medical monitor/pharmacovigilance: Provide safety oversight and guidance on medically complex cases (e.g., suspected ILD, cardiac events), ensure appropriate follow-up of trial-related harm, and oversee reporting compliance [2].
- IRBs: Review and approve consent language on injury compensation and post-trial access, and oversee participant protections during ancillary and post-trial care activities [2–4].
- Treating physicians: Receive and act upon transition communications, continue medical management, and coordinate with investigators as needed.

Communication in the Informed Consent Form

The IRB-approved informed consent will describe:

- What medical care is available for trial-related injury and how costs are covered.
- The extent of ancillary care during the trial and potential referrals to outside providers.
- Post-trial care and follow-up procedures, including survival follow-up and how unresolved AEs will be managed.
- The possibility and conditions for post-trial access to T-DXd, including that access depends on regulatory/IRB authorization, clinical benefit, safety, and drug availability, and may stop if risks outweigh benefits or standard options become available.
- Any insurance/indemnity or compensation arrangements, consistent with applicable regulations and institutional requirements. Language will be clear, non-promotional, and aligned with 21 CFR 50.25 and ICH-GCP [1,2,4].

Documentation and Governance

Ancillary and post-trial care activities will be documented in:

- Source records, AE/SAE reports, adjudication outputs for ILD, referral notes, follow-up logs, discharge/transition summaries, and communications with treating physicians.
- Insurance/indemnity and compensation files, IRB approvals/acknowledgments, FDA/IRB authorizations for expanded access, and participant re-consent for post-trial access.
- The trial master file and investigator site file, with version control for any changes to ancillary care, compensation, or post-trial access plans, and required notifications to IRBs and FDA when applicable [1–3,5,6].

If No Ancillary or Post-Trial Care Is Planned

Not applicable; ancillary care during the trial is planned, and post-trial access to investigational T-DXd may be available for eligible participants as described above. If site- or state-specific constraints affect compensation or access, the sponsor and site will finalize provisions and update the protocol and consent before activation at the affected site(s) [2,4–6].

Summary

These ancillary and post-trial care provisions operationalize investigator responsibilities under ICH-GCP and U.S. regulations, reflect the ethical obligation to address medically important findings and trial-related harm, and establish clearly governed pathways for transition to standard care and ethically justified post-trial access. Together, they support participant protection, continuity of care, transparent communication, and regulatory compliance for this Phase II study [1–6].

References

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19 STATISTICAL CONSIDERATIONS

Overview and Analysis Framework

This single-arm, open-label Phase II study will estimate antitumor activity of investigational trastuzumab deruxtecan (T-DXd) monotherapy using confirmed objective response rate (ORR) by independent central review as the primary endpoint, analyzed with an exact binomial framework and two-sided 95% confidence intervals (CIs). Time-to-event endpoints will use nonparametric survival methods. Analyses will follow ICH E9 and E9(R1) principles, including prespecification of analysis sets, estimands, and handling of intercurrent events and missing data [1,2]. Efficacy assessments use RECIST v1.1 with confirmation of responses on a subsequent scan at least 4 weeks later, determined by independent central review [3]. For oncology time-to-event endpoints, endpoint definitions and censoring align with FDA guidance [4].

Analysis Populations

- Full Analysis Set (FAS): All participants who receive at least 1 dose of T-DXd; primary efficacy and all time-to-event analyses will use the FAS, consistent with a conservative, treatment-exposed analysis in a single-arm design [1,2].
- Safety Analysis Set: Identical to the FAS; all safety summaries will use this set [1].
- Response Evaluable Set (RES): Participants in the FAS with measurable disease at baseline by independent review and at least one post-baseline tumor assessment or documented progression/death; used for a supportive ORR analysis [3,4].

Estimands

Primary estimand for ORR:

- Population: Adults with centrally confirmed HER2-positive unresectable/metastatic gastric or gastro-oesophageal junction adenocarcinoma who receive at least one dose of T-DXd under the protocol’s eligibility criteria.
- Variable: Confirmed ORR (proportion with best overall response of confirmed complete or partial response by independent central review, RECIST v1.1) [3,4].
- Intercurrent events: Initiation of new anticancer therapy, missing confirmation scans, treatment discontinuation for reasons other than progression, or death before confirmation. Strategy: Non-responder imputation for any participant without a confirmed response at the time of analysis (treat as non-responders), consistent with RECIST/frequentist regulatory practice [3,4].
- Summary measure: Proportion with exact (Clopper–Pearson) two-sided 95% CI; the study targets a lower CI bound exceeding 27% [5,6].

Key secondary estimands:

- PFS (key secondary): Time from first dose to first documented progression by independent central review (RECIST v1.1) or death from any cause, whichever occurs first. Intercurrent initiation of new anticancer therapy without prior progression leads to censoring at the last adequate assessment before new therapy; sensitivity analyses will treat new therapy as an event at its start date [3,4].
- OS: Time from first dose to death from any cause; participants alive at analysis cut are censored at last known alive date [4].
- Duration of Response (DoR): Time from first documented response (CR or PR) to progression by independent review or death; responders without events are censored at last adequate tumor assessment [3,4].
- Safety: Incidence, severity (NCI CTCAE v5.0), seriousness, and relatedness of treatment-emergent AEs, including adverse events of special interest (ILD/pneumonitis; LVEF decrease) [7].

Primary Endpoint Analysis

- The primary analysis will estimate ORR in the FAS with a two-sided exact Clopper–Pearson 95% CI and present the point estimate with the CI [5,6].
- Decision framework: The study is designed so that, if the true ORR is 45% (supported by randomized data in a related population) [8], the study has high probability that the lower bound of the two-sided 95% CI exceeds 27%. No formal hypothesis test or go/no-go efficacy threshold will be applied; inference focuses on the CI and its lower bound relative to 27% [2,5,8].
- Supportive analyses: ORR in the RES [3,4].

Secondary and Safety Analyses

- PFS, OS, DoR: Kaplan–Meier (KM) curves; medians and two-sided 95% CIs (Brookmeyer–Crowley with log–log transformation), event rates at prespecified timepoints with Greenwood standard errors; number and proportion of events; and KM estimates at 6, 9, and 12 months for PFS and OS, as data allow [4,9].
- Censoring rules:

- PFS: Event = independent central review progression or death. Censor at last adequate tumor assessment before new therapy if started without prior progression; censor at last adequate assessment for participants without event by data cut; inadequate/missing baseline assessment leads to censoring at the date of first dose with missing baseline treated as non-evaluable, but participant remains in FAS [3,4].
- OS: Event = death from any cause; censor at last known alive date [4].
- DoR: Event = independent review progression or death; censor at last adequate assessment for responders without event [3,4].

- Safety: Summaries include TEAEs, treatment-related TEAEs, Grade ≥3 TEAEs, SAEs, AESIs (ILD/pneumonitis; LVEF decrease), TEAEs leading to dose modification/interruption/discontinuation, and deaths. AEs coded by MedDRA and graded per CTCAE v5.0; incidence summarized by system organ class and preferred term, maximum grade, and relationship [1,7]. ILD/pneumonitis and LVEF decrease are summarized with onset timing, severity, management, and outcomes.

Missing Data and Intercurrent Events

- ORR: Participants without a confirmed response by independent review (including those with missing or non-confirmatory assessments, early discontinuation, death, or initiation of new therapy before confirmation) will be considered non-responders in the primary analysis, consistent with RECIST and FDA oncology endpoint guidance [3,4].

- Time-to-event endpoints: Defined censoring rules as above will be applied. Lost to follow-up or withdrawal without event are censored at the date of last adequate assessment (PFS, DoR) or last known alive (OS). Initiation of new therapy without prior progression leads to censoring for PFS in the primary analysis; a sensitivity analysis will treat new therapy as an event at its start date [4].
- Data cut and follow-up: Time-to-event endpoints use data up to the prespecified analysis cut approximately 12 months after last patient first dose. Survival follow-up continues every 12 weeks until study end; late data may be included in updated analyses if planned.

Sensitivity and Subgroup Analyses

- Sensitivity analyses:

- ORR in the RES.
- PFS with new anticancer therapy counted as an event at therapy start; additional sensitivity excluding participants without central baseline measurable disease confirmation.

- Exploratory subgroup summaries: Descriptive ORR and KM estimates by baseline HER2 category (IHC 3+ vs IHC 2+/ISH+), ECOG PS (0 vs 1), prior best response to first-line trastuzumab (responder vs non-responder if available), sex, age group (<65 vs ≥65), and number of metastatic sites. Forest plots will display subgroup ORR point estimates and 95% CIs without interaction testing or multiplicity adjustment [1,2].

Multiplicity

No formal adjustment for multiplicity is planned. The primary endpoint (ORR) is the sole inferential objective; secondary endpoints are summarized descriptively with two-sided 95% CIs where appropriate and interpreted as supportive [1,2,4].

Statistical Hypotheses, Significance Level, and Confidence Intervals

- Primary endpoint: Estimation-focused; two-sided 95% CIs for ORR using exact methods. The design targets a lower CI bound above 27%; no formal alpha-controlled hypothesis test is planned [2,5,6].
- Secondary endpoints: Two-sided 95% CIs will be provided for KM medians and selected timepoint estimates; p-values will not be emphasized [4,9].

Sample Size Determination

The planned enrollment is approximately 80 participants to obtain about 72 evaluable participants in the FAS. With n=72 and assuming a true ORR of 45% (supported by randomized evidence of high response with T-DXd in a related population) [8], the probability is approximately 90% that the lower bound of the two-sided exact (Clopper–Pearson) 95% CI for ORR exceeds 27%. No interim analyses or sample-size adaptations are planned.

Protocol Deviations and Analysis Inclusion

Major eligibility deviations will be summarized. All participants receiving ≥1 dose are included in the FAS primary analysis regardless of protocol deviations, consistent with ICH E9 principles to preserve interpretability; sensitivity analyses may exclude participants without central confirmation of baseline measurable disease for supportive context [1,2,3].

Interim Analyses and Data Monitoring

No interim efficacy or futility analyses are planned. Ongoing sponsor safety review will be conducted throughout the trial under the U.S. IND, including expedited reporting per 21 CFR 312.32, with

independent adjudication for suspected ILD/pneumonitis [4,7].

Statistical Software and Data Standards

Analyses will be performed using validated statistical software (e.g., SAS or R) under a controlled programming environment, following ICH E9/E6(R3) principles. Outputs will adhere to prespecified shells and data standards suitable for regulatory review [1,2].

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20 PUBLICATION PLAN

Results dissemination and timelines

This Phase II trial will adhere to ethical and regulatory requirements to make results publicly available, regardless of outcome, in a timely, accurate, and non-promotional manner [1–4]. The trial will be registered on ClinicalTrials.gov prior to first participant enrollment; results information (including prespecified outcomes, participant flow, baseline characteristics, adverse events, and the IRB-approved protocol and statistical analysis plan) will be submitted to ClinicalTrials.gov no later than 12 months after the primary completion date, unless a permitted certification or extension applies under 42 CFR Part 11 [1,2]. If a lawful delay is invoked (e.g., for initial FDA approval or clearance of a new product or use), timelines and certification will follow 42 CFR 11.44; any extension requests will comply with 42 CFR 11.44 and 11.64 [1].

Acceptable initial dissemination formats include submission of top-line results for presentation at scientific congresses (e.g., oral or poster abstracts) after database lock and completion of prespecified primary analyses, provided that the content is accurate, non-misleading, and consistent with the protocol and statistical analysis plan, and that all required safety information is included per

good publication practice and abstract reporting standards [3–6]. Abstracts and congress presentations will aim to follow CONSORT for Abstracts guidance for randomized trials as applicable to single-arm designs (structured format, prespecified outcomes, numbers analyzed, and harms) adapted appropriately for a nonrandomized study [5,6]. Press communications related to congress dissemination will be factual and balanced and must not precede scientific disclosure at the congress.

Comprehensive reporting will include:

- A Clinical Study Report (CSR) prepared to ICH E3 standards, targeted for finalization within approximately 6 months of database lock to support regulatory and scientific transparency [4].
- A full-length peer-reviewed manuscript, prepared in accordance with ICMJE authorship and reporting standards and the CONSORT 2010 statement (as applicable to single-arm trials, including transparent harms reporting), targeted for submission within 12 months after primary results are available to the sponsor, barring journal-specific constraints or legal delays [3,5].

Negative or inconclusive findings will be disseminated with the same rigor and timelines as positive findings, consistent with the Declaration of Helsinki [2]. Any secondary or post-hoc analyses will be clearly identified as such and will not precede publication of the primary results unless scientifically justified and approved under the processes below [3].

Publication responsibilities and investigator–sponsor agreement

All publications and presentations derived from this multicenter study will be coordinated to ensure accuracy, completeness, and protection of participant confidentiality and legitimate intellectual property, consistent with ICMJE authorship criteria and Good Publication Practice (GPP 2022) [3,4]. Investigators agree that:

- The sponsor (Sample Pharma Co., Ltd.) will prepare and lead the primary global manuscript for the multicenter dataset. No site-specific or subset publications of primary outcomes may be submitted before the primary multicenter publication or 12 months after database lock (whichever occurs first), unless the sponsor provides prior written consent, to avoid duplicate or fragmented reporting and to maintain fidelity to the prespecified analyses [3,4].
- Draft abstracts, posters, slides, manuscripts, and any other public communications based on study data must be submitted to the sponsor for medical, scientific, statistical, legal, and compliance review at least 30 business days before the planned submission or public disclosure for abstracts and at least 45 business days for manuscripts. Where necessary to protect patentable inventions or confidential information, the sponsor may request reasonable delay of public disclosure for up to 60–90 days to allow for intellectual property filings; such delay will not be used to suppress unfavorable results and will not contravene mandatory ClinicalTrials.gov results posting timelines under 42 CFR Part 11 [1,3,4].
- The sponsor has the right to review, comment on, and request correction of factual inaccuracies, inconsistent data displays, or disclosures of proprietary information. Editorial control of scientific content resides with the authors; however, authors are expected to consider and reasonably incorporate sponsor feedback to ensure accuracy, alignment with the protocol and statistical analysis plan, and compliance with applicable regulations and ethical standards [2–4].
- Authorship will reflect substantive intellectual contribution per ICMJE criteria; professional medical writing and statistical support will be acknowledged, and funding and potential conflicts of interest will be fully disclosed in all public communications [3,4].
- All safety data, including adverse events of special interest (interstitial lung disease/pneumonitis and decreases in left ventricular ejection fraction), will be reported transparently and in accordance with CONSORT harms reporting and congress/journal requirements [5,6].
- Data included in publications and presentations must derive from quality-controlled, locked datasets (or clearly identified interim data when applicable), be consistent with the final SAP, and reference the trial registration number once assigned, consistent with ICMJE trial registration requirements [3].

If disagreements arise regarding content, the corresponding author(s) and sponsor will work in good faith to resolve them; if unresolved, authors may include a statement explaining differing interpretations, provided confidential information is not disclosed and regulatory obligations are met [3,4]. Nothing in this plan limits required safety reporting to regulators or public posting obligations

under 42 CFR Part 11 [1].

References

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21 Synopsis

Protocol: SP-TDXD-GC-201, Version 1.0, 24 October 2026. Sponsor: Sample Pharma Co., Ltd.

Title: Phase 2, open-label, single-arm, multicentre study of trastuzumab deruxtecan (T-DXd) in adults with HER2-positive unresectable or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma after progression on first-line trastuzumab-containing therapy in the United States.

Design: Phase 2, open-label, single-arm, multicentre study at US sites, conducted under a US IND. No randomisation, blinding or comparator.

Population: Adults (≥18 years) with HER2-positive (IHC 3+ or IHC 2+/ISH+) gastric or GEJ adenocarcinoma, centrally confirmed on a new biopsy taken after progression on first-line trastuzumab-containing therapy; ECOG performance status 0–1; at least one measurable lesion per RECIST v1.1; LVEF ≥50%; adequate organ function. Key exclusions: any anticancer therapy after the first-line trastuzumab regimen; history of non-infectious ILD/pneumonitis requiring steroids or current/suspected ILD; untreated or symptomatic brain metastases.

Study treatment: T-DXd 6.4 mg/kg IV every 3 weeks (first infusion over ≥90 minutes, later infusions ≥30 minutes if tolerated) until disease progression, unacceptable toxicity or withdrawal. Up to two dose reductions (5.4 mg/kg, then 4.4 mg/kg); no re-escalation.

Primary objective and endpoint: To evaluate antitumour activity: confirmed objective response rate (ORR) by independent central review (ICR) per RECIST v1.1.

Secondary endpoints: Progression-free survival by ICR (key secondary); overall survival; duration of response by ICR; safety and tolerability (NCI CTCAE v5.0), with ILD/pneumonitis and LVEF decrease as adverse events of special interest.

Assessments: Tumour imaging every 6 weeks (±7 days) in year 1, then every 12 weeks; ECHO/MUGA at screening, Cycle 5 Day 1 and every 4 cycles; triplicate ECG at screening, then ECG before each infusion; independent adjudication of all potential ILD cases; safety follow-up visit 40 days (+7) after the last dose; survival follow-up every 12 weeks.

Sample size: Approximately 80 participants enrolled to obtain 72 evaluable participants, giving 90% power for the lower bound of the two-sided 95% exact confidence interval for ORR to exceed 27% if the true ORR is 45%.

Statistical analysis: Full analysis set (all participants who receive ≥1 dose; also the safety set) for primary efficacy and safety; response-evaluable set for supportive ORR analysis. ORR with Clopper–Pearson 95% CI; Kaplan–Meier estimates for time-to-event endpoints. No interim analyses.

Study duration: Enrolment over approximately 18–24 months; study end about 12 months after the last participant's first dose (about 30–36 months in total).

22 Phase II Drug Study Informed Consent Form Template

You are being asked to consider a research study of trastuzumab deruxtecan (T-DXd) for adults with HER2-positive stomach or gastro-oesophageal junction cancer that has grown during or after first treatment with trastuzumab. T-DXd is investigational in this setting. This study is sponsored by Sample Pharma Co., Ltd. (protocol SP-TDXD-GC-201).

Taking part is your choice. Before you decide, please read this entire form carefully. Take the time you need. You may discuss it with your family, friends, or your own doctor. Please ask the study team any questions you have and make sure you understand what the study involves before you sign.

If you choose not to join, your regular medical care will not be affected. You can change your mind and leave the study at any time.

22.1 Official Study Title and Trial Registration Information

Official Study Title and Trial Registration Information

Item	Details
Official study title (exact protocol title)	Phase 2, open-label, single-arm, multicentre study of trastuzumab deruxtecan (T-DXd) monotherapy to evaluate antitumour activity (primary endpoint: confirmed objective response rate by independent central review per RECIST v1.1) in adults with centrally confirmed HER2-positive unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma after progression on first-line trastuzumab-containing therapy in the United States.
Protocol number	SP-TDXD-GC-201
Protocol version and date	Version 1.0, 24 October 2026
Sponsor	Sample Pharma Co., Ltd.
Principal Investigator (overall)	Not yet assigned; to be confirmed prior to site activation.
Study phase and design	Phase 2, open-label, single-arm, multicentre study of investigational trastuzumab deruxtecan (T-DXd) monotherapy in adults with HER2-positive unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma in the United States.
Regulatory status	Conducted under a US IND with IRB approval and written informed consent in accordance with ICH E6(R3) and the Declaration of Helsinki (2024). [1,2]
Trial registration registry	ClinicalTrials.gov (United States). The study will be registered before enrollment, consistent with US law and ethical standards. [2,3]
ClinicalTrials.gov identifier (NCT)	Not yet assigned.
Public registry URL	To be provided once the NCT number is issued.

The study will be registered on ClinicalTrials.gov prior to first participant enrollment as required by 42 CFR Part 11 and as mandated by the Declaration of Helsinki; the registry identifier (NCT number) and

public URL will be added to the ICF and protocol documents once assigned. [2,3]

References

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22.2 Short Invitation and Consent Summary

You are being invited to consider a Phase 2 research study in the United States. It is testing a study medicine called trastuzumab deruxtecan (T-DXd) for adults with HER2-positive stomach or gastro-oesophageal junction cancer that has grown during or after first treatment with trastuzumab. T-DXd is investigational for this use. Taking part is your choice. Please read this information carefully, ask questions, and take the time you need before deciding. You may choose not to join, or to leave later, and your regular care will not be affected [1,2].

The main aim is to see in how many people the tumors shrink. Everyone in the study receives T-DXd through a vein about every 3 weeks. Before joining, you will need a new tumor biopsy to confirm your HER2 status, because HER2 can change over time. This retesting helps make sure the study medicine is appropriate for you [3]. During the study, you will have CT or MRI scans every 6 weeks in the first year, then every 12 weeks, plus regular blood tests and heart checks (such as an echocardiogram). You can stay on treatment until the cancer grows again or side effects become too much.

Important risks include lung inflammation (interstitial lung disease) that can be severe, life-threatening, or fatal—contact the study team right away if you have new or worsening cough, fever, or shortness of breath. Other risks include a drop in how well the heart pumps, low blood counts, nausea, tiredness, hair loss, and harm to an unborn baby. You may or may not benefit. Other options may include standard treatment, another research study, or care focused on comfort. An earlier study in Japanese and Korean patients showed more tumor shrinkage and longer survival with T-DXd than with chemotherapy; this study will look at patients in the United States [4].

References

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22.3 Why am I being asked to take part?

You are being asked to consider this study because you may have characteristics that match the population the study is designed to evaluate. In general, you may be suitable for screening if the following apply to you:

- You are an adult (18 years or older) with stomach (gastric) or gastro-oesophageal junction adenocarcinoma that cannot be removed by surgery or has spread (metastasized), and your cancer grew during or after your first treatment that included trastuzumab. Your tumor must currently be HER2-positive (IHC 3+ or IHC 2+ with ISH amplification by the ASCO-CAP guideline), confirmed by central testing on a new biopsy taken after your cancer progressed, because HER2 status can change over time and after trastuzumab exposure [1].
- You have at least one tumor lesion that can be measured by CT or MRI according to RECIST v1.1; this is needed to assess whether the study drug is shrinking tumors (the main goal of the study) [2].
- Your overall physical functioning is good (Eastern Cooperative Oncology Group [ECOG] performance status of 0 or 1), meaning you are fully active or restricted in physically strenuous activity but able to carry out light work [3].
- Your heart function is adequate (left ventricular ejection fraction of 50% or higher), and you have adequate bone marrow, liver, and kidney function on blood tests, for example: absolute neutrophil count ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, hemoglobin ≥9 g/dL; AST and ALT ≤3 × the upper limit of normal (≤5 × if you have liver metastases); total bilirubin ≤1.5 × the upper limit of normal; and creatinine clearance ≥50 mL/min. These thresholds help ensure it is safe to receive the investigational treatment and to interpret study results reliably.
- You have not received any anticancer therapy after your first-line trastuzumab-containing regimen.
- You do not have medical conditions that would increase risk with this investigational medicine, including: a history of non-infectious interstitial lung disease (ILD)/pneumonitis that required steroids, current or suspected ILD at screening, clinically severe lung disease, significant heart disease, or untreated/symptomatic brain metastases. These exclusions reflect known risks such as ILD/pneumonitis and decreases in heart pumping function observed with trastuzumab deruxtecan in prior studies and are intended to protect participant safety [4].
- You are receiving care at a participating site in the United States. The study is being conducted under a US Investigational New Drug application with Institutional Review Board approval and written informed consent, consistent with ICH Good Clinical Practice and US regulations [5–8].

Final eligibility will be decided by the study doctors after a screening process that includes review of your medical history, imaging, heart tests, and laboratory tests, and confirmation of your tumor's HER2 status on a new biopsy, in line with ethical and regulatory standards for clinical research [5,7,8].

References

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22.4 What is the usual approach to treating this disease or condition?

Once stomach or gastro-oesophageal junction cancer has spread or cannot be removed by surgery, it cannot usually be cured. Treatment focuses on controlling the cancer, easing symptoms, and helping people live longer [1].

If HER2-positive cancer grows after first treatment with trastuzumab, usual options include chemotherapy. Many people are offered paclitaxel with ramucirumab (a medicine that targets blood vessel growth), or ramucirumab alone. Another common option is a different chemotherapy drug such as irinotecan. Later on, trifluridine/tipiracil tablets may be used [1–3]. These treatments can slow the cancer and relieve symptoms for a time, but they often stop working as the cancer adapts, and they can cause side effects such as tiredness, low blood counts, and stomach or bowel symptoms [1–3].

Care to manage symptoms and support quality of life—known as palliative care—is offered alongside any cancer treatment and can start early. Palliative care teams help with pain, nausea, appetite, mood, sleep, and family support [4].

Your own doctor can explain these standard options, their potential benefits and risks, and which may fit your situation. You can receive any of these treatments without joining this study [1–4].

References

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22.5 What are my other choices if I do not take part?

You do not have to join this study to receive care. Choosing not to take part—or deciding to leave later—will involve no penalty or loss of medical benefits or other care to which you are otherwise entitled, consistent with US regulations and international ethical standards [1,2].

Reasonable alternatives to participation may include:

- Standard systemic therapy options used when HER2-positive gastric or gastro-oesophageal junction cancer grows after first-line trastuzumab, such as paclitaxel plus ramucirumab,

ramucirumab alone, or irinotecan, and later on trifluridine/tipiracil. Your doctor can explain the potential benefits and risks of each option for your situation [3–5].
- Enrollment in another clinical trial that you may be eligible for. Clinical trials conducted in the United States are publicly registered, and your care team can help you explore options [6].
- Observation/active monitoring with treatment started if the cancer worsens or symptoms change, when clinically appropriate [3].
- Supportive and palliative care focused on symptom relief and quality of life, which can be provided alongside or instead of cancer-directed therapy; hospice care may be appropriate when goals of care are comfort-focused [3,7].
- No study treatment. You may continue routine care with your oncology team and receive treatments or services outside this research study, as you and your doctor decide [1–3,7].

If you prefer any of these options, you can pursue them with your regular care team without joining this study. You may also take time to consider a second opinion. Participation in this research is entirely voluntary [1,2].

References

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22.6 Why is this study being done?

This Phase 2 study is being done to learn if the investigational medicine trastuzumab deruxtecan (T-DXd) can shrink tumors and help control cancer in adults in the United States who have HER2-positive stomach or gastro-oesophageal junction adenocarcinoma that has grown during or after first-line treatment that included trastuzumab. The main question is how many participants have their tumors shrink (confirmed objective response) when they receive T-DXd alone, given every 3 weeks, and whether that level of tumor shrinkage is meaningfully higher than what has been seen historically with standard second-line chemotherapy in this setting [1,2].

Why this question matters now:
- In a prior randomized Phase 2 study in Japan and Korea, people treated with T-DXd had more tumor shrinkage and lived longer than those who received chemotherapy chosen by their physician, suggesting T-DXd can be active after trastuzumab in HER2-positive gastric cancer [1]. We need to understand how well T-DXd works and how safe it is for people treated at sites in the United States.
- Standard second-line options such as paclitaxel plus ramucirumab produce tumor shrinkage in about one quarter to one third of patients; this study is designed to see if the proportion responding to T-DXd is around 45%, with results precise enough that the lower end of the

95% confidence interval is above about 27% (a commonly cited historical benchmark in this setting) [2].

What will be measured:

- Primary goal (most important): the percentage of participants whose tumors get smaller (complete or partial response) and stay smaller on a follow-up scan at least 4 weeks later. All scans are read by an independent central review using standard RECIST v1.1 rules to provide an objective assessment [3].
- Other goals: how long people live without their cancer worsening (progression-free survival), how long they live overall (overall survival), and how long responses last once tumors shrink (duration of response). These time-to-event outcomes will be summarized to give a clear picture of how long benefits may last [3].

Safety and tolerability focus:

- All participants receive T-DXd, so there is no randomization or comparison arm. The study closely tracks side effects to understand safety and tolerability, with special attention to lung inflammation (interstitial lung disease/pneumonitis) and heart pumping function (left ventricular ejection fraction), based on known risks with this type of medicine [1].
- Because HER2 levels can change after prior trastuzumab, a new tumor biopsy is required before enrollment to confirm current HER2-positive status, ensuring the study evaluates activity in the intended biomarker-defined group [4].

How the results will be used:

- If T-DXd shows a high and precisely estimated response rate, along with acceptable safety and encouraging measures of cancer control, the results can support further development in this population in the United States. The study is conducted under Good Clinical Practice and ethical principles, with oversight by Institutional Review Boards and public trial registration to promote transparency [5–7].

References

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22.7 What study treatment or study groups are involved?

Everyone in this study receives the same treatment, called trastuzumab deruxtecan (T-DXd). There is no placebo and no other treatment group, and nobody is picked at random for a different treatment.

T-DXd is given as a drip (infusion) into a vein every 3 weeks at a starting dose of 6.4 mg per kilogram of body weight. The first drip takes at least 90 minutes. If that goes well, later drips take at least 30 minutes. If side effects happen, your study doctor may pause treatment or lower the dose, up to two times (first to 5.4 mg/kg, then to 4.4 mg/kg). Once lowered, the dose is not raised again.

If lung inflammation is suspected (for example, new or worsening cough, fever, or shortness of breath), T-DXd is paused straight away and tests are done. If lung inflammation is confirmed and is more than mild, T-DXd is stopped for good and you will be treated with steroids as needed. Heart scans (echocardiogram or MUGA) are done regularly to check how well your heart pumps because this medicine can affect heart function. [1]

While you are on T-DXd, you will not receive other cancer treatments. Medicines to help with symptoms such as nausea, diarrhea, or pain are allowed. Please tell the study team about every medicine, supplement, or herbal product you take. You can stay on treatment until the cancer grows, side effects become too much, or you decide to stop. [1]

References

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22.8 . How will my study group be chosen?

Because this is a single-arm, open-label study, there is no random assignment and no placebo group. If you are eligible and choose to participate, you will be placed in the only study group and receive the investigational treatment trastuzumab deruxtecan (T-DXd) by intravenous infusion every 3 weeks, as described in this consent. There is no element of chance in group assignment, and both you and your study doctor will know the treatment you receive [1,5].

Before you can enter the study group, the study team will confirm that you meet all eligibility criteria during screening. This includes verifying that your tumor is currently HER2-positive on a new biopsy using centralized testing (IHC 3+ or IHC 2+/ISH+ by ASCO-CAP guideline), confirming that you have at least one measurable lesion on CT or MRI per RECIST v1.1, and assessing your general fitness (ECOG performance status 0–1), heart function, and organ function to ensure it is appropriate to proceed with study treatment [2–5].

Your placement in the study group occurs only after you have provided informed consent and all required reviews and approvals are in place, in keeping with Good Clinical Practice, US regulations, and the ethical principle of transparency in research participation [1,5,6].

References

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22.9 How long will I be in the study?

Your total time in the study has several parts. The exact length varies by person and depends on how long the cancer is controlled and how you feel on treatment. You may leave the study at any time for any reason without penalty or loss of benefits to which you are otherwise entitled [1,2].

- Screening: Before receiving study treatment, you will complete screening tests to confirm eligibility, including confirmation of HER2 status on a new biopsy taken after progression on trastuzumab. Screening can take up to 28 days; if you do not meet all requirements, you will not enter the treatment phase [2,3].

- Treatment: If eligible, you will receive the investigational medicine trastuzumab deruxtecan (T-DXd) by intravenous infusion every 3 weeks (a 21-day cycle). Treatment continues until your cancer grows on scans, side effects become unacceptable, you withdraw consent, another discontinuation reason occurs, or the study ends. Dose delays of up to 28 days may be used to allow recovery; a longer delay leads to treatment discontinuation. There is no maintenance therapy, retreatment, or extension phase in this study [3].

- Scans and disease checks while on treatment: CT/MRI scans are planned every 6 weeks (±7 days) during the first year and then every 12 weeks after that, until your cancer worsens or you begin another anticancer therapy. Responses on scans must be confirmed at least 4 weeks later [4].

- End-of-treatment assessments: When study treatment stops for any reason, end-of-treatment assessments will be performed as outlined in the study schedule, followed by a safety follow-up visit 40 days (±7 days) after your last dose [3].

- After treatment follow-up: After the safety visit, the study team will contact you about every 12 weeks to check your health status and whether you have started any new anticancer therapy. This survival follow-up continues until the study ends, you withdraw permission to be contacted, or you are lost to follow-up [2,3].

- Overall study timeframe: Enrollment is planned over about 18–24 months, and the study is expected to finish about 12 months after the last participant’s first dose (about 30–36 months in total). Depending on when you join, your participation (from screening through follow-up contacts) could last from a few months to as long as the study remains open for follow-up [5].

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22.10 What will happen if I take part?

Before you start treatment (screening and consent)

- You will meet with the study team to discuss the study, your options, potential risks and benefits, and your rights. If you choose to join, you will sign a written informed consent form approved by an Institutional Review Board (IRB). Your privacy and safety will be protected under US regulations and Good Clinical Practice, and you may withdraw at any time without penalty [1–4].
- Screening tests (about 28 days or less before your first dose) will check if the study is appropriate for you. These include:

- Medical history, review of your medicines, a physical exam, height and weight, vital signs (blood pressure, pulse, temperature, breathing rate), and performance status.
- Blood and urine tests to check your blood counts, liver and kidney function, electrolytes, and other routine safety labs; a pregnancy test if you could become pregnant.
- A new tumor biopsy taken after your prior trastuzumab-containing therapy to confirm current HER2-positive status by centralized testing, because HER2 levels can change over time. The biopsy procedure and its risks will be explained before it is done [5].
- Scans to measure your cancer (CT or MRI). At least one measurable tumor is required. These baseline images will be used to compare future scans using standard RECIST v1.1 rules [6].
- Heart function testing with an echocardiogram (ECHO) or MUGA scan, and a 12-lead electrocardiogram (ECG), to make sure it is safe to proceed.

- If all eligibility criteria are met, you will be scheduled to begin study treatment.

During treatment

- You will receive trastuzumab deruxtecan (T-DXd) through a vein every 3 weeks (one 21-day cycle). The first infusion takes at least 90 minutes; if tolerated, later infusions take at least 30 minutes. If side effects occur, your doctor may pause treatment or lower the dose to 5.4 mg/kg, and then to 4.4 mg/kg if needed; once lowered, the dose will not be increased again. Treatment continues until your cancer grows, side effects become unacceptable, you withdraw, or another stopping rule is met.
- At each visit before infusion, the team will:

- Ask about your health, any side effects, and any medicines you are taking, and check vital signs.
- Do blood and urine tests; a pregnancy test will be done when required.
- Perform ECGs as scheduled and examine you. Heart function (ECHO or MUGA) will be checked at screening, on Cycle 5 Day 1, and about every 4 cycles thereafter, using the same method each time, because this medicine can affect how well the heart pumps [3,7].
- Monitor carefully for cough, shortness of breath, fever, or new lung symptoms. If lung inflammation (interstitial lung disease/pneumonitis) is suspected, T-DXd will be interrupted immediately and you will have tests (such as imaging). If ILD/pneumonitis is confirmed and is more than mild (Grade 2 or higher), T-DXd will be stopped permanently and you may receive steroids. All suspected lung events may be reviewed by an independent committee to help confirm the diagnosis [3,7].

- Scans to check your cancer (CT or MRI) will be done every 6 weeks (±7 days) during the first year and then every 12 weeks. If your tumors shrink, a follow-up scan at least 4 weeks later

must confirm the change. Scans are also reviewed by an independent central team using RECIST v1.1 [6].
- You will not receive other anticancer therapy while on study treatment. Supportive medicines (for example, for nausea, diarrhea, pain, or infection) are allowed. Dose delays of up to 28 days may be used to allow recovery from side effects.
- There are no patient questionnaires, no extra research blood draws, and no additional biopsies beyond the screening biopsy. There are no pharmacokinetic, immunogenicity, or genetic tests planned.
- Serious and unexpected safety issues that meet federal reporting rules will be reported to authorities under US IND safety reporting requirements; the sponsor will review safety on an ongoing basis [3,8].

When study treatment ends

- When you stop study treatment for any reason, you will have an end-of-treatment visit. This usually includes a review of side effects and medicines, a physical exam, vital signs, blood and urine tests, an ECG, and imaging if a recent scan is not available. Heart testing may be repeated if needed based on your doctor's judgment.
- About 40 days (±7 days) after your last dose, you will have a safety follow-up visit to check for any ongoing or new side effects and to confirm your recovery [3].

After treatment (follow-up)

- After the safety visit, the study team will contact you about every 12 weeks to check on your health, whether you have started any new cancer treatment, and, if you agree, your survival status. These contacts may be by clinic visit, phone, or secure electronic communication. You may choose to stop these follow-ups at any time [3,4].

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22.11 What extra tests, samples, or research procedures will I have?

Overview: what is “extra” in this study

- This study includes some research-specific assessments in addition to routine cancer care. These help confirm eligibility (for example, HER2 testing on a new biopsy), measure the study’s main outcomes (independent central review of scans using RECIST v1.1), and closely monitor known risks of the study drug (heart and lung checks). All required tests are described below with their purpose and frequency. [1,5].

Required research tests and procedures

- New tumor biopsy for central HER2 testing (screening, required): A tissue sample will be taken after your cancer progressed on trastuzumab to confirm current HER2-positive status by centralized testing (IHC 3+ or IHC 2+/ISH+ per ASCO-CAP). This is required because HER2 expression can change over time and accurate, current confirmation is needed for eligibility [3].
- CT/MRI scans for tumor assessment (required): Scans are done every 6 weeks (±7 days) in the first year, then every 12 weeks, to measure tumors per RECIST v1.1. If your tumors shrink, a follow-up scan at least 4 weeks later must confirm the change. An independent central team will also review your scans for the study’s endpoints; your treating team will use local results to guide your care [2].
- Heart function monitoring (required): An echocardiogram (ECHO) or MUGA will be performed at screening, on Cycle 5 Day 1, and about every 4 cycles thereafter (using the same method each time) to monitor left ventricular ejection fraction (LVEF), because decreased LVEF has been observed with HER2-directed therapies including T-DXd in prior studies [6].
- Lung safety checks and ILD adjudication (required): You will be monitored for cough, fever, and shortness of breath at each visit. If interstitial lung disease (ILD)/pneumonitis is suspected, T-DXd will be interrupted and you may have additional imaging. All potential ILD cases will be reviewed by an independent adjudication committee, reflecting known ILD risk observed with T-DXd in earlier trials [6].
- Electrocardiograms (ECGs) and vital signs (required): Triplicate ECGs at screening and additional ECGs during treatment as scheduled, along with vital signs at study visits, to monitor your heart rhythm and overall safety [4].
- Blood and urine tests (required): Routine safety labs (for example, blood counts; liver, kidney, and electrolyte panels) will be done regularly to check organ function and treatment tolerance. Adverse events will be assessed and graded using CTCAE v5.0 [1,4].
- Pregnancy testing (required when applicable): Pregnancy tests will be performed at screening and during treatment when required to protect potential fetuses from risk, consistent with ethical and regulatory standards for research in humans [4,5].
- Safety follow-up and survival checks (required): About 40 days (±7) after your last dose, there will be a safety follow-up to assess recovery from any side effects, and then brief contacts about every 12 weeks to check your health status until the study ends [4].

Procedures not included in this study

- Not planned: pharmacokinetics, pharmacodynamics, immunogenicity, genetic or pharmacogenetic testing, exploratory biomarker testing, optional tissue or blood biobanking, additional research biopsies, ophthalmologic exams related to study drug, patient-reported outcome questionnaires, or electronic diaries. None of these assessments will be collected in this study [4].
- No comparator procedures: There is no randomization or placebo and therefore no procedures related to blinding or crossover [4].

Which results will you receive

- Your treating team will discuss results used for your care (for example, local scan reports, safety labs, heart tests, and the central HER2 test that determines eligibility).

- The independent central review of imaging and the ILD adjudication are performed for research analyses and oversight; they are not intended to direct your day-to-day medical decisions.
- Any serious and unexpected risks identified during the study will be handled and reported according to US IND safety reporting requirements, with ongoing sponsor safety review [7]. You will be informed of new information that might affect your willingness to continue, in line with Good Clinical Practice and the Declaration of Helsinki [4,5].

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22.12 Will my samples or data be used in the future?

Will my samples be stored or used for other research in the future?

- No extra research samples are collected in this study. The only tissue used is the required screening biopsy to confirm current HER2 status at a central laboratory. There is no plan to store leftover tissue or blood for future genetic, biomarker, pharmacogenetic, or other secondary research, and no optional biobanking is included in this study [1–3].
- Because no future-use biobanking is planned, you will not be asked to provide separate consent for optional future use of samples [1–3].
- Authorized monitors, auditors, the study sponsor (Sample Pharma Co., Ltd.), and regulatory authorities may review your source records to check study data. These reviews are for oversight and quality purposes and are conducted under confidentiality protections required by Good Clinical Practice and US regulations [1,4].

How your study data may be used and shared in the future

- Your identifiable information will be protected. Study data are recorded with a code and handled confidentially; people outside the study will not be able to identify you in reports or publications. Regulators and ethics boards may review identifiable records under confidentiality to verify the study is conducted properly, consistent with Good Clinical Practice and US regulations [1,4].

- Summary results from this study will be made public in scientific publications and presentations and will be posted on ClinicalTrials.gov as required. These results are presented in aggregate and will not include information that can identify you [2,6].
- Sharing of individual participant data (the detailed data from each person) with other researchers is not planned for this study. If any future proposal to share de-identified individual data arises, it would occur only in accordance with applicable laws, ethics approval, and consent requirements [1–3].
- Study records will be retained for the time required by US regulations (for example, investigator records for IND studies are typically kept for at least 2 years after the study ends or after any marketing application is approved or discontinued) and may be reviewed during that period by regulators or auditors; retention does not change the confidentiality protections described above [1,5].

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22.13 What possible risks or discomforts can I expect?

Overview: common, serious, and unknown risks

- Trastuzumab deruxtecan (T-DXd) is investigational in this study. Like all medicines, it can cause side effects. Some are common and manageable; others can be serious or life-threatening. Not everyone has every side effect.
- Serious risks include lung inflammation (interstitial lung disease/pneumonitis), low white blood cells with infection or fever, heart problems, and severe allergic or infusion reactions. These can require hospitalization and, rarely, can be fatal [1,2].
- Because this is research, there may be side effects we do not know about yet. You will be told about any new information that may affect your willingness to continue, and serious unexpected risks will be reported to regulators as required [3,7,8].

Blood problems

- Low white blood cells (neutropenia), which can raise your risk of infection; fever with low white cells (febrile neutropenia) is a medical emergency. Low red blood cells (anemia) can cause tiredness or shortness of breath. Low platelets (thrombocytopenia) can cause easy bruising or bleeding [1,2].
- What we will do: check your blood counts regularly; delay or reduce doses; use antibiotics, growth factors, or transfusions if needed; instruct you to seek urgent care for fever of 100.4°F (38°C) or higher or signs of infection [1,3,4].

Infection

- You may develop infections (for example, chest, urinary, or bloodstream infections), especially if your white blood cells are low. Sepsis is a severe bloodstream infection that can be life-threatening and needs immediate care [1,4].
- What we will do: educate you on infection signs, provide prompt evaluation, and treat with antibiotics and supportive care as needed. Call right away for fever, chills, cough, burning with urination, or new confusion [3,4].

Stomach and bowel problems

- Nausea, vomiting, loss of appetite, diarrhea or constipation, abdominal discomfort, and mouth sores can occur. Dehydration and weight loss can result if symptoms are not controlled [1,2].
- What we will do: prescribe anti-nausea and anti-diarrheal medicines, recommend diet and hydration strategies, and adjust or delay doses if needed [1,3].

Heart or circulation problems

- Decreased heart pumping strength (left ventricular ejection fraction decrease) and heart failure have been seen with HER2-directed therapies including T-DXd. Symptoms can include shortness of breath, swelling of legs, rapid weight gain, cough, chest pain, or new fatigue [1,2].
- What we will do: check heart function with echocardiogram (ECHO) or MUGA at screening, on Cycle 5 Day 1, and about every 4 cycles; monitor ECGs and vital signs; interrupt, reduce, or stop treatment if your heart function worsens or symptoms develop [1,3].

Lung and breathing problems (including interstitial lung disease/pneumonitis)

- Inflammation of the lungs (ILD/pneumonitis) is a known and potentially serious risk with T-DXd. In an earlier study of T-DXd in stomach cancer, about 1 in 10 people developed it. It can cause cough, shortness of breath, fever, chest tightness, or new/worsening fatigue. ILD/pneumonitis can be severe or fatal if not recognized and treated quickly [1,2].
- What we will do: ask about breathing symptoms at every visit; if ILD/pneumonitis is suspected, we will immediately pause T-DXd, do tests (such as imaging), and may start steroids. If ILD/pneumonitis is confirmed and is more than mild, T-DXd will be stopped permanently. An independent committee will review all potential ILD cases [1–3].

Liver or kidney test changes

- Blood tests may show increases in liver enzymes (for example, AST/ALT) or bilirubin. Rarely, more serious liver problems can occur. Changes in kidney tests may also happen, often related to dehydration or other factors [1,2].
- What we will do: monitor liver and kidney tests regularly; adjust, delay, or stop treatment if significant changes occur; treat contributing factors such as dehydration [1,3].

Allergic or infusion reactions

- Reactions during or after infusion may include fever, chills, flushing, rash, hives, itching, dizziness, headache, nausea, shortness of breath, chest tightness, low or high blood pressure, or, rarely, a severe life-threatening allergic reaction (anaphylaxis) [1].
- What we will do: monitor you closely during infusions; slow or stop the infusion and give medicines (such as antihistamines or steroids) if a reaction occurs; for severe reactions, treatment will be stopped and emergency care provided [1,3].

Fatigue, pain, and other general symptoms

- Tiredness, weakness, hair loss, changes in taste, headache, muscle or joint aches, and sleep disturbance are common with anti-cancer drugs including T-DXd. These can affect daily activities and mood [1,2].
- What we will do: recommend activity pacing, nutrition, and symptom-relief strategies; adjust treatment as needed if symptoms become severe [1,3].

Neurological symptoms

- Dizziness and headache can occur. Numbness or tingling may happen but are less common. Report any new confusion, severe headache, visual changes, or weakness right away [1,2].
- What we will do: assess symptoms, rule out other causes (such as infection or electrolyte changes), and adjust treatment if needed [1,3].

Reproductive and pregnancy-related risks

- T-DXd can harm an unborn baby (embryo-fetal toxicity). You should not become pregnant or father a child while on this study. Do not breastfeed during treatment and for a period after the last dose, because the medicine may pass into breast milk and harm a nursing infant [1].
- What we will do: perform pregnancy testing when required; counsel on effective birth control during treatment and for the recommended time after the last dose; stop study treatment immediately if pregnancy occurs and discuss options and risks [1,3].

Other study-related procedure risks

- Biopsy (screening): Pain, bleeding, bruising, infection, and, depending on the biopsy site, rare complications such as a collapsed lung (with some lung biopsies) can occur [5].
- IV line and blood draws: Pain, bruising, bleeding, infection, or vein irritation can occur at the needle site.
- CT/MRI scans and contrast: CT uses ionizing radiation. Contrast dyes (iodinated for CT or gadolinium-based for MRI) can rarely cause allergic reactions or affect kidney function in at-risk people; most reactions are mild and treatable [6].
- What we will do: use sterile technique; monitor for and treat reactions; screen kidney function and allergy history; use contrast only when needed and with precautions; minimize radiation exposure consistent with clinical need [3,6].

Unknown or unexpected risks

- Side effects not known today could occur, including those that are serious or long-lasting. The risk may be higher in people with other medical conditions or when combined with other medicines [1,3].
- What we will do: monitor you closely at every visit with exams, labs, heart and lung checks; change the dose, delay, or stop treatment if needed; give supportive care; promptly report serious and unexpected risks to regulators; and inform you of new findings that could affect your decision to continue [1,3,7,8].

When to seek urgent care

- Call the study team or seek emergency help immediately for any of the following: fever of 100.4°F (38°C) or higher, shaking chills, new or worsening cough or shortness of breath, chest pain, severe headache or confusion, severe diarrhea or vomiting, signs of allergic reaction (hives, swelling of face or throat, trouble breathing), heavy bleeding, or sudden swelling of legs [1,3,4].

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22.14 Pregnancy, contraception, fertility, and breastfeeding risks

Why pregnancy and breastfeeding precautions are needed

- The study drug, trastuzumab deruxtecan (T-DXd), can harm an unborn baby. Based on how it works and data from studies, there is a risk of embryo-fetal harm if exposure occurs during pregnancy. Do not become pregnant or father a child while receiving T-DXd [1].
- T-DXd may pass into breast milk and could harm a nursing infant. Do not breastfeed while on treatment and for a period after the last dose [1].

Contraception: who needs it and for how long

- If you can become pregnant: Use effective birth control during the study and for 7 months after your last dose of T-DXd [1].
- If you are a male with a partner who can become pregnant: Use effective birth control during the study and for 4 months after your last dose of T-DXd [1].
- What “effective” birth control means: Highly effective methods include intrauterine devices (IUDs), implants, sterilization, or correctly used hormonal methods; barrier methods (for example, condoms) help reduce risk and are recommended in combination with another method. Your study team can help you choose options that fit your situation [2].
- If a method fails or is missed: Use emergency contraception as appropriate and contact the study team promptly for guidance [2].

Pregnancy testing

- If you can become pregnant, a pregnancy test will be done before you start treatment and during the study when required to protect against fetal exposure [1,3].

If pregnancy happens during the study

- If you become pregnant: Tell the study team immediately. Study treatment will be stopped. You will be counseled about potential risks, and the pregnancy will be followed to outcome with your permission [1,3].
- If your partner becomes pregnant (for male participants): Tell the study team immediately. With the partner’s permission, the pregnancy will be followed to outcome. No study drug is given to partners [3].
- The study team will report pregnancies and outcomes as required by research regulations and good clinical practice [3].

Breastfeeding

- Do not breastfeed during treatment and for 7 months after your last dose of T-DXd, because the medicine may harm a nursing infant [1].

Fertility and family planning

- T-DXd may affect fertility in males based on findings from animal studies. If having children in the future is important to you, talk with your doctor about options such as sperm banking before starting treatment. Fertility preservation counseling is recommended as early as possible in cancer care [1,4].

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22.15 What possible benefits can I expect?

You may or may not receive direct medical benefit from taking part. The main reason for this study is to learn whether the investigational drug trastuzumab deruxtecan (T-DXd) can shrink tumors or keep them from growing in people with HER2-positive gastric or gastro-oesophageal junction cancer after prior trastuzumab, and how long any benefits last, using standard imaging rules for defining tumor response [1,2].

Possible individual benefits, which cannot be guaranteed, include:

- Tumor shrinkage (response). In a prior randomized Phase 2 study conducted in Japan and Korea in a similar setting, people who received T-DXd had a higher rate of tumor shrinkage than those who received standard chemotherapy (51% vs. 14%) [1].
- Longer time before the cancer worsens and longer survival. In that same study, people treated with T-DXd lived longer without their cancer getting worse (median 5.6 vs. 3.5 months) and lived longer overall (median 12.5 vs. 8.4 months) than those who received physician’s choice chemotherapy [1].

However, results from earlier studies may not be the same for every person or in this US study, and there is no guarantee that you will experience tumor shrinkage, disease control, or longer survival [1–3].

Even if you do not benefit directly, information from this study may help doctors learn more about T-DXd and HER2-positive gastric/GEJ cancer and could help future patients, in line with ethical principles for medical research [3,4].

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22.16 What are the costs, payments, and reimbursements?

What will the study pay for

- The study drug, trastuzumab deruxtecan (T-DXd), is investigational in this setting and will be provided to you at no cost by the study sponsor, Sample Pharma Co., Ltd.
- Tests and procedures done only for this study will be paid for by the sponsor. This includes:

- The central HER2 test on the new biopsy that confirms your current HER2 status.
- The independent central review of your scans used for the study's main results.

- These arrangements are part of what must be explained to you in this consent form under US and international research standards [1–3].

What your insurance may be billed for

- Routine cancer care you would receive even if you were not in this study will be billed to you or your health insurance in the usual way. This typically includes regular clinic visits, standard blood and urine tests, routine imaging done for your care, and supportive medicines (for example, anti-nausea drugs, antibiotics, growth factors, or transfusions) when needed.
- Your normal copayments, coinsurance, and deductibles apply. The study team can help you check coverage with your insurer before you start.

Travel and parking reimbursement

- Reasonable travel and parking costs for required study visits can be reimbursed with receipts, following the site's reimbursement policy. Ask the study team how to submit receipts and the limits that apply.

Payment for taking part

- You will not be paid for taking part in this study.

If you are injured or hurt because of the study

- Please see the section titled "What happens if I am injured or hurt because of the study?" for information on medical care and who to contact if an injury occurs [1–3].

Who to contact with billing questions

- If you have questions about what will be billed to you or your insurance, or what the study pays for, contact the study team. They can explain which items are covered by the study and which may appear on your medical bills, consistent with consent guidance for clinical research [1–4].

References

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22.17 What happens if I am injured or hurt because of the study?

If you need urgent help

- If you have a medical emergency, call 911 or go to the nearest emergency room right away. As soon as you can, tell the study team what happened.
- For non-emergencies, contact the study team first. They will tell you what to do and help arrange care.

Medical care and payment if you are injured by the study

- If you are hurt or become ill as a direct result of the investigational study drug trastuzumab deruxtecan (T-DXd) or a procedure required only for this study, you will get the medical care you need.
- Sample Pharma Co., Ltd., the study sponsor, holds clinical trial insurance for this study. The sponsor (through its insurance) will pay the reasonable costs of that care that are not covered by your health insurance.
- You will not have to pay the part that the sponsor agrees to cover under this arrangement. This approach follows accepted ethical and good clinical practice standards for research-related injuries [1,2].

What is not covered

- The sponsor will not pay for:

- Care for your underlying cancer or other standard medical care you would have received even if you were not in this study.
- Injuries or illnesses that are not directly caused by T-DXd or a study-required procedure.
- Injuries that happen because you did not follow the study team’s instructions.

No other payments

- There is no additional payment for other costs such as lost wages, time away from work, or discomfort.

Your legal rights

- By signing this form, you do not give up any of your legal rights. Research ethics and US regulations do not allow consent forms to include language that makes you waive your legal rights [3,4].

Who to contact about an injury or your rights

- If you think you have been injured or made ill by the study, contact the study doctor as soon as possible. If you have questions about your rights as a research participant, contact the

Institutional Review Board (IRB). Their phone numbers and emails are listed in the Contacts section of this form [1,4].

References

1. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
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22.18 Can I stop taking part in the study?

Your choice to take part

Taking part in this study is your choice. You may stop participating at any time, for any reason, without penalty, without giving a reason, and without losing access to your usual medical care or benefits to which you are otherwise entitled [1–3].

If you decide to leave the study, tell the study team so they can stop study procedures safely and discuss your care options [1–3].

When the study team may stop your participation

The study doctor, the sponsor (Sample Pharma Co., Ltd.), the Institutional Review Board (IRB), or a regulatory authority may stop your study treatment or remove you from the study to protect you or to maintain study integrity, including for the following reasons [2–6]:

- Safety concerns such as serious or unacceptable side effects, interstitial lung disease/pneumonitis, heart problems, allergic/infusion reactions, or other medical issues that make continued treatment unsafe under the protocol.
- Pregnancy or intent to become pregnant; if pregnancy occurs, study treatment will be stopped immediately.
- Disease progression, lack of benefit, or clinical deterioration where continued study treatment is not in your best medical interest.
- Non-compliance with study visits, tests, or instructions that prevents safe conduct of the study.
- Need for treatments or procedures not allowed by the protocol.
- Study closure or administrative reasons, such as study termination by the sponsor, IRB suspension/termination, or a regulatory action (for example, an IND clinical hold) [4–6].
- Other protocol-defined reasons for stopping that apply to your situation.

You will be told about any new information that may affect your willingness to continue in the study [1–3].

What follow-up may be requested if you stop

If you stop study treatment early, you may be asked to:

- Complete an end-of-treatment visit and a safety follow-up visit about 40 days (+7) after your last dose to check on your health and any ongoing side effects, including those that can appear after treatment stops (for example, lung or heart problems) [1–3].
- Allow continued contact every 12 weeks to ask about your health and survival until the study ends, unless you decline further contact [1–3].

These follow-up activities help monitor your safety and support accurate study results. You may refuse any or all follow-up after withdrawal; your decision will be respected, and your usual medical care will continue [1–3].

Use of your information if you leave the study

If you withdraw, the study team may continue to use information already collected about you to protect your safety, meet legal/regulatory obligations, and ensure the reliability of the research. You can choose whether the study team may continue to collect new information about you after you leave; if you do not want additional information collected, tell the study team, and no further data will be gathered except where required by law or to ensure safety and data integrity [1–3].

References

1. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
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22.19 What are my rights in this study?

Your participation is voluntary

- Taking part is your choice. You may refuse or agree to join, and you may leave at any time without penalty or loss of benefits or care to which you are otherwise entitled [1,3].
- You do not give up any of your legal rights by signing this form. Consent forms may not include language that waives your legal rights or releases the researchers, sponsor, or institution from liability for negligence [4].

Your right to ask questions and get a copy of this form

- You can ask questions at any time before, during, and after the study, and you will get clear answers from the study team [2,3].
- You will receive a copy of the consent form that you sign [5].

Your right to receive new information

- If new information becomes available that might affect your willingness to continue (for example, new safety findings or changes in procedures), you will be told promptly so you can decide whether to stay in the study [1–3].

Your right to stop participating

- You may withdraw from the study at any time, for any reason. This will not affect your regular medical care or benefits [1,3].
- If you leave the study, you can choose whether the team may continue to collect new health information about you; information already collected may still be used as needed to protect your safety and meet legal or regulatory duties [2].

Independent ethics review and oversight

- This study has been reviewed and approved by an Institutional Review Board (IRB), an independent committee that makes sure the study is ethical and that your rights and welfare are protected [6]. The IRB also checks that risks are minimized, that informed consent is adequate, and that your privacy and the confidentiality of your data are protected [6].
- Research must follow recognized ethical standards, including the Declaration of Helsinki and Good Clinical Practice (GCP) [2,3].

Your privacy and confidentiality

- Your personal information will be handled as confidential to the extent allowed by law and regulations. People who are authorized to review research records to ensure the study is done properly may look at your identifiable records, including the study sponsor's monitors, the IRB, and the U.S. Food and Drug Administration (FDA) [1,2,7–9].
- The consent process will describe who may access, use, share, and protect your identifiable health information, and for how long, and will ask for your authorization as required by U.S. privacy rules [1,2,10].
- Any public reports or publications from this study will not include information that can directly identify you [2,3].

Your choices about optional samples or future research

- This study does not include any optional samples or future research use of your samples, so there are no extra choices to make [1–3,10].
- If you agree now, you can change your mind later and withdraw your authorization for future use that has not yet occurred, as allowed by law and the terms described in the consent [10].

Your access to study results

- You have the right to be informed about the overall results of the study. A lay summary or results information will be made available after the study ends, consistent with ethical guidance and good practice for protocol transparency and dissemination [3,11].

References

1. US Food and Drug Administration. Informed consent elements. 21 CFR 50.25. Silver Spring (MD): FDA; current as of 2026. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/section-50.25
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22.20 Who will see my medical information?

Who may see and use your study information

Your medical information for this study will be handled as confidential and shared only with authorized people for research, oversight, or legal/regulatory purposes, as described below and consistent with Good Clinical Practice and U.S. regulations [1,4,8]:

- The study team at your site (investigator, research nurses/coordinators, and authorized clinic staff) to provide your care, collect data, and manage your participation [1].
- The sponsor, Sample Pharma Co., Ltd. (and its authorized contract research organizations), for study management, safety monitoring, data analysis, and quality assurance. Sponsor-appointed monitors and auditors may review your identifiable source records at the site to verify that the study data are accurate and complete [1].
- Independent reviewers and vendors that support the study, using coded data wherever possible:

- The central laboratory that confirms HER2 status on your biopsy.
- The independent central imaging review organization that evaluates your scans for the study endpoints.
- The independent committee that reviews potential interstitial lung disease (ILD/pneumonitis) cases.
- Secure electronic data capture and trial management system providers that host the study database [1].

- The Institutional Review Board (IRB) that oversees the study's conduct and your rights and welfare. The IRB may review identifiable research records and consent documentation as part of its oversight [8].
- U.S. regulatory authorities (for example, the U.S. Food and Drug Administration) that may inspect the study, the site, or the sponsor. Inspectors can review, copy, and verify study records that identify you, including medical records relevant to the research [3].
- Required safety reporting recipients. Certain safety reports (for example, serious and unexpected adverse events) must be submitted to the FDA and IRB according to law and may include the minimum necessary information to evaluate the event [6].

You will also be asked to sign a separate authorization form that explains in detail how your health information will be used and shared for this study, how long the authorization lasts, and how to cancel it in writing [4].

How your information will be protected

- Your study data will be coded with a unique study identification number. The document that links your name or other direct identifiers to this code (the "linking log") will be kept only at the site in secure files with access restricted to authorized site staff. Data sent to the sponsor,

central reviewers, labs, or vendors will ordinarily use this study code and not your name or other direct identifiers [1,4].
- Only the minimum necessary information will be collected, used, and disclosed to accomplish the research and oversight purposes described in this form, consistent with HIPAA requirements [4].
- Electronic systems used for the study will employ role-based access controls and security safeguards; data transfers will use secure methods consistent with GCP and institutional policies [1].
- If data are de-identified in accordance with HIPAA standards (removal of specified direct identifiers or expert determination), they may be used for additional analyses, quality assurance, or lawful secondary uses without further authorization, as permitted by law [5]. Any such use will not allow direct identification of you.

Publications, trial registration, and public reports

Results from this study may be presented at scientific meetings, posted to public registries, and published in journals. These reports will describe aggregate findings and will not include information that directly identifies you, in line with ethical principles for research [7,9].

Record retention and regulatory access

The site will keep your study records as required by law and regulation. Under FDA regulations, investigators must maintain required study records for at least 2 years after the marketing application is approved for the drug for the indication studied or, if no application is filed or approved for that indication, for 2 years after the investigation is discontinued and FDA is notified. During this retention period, the FDA may inspect these records, including identifiable source documents relevant to the study [2,3].

If you withdraw from the study

If you withdraw, information already collected may still be used to protect your safety, ensure data reliability, and meet legal or regulatory requirements. You may choose whether the study team can continue to collect new information about you after withdrawal, except where continued collection is required by law or necessary for safety and data integrity, as described in this form and allowed by GCP and HIPAA [1,4].

References

1. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
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22.21 Will I be told about new information or study results?

New information during the study

- You will be told promptly about any important new information that becomes available during the study and could affect your willingness to continue (for example, new safety findings, changes in study procedures, or new alternatives). If this happens, the study team will explain the information and what it may mean for you so you can decide whether to stay in the study [1–3].
- If the consent form needs to be updated because of new information, you may be asked to sign a new consent before continuing, in accordance with Good Clinical Practice and IRB requirements [2,3].

Important safety findings

- If new or increased risks are identified (such as safety concerns related to trastuzumab deruxtecan [T-DXd], including interstitial lung disease/pneumonitis or effects on heart function), you will be informed as soon as possible and advised about any changes to monitoring, treatment, or follow-up that may be needed [1–3].
- Urgent safety information may be shared first by phone or at a visit and then followed by a written update or revised consent, as appropriate and approved by the IRB [1–3].

Protocol changes that may affect you

- If the protocol is changed in a way that could affect you (for example, visit schedules, procedures, or eligibility), the study team will explain the change and any impact on your participation. You may be asked to re-consent before continuing under the amended protocol, as required by the IRB [2,3].

How you will be updated

- The study team will communicate new information through in-person discussions during clinic visits, secure phone calls, or written notices. Copies of any revised consent form that you sign will be provided to you [1–3].

Study results, publications, and summaries

- After the study ends and the data are analyzed, a summary of the overall results will be made available. Results may be presented at scientific meetings and published in medical journals; these reports will not include information that directly identifies you [2,3].
- The sponsor will register the trial on ClinicalTrials.gov and will post summary results as required by U.S. law and policy (42 CFR Part 11). The study team can tell you when results are posted and how to find them [4].
- A plain-language (lay) summary of the overall study results will be offered or made accessible to participants after results are available, consistent with ethical guidance and good practice for protocol transparency and dissemination [3,5].

Your own clinical findings

- Your treating study doctor will discuss your own clinically relevant test results with you (for example, imaging assessments, heart function tests, and evaluations for possible lung inflammation) during the study, and will explain what they may mean for your care [2,3].

References

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22.22 What happens after the study ends?

After your last study dose

- You will have a safety follow-up visit about 40 days (+7) after your last infusion to check your health and any ongoing or new side effects. Safety findings of concern (for example, possible interstitial lung disease/pneumonitis or heart function changes) will be followed until they resolve or stabilize, even if this extends beyond your last scheduled study visit [1,2].
- After the safety visit, the study team may contact you about every 12 weeks to ask about your health and survival until the study ends, unless you decline further contact. These contacts help monitor safety and support accurate study outcomes [1,3].

After the study ends

- Your participation in study-specific procedures will stop. If any study-related side effects are ongoing at study end, the study doctor will continue appropriate medical follow-up or coordinate this with your regular healthcare providers until the issue resolves or stabilizes, consistent with ethical requirements for post-research care and Good Clinical Practice [1,2].
- Your regular medical care will continue with your usual doctors. The study team will share clinically relevant information needed for your ongoing treatment with your permission and consistent with privacy rules [1].

Return to usual care and transfer of care

- You and your primary oncology team will decide on next steps for your treatment based on standard care options available to you. The study doctor will provide a treatment summary and relevant test results to your regular doctors, when appropriate, to support a smooth transition back to usual care [1,2].
- Costs for your ongoing, non-research medical care after the study will be handled in the usual way by you and your health insurance.

Access to further treatment with the study drug

- If you are still benefiting from T-DXd without unacceptable side effects when your study treatment ends or the study closes, and no suitable alternative is available, the sponsor plans to keep providing T-DXd through a continued-access or expanded-access program, if the FDA and the IRB allow it. This would continue until your cancer grows, side effects become

too much, you decide to stop, or T-DXd becomes available to you outside the study. Your study doctor will discuss this with you [2].

Ongoing safety information and contacts

- Important new safety information that becomes known after you finish study visits but before the study closes will be shared with you if it could affect your health or the advice you should follow, consistent with Good Clinical Practice and informed consent regulations [1,3].
- You may be contacted after the study ends if additional safety follow-up is necessary or if regulators require confirmation of important safety information related to your participation [1].

How overall study results will be shared

- After data are analyzed, a summary of the overall results will be shared in publications or scientific meetings and posted to ClinicalTrials.gov as required by U.S. law (42 CFR Part 11). These reports will not include information that directly identifies you [2,4].
- A plain-language (lay) summary of the overall study results will be made available to participants or accessible through appropriate channels after results are available, consistent with Good Clinical Practice and trial protocol guidelines [1,5].

References

1. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
2. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants. Adopted by the 75th WMA General Assembly, Helsinki, October 2024. Ferney-Voltaire (France): WMA; 2024. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-participants/
3. US Food and Drug Administration. Informed consent elements. 21 CFR 50.25. Silver Spring (MD): FDA; current as of 2026. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/section-50.25
4. US Department of Health and Human Services. Clinical Trials Registration and Results Information Submission. 42 CFR Part 11. Washington (DC): HHS; current as of 2026. Available from: https://www.ecfr.gov/current/title-42/chapter-I/subchapter-D/part-11
5. Chan A-W, Boutron I, Hopewell S, Moher D, Schulz KF, Collins GS, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. BMJ. 2025;389:e081477. doi:10.1136/bmj-2024-081477. Available from: https://www.bmj.com/content/389/bmj-2024-081477

22.23 Where can I get more information?

Who to contact

- Study doctor and research team: For questions about the study procedures, visits, side effects, new or worsening symptoms, or to withdraw from the study, contact your study doctor or research coordinator. Daytime and after-hours contact details will be provided on your consent form and site contact card, as required by U.S. regulations and Good Clinical Practice [1,2].
- Medical emergencies: In a medical emergency, call 911 or seek immediate care. As soon as you can, notify the study doctor using the after-hours contact provided to you [1,2].
- Your rights and concerns: For questions about your rights as a research participant or to discuss concerns or complaints confidentially, you may contact the Institutional Review Board (IRB) that reviewed this study. The IRB's name and contact information are listed on your consent form, consistent with U.S. regulations on informed consent and IRB oversight [1,3].
- Privacy and authorization: For questions about how your identifiable health information is used or shared for this study, or to exercise your privacy rights under the authorization you sign, contact the Privacy Office listed in your HIPAA research authorization form [4].

Sponsor contact

- Sponsor: Sample Pharma Co., Ltd. For general information about the study or to report a product complaint, you may contact the sponsor using the details provided on your consent form or site contact sheet [2].

Public information

- Clinical trial registry: A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. You can ask the study team for the study's registry number (NCT number) [5,6].

Copies of documents

- You will receive a copy of the consent form that you sign. You may request additional copies or updates (for example, if the consent is revised) at any time [1,2,7].

References

1. US Food and Drug Administration. Informed consent elements. 21 CFR 50.25. Silver Spring (MD): FDA; current as of 2026. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/section-50.25
2. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
3. US Food and Drug Administration. Protection of human subjects; IRBs—IRB functions and operations. 21 CFR 56.109. Silver Spring (MD): FDA; current as of 2026. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-56/section-56.109
4. US Department of Health and Human Services. HIPAA Privacy Rule—Uses and disclosures for research (Authorizations and Waivers). 45 CFR 164.508 and 45 CFR 164.512(i). Washington (DC): HHS; current as of 2026. Available from: https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-C/part-164/subpart-E
5. US Department of Health and Human Services. Clinical Trials Registration and Results Information Submission. 42 CFR Part 11. Washington (DC): HHS; current as of 2026. Available from: https://www.ecfr.gov/current/title-42/chapter-I/subchapter-D/part-11
6. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants. Adopted by the 75th WMA General Assembly, Helsinki, October 2024. Ferney-Voltaire (France): WMA; 2024. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-participants/
7. US Food and Drug Administration. Documentation of informed consent. 21 CFR 50.27. Silver Spring (MD): FDA; current as of 2026. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/section-50.27

22.24 Who can answer my questions?

The following contacts will be provided to you and kept current, consistent with U.S. informed consent requirements and Good Clinical Practice. You will receive daytime and after-hours details for the study doctor, a contact for participant rights, and administrative contacts before enrollment [1,2]. Independent ethics oversight information will be provided, and contacts must be clearly stated in consent materials as required by ethical principles and protocol guidelines [3,4].

Purpose	Primary contact (role)	Phone	Email	Site/Organization
Medical questions about the study treatment (for example,	Principal Investigator (Study Doctor)	Daytime: to be provided;	to be provided	Your study site (site name and

trastuzumab deruxtecan dosing, visits, side effects)		After-hours: to be provided		address to be provided)
Urgent study-related health concerns (24/7)	On-call Study Physician or Qualified Sub-Investigator	24/7 phone: to be provided	to be provided	Your study site (site name and address to be provided)
Questions about your rights as a research participant or to report a complaint	Institutional Review Board (IRB) Office (not part of the study team)	to be provided	to be provided	IRB name and address to be provided
General study administration (appointments, scheduling, transportation/reimbursement, records requests, withdrawal)	Research Coordinator/Study Nurse	Daytime: to be provided	to be provided	Your study site (site name and address to be provided)

Sponsor information (for general study information or product complaints): Sample Pharma Co., Ltd.; contact details will be provided on your site-specific contact sheet [2].

References

1. US Food and Drug Administration. Informed consent elements. 21 CFR 50.25. Silver Spring (MD): FDA; current as of 2026. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/section-50.25
2. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
3. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants. Adopted by the 75th WMA General Assembly, Helsinki, October 2024. Ferney-Voltaire (France): WMA; 2024. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-participants/
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22.25 Consent declaration and signatures

Participant statement and consent

By signing below, I confirm that:

- I have read this consent form, or it has been read to me in a language I understand, and I have had the opportunity to ask questions. My questions were answered to my satisfaction [1,3,4].
- I understand the purpose of the study, the procedures involved, the reasonably foreseeable risks and discomforts, potential benefits, and my alternatives, as described in this form [1,3,4].
- I understand that taking part in this research is voluntary. I may refuse to participate or withdraw at any time without penalty or loss of benefits to which I am otherwise entitled, and my medical care will not be affected by my decision [1,4].
- I authorize the collection and use of my study information and the access to my study records by the study team, the sponsor (Sample Pharma Co., Ltd.), oversight bodies (including the IRB), and regulatory authorities, as described in this consent form. I understand I will also be asked to sign a separate HIPAA authorization for the use and disclosure of my protected health information for research, and that I will receive a copy of any consent/authorization I sign [1–3,5].
- I voluntarily agree to take part in this study (protocol SP-TDXD-GC-201), including receiving the investigational drug trastuzumab deruxtecan (T-DXd) as described in this form [1,3,4].

I will receive a copy of this signed and dated consent form [2].

Documentation of consent and signatures

Participant (or Legally Authorized Representative) and study personnel must complete all applicable fields at the time consent is obtained, before any study-specific procedures.

Role	Printed name	Signature	Date (YYYY-MM-DD)	Time (HH:MM, local)
ParticipantParticipant				

If consent is provided by a Legally Authorized Representative (LAR), complete the following and provide reason LAR is signing (e.g., lack of decision-making capacity). If participant is able, obtain participant's assent below.

Role	Printed name	Signature	Date (YYYY-MM-DD)	Time (HH:MM, local)	Relationship to participant	Reason LAR is signing
Legally Authorized Representative (if applicable)Legally Authorized Representative (if applicable)						

Participant assent (if applicable):

Role	Printed name	Signature	Date (YYYY-MM-DD)	Time (HH:MM, local)
Participant assentParticipant assent				

Person obtaining consent (must be authorized on the study delegation log) — attestation:
"I have explained the research, including its purpose, procedures, risks, potential benefits, and alternatives, answered all questions, and confirmed that consent was given freely without coercion or undue influence." [1–4]

Role	Printed name	Signature	Date (YYYY-MM-DD)	Time (HH:MM, local)
Person obtaining consentPerson obtaining consent				

Investigator (if required by IRB/site policy) — acknowledgment:
"I confirm that the participant (or LAR) provided informed consent prior to any study procedures." [2,3]

Role	Printed name	Signature	Date (YYYY-MM-DD)	Time (HH:MM, local)
InvestigatorInvestigator				

Impartial witness (required when the participant or LAR cannot read or when a short-form consent process is used) — statement:
"I was present for the entire consent discussion. The information in the consent form and any other written information was accurately explained, appeared to be understood, and consent was given freely." [2,3]

Role	Printed name	Signature	Date (YYYY-MM-DD)	Time (HH:MM, local)	Language of discussion (if not English)
Impartial witness (if required)Impartial witness (if required)					

Administrative fields

- IRB-approved consent version/date:
- Site name/number:
- Participant study ID:

References

1. US Food and Drug Administration. Informed consent elements. 21 CFR 50.25. Silver Spring (MD): FDA; current as of 2026. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/section-50.25
2. US Food and Drug Administration. Documentation of informed consent. 21 CFR 50.27. Silver Spring (MD): FDA; current as of 2026. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/section-50.27
3. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf
4. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants. Adopted by the 75th WMA General Assembly, Helsinki, October 2024. Ferney-Voltaire (France): WMA; 2024. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-participants/
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22.26 Optional consent modules

This study does not include any optional activities or add-on research modules; your decision to join the main study is the only consent decision. No leftover blood or tissue samples will be stored for future research (no biobanking, genetic or other future studies), and your individual study data will not be shared with other researchers or linked with outside records. There are no extra choices to make or initial, and no separate optional consents apply in this study [1,2].

References

1. US Food and Drug Administration. Informed consent elements. 21 CFR 50.25. Silver Spring (MD): FDA; current as of 2026. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/section-50.25
2. International Council for Harmonisation. ICH E6(R3) Guideline for Good Clinical Practice. Final version, 16 June 2026. Geneva: ICH; 2026. Available from: https://database.ich.org/sites/default/files/ICH%20E6%28R3%29_Step4_FinalConsolidatedGuideline_2026_0616_.pdf