CLINICAL STUDY PROTOCOL

SBT777101-01

Protocol Number:	**SBT777101-01**
Study Title:	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Activity of Single Ascending Doses of SBT777101 in Subjects with Rheumatoid Arthritis
Investigational Product:	SBT777101
IND Number:	
Sponsor Name:	Sonoma Biotherapeutics, Inc.
Legal Registered Address:	201 Haskins Way, Suite 203 South San Francisco, CA 94080
Sponsor's Medical Director	Leonard L. Dragone MD, PhD Chief Medical Officer
Medical Monitor	Same as above
Version Number / Approval Date:	1.0 / June 03, 2022

Sponsor Signatory:

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6/7/2022

Leonard L. Dragone MD, PhD
Chief Medical Officer

Date

INVESTIGATOR SIGNATURE PAGE

A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Activity of Single Ascending Doses of SBT777101 in Subjects with Rheumatoid Arthritis

Protocol Number: SBT777101-01

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with Food and Drug Administration (FDA) regulations, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and all applicable regulations.

Signature:	**Date:**
Principal Investigator (PI) Name:	**Title:**
Institution:	**Site Number:**

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PROTOCOL SYNOPSIS

Protocol Title:	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Activity of Single Ascending Doses of SBT777101 in Subjects with Rheumatoid Arthritis	
Protocol No.:	SBT777101-01	
Sponsor:	Sonoma Biotherapeutics, Inc.	
Investigational Medicinal Product:	SBT777101	
Objectives and Endpoints:	**Objectives**	**Endpoints**
	Primary	
	To evaluate and characterize the safety and tolerability of SBT777101	• Incidence, nature, and severity of adverse events • Incidence and nature of dose-limiting toxicities (DLTs) • Change from baseline in targeted vital signs, clinical laboratory tests and ECG parameters
	Exploratory	
	To assess and characterize SBT777101 pharmacokinetic profile in peripheral blood and synovium	• Peripheral blood CAR transgene PK parameters including, but not limited to, T_{max}, C_{max}, AUC_{0-28}, and C_{last} • Presence of SBT777101 in synovial tissue and/or fluid
	To assess and characterize SBT777101 mechanism of action and pharmacodynamic parameters in peripheral blood and synovium	• Levels of inflammatory cells and biomarkers in synovial tissue and/or fluid pre-dose and following SBT777101 administration • Levels of systemic markers of inflammation in peripheral blood, including but not limited to TNFα, CRP, and IL-6, pre-dose and following SBT777101 administration • Change from baseline in phenotypic and molecular signatures in T cells and other immune cell subsets in peripheral blood and synovial tissue and/or fluid following SBT777101 administration

	To assess immunogenicity of SBT777101	• Presence of circulating anti-drug antibodies (ADA) pre-dose and following SBT777101 administration • Detection of cellular immunogenicity pre-dose and following SBT777101 administration
	To evaluate the preliminary efficacy of SBT777101	• ACR20, ACR50 and ACR70 response rates following SBT777101 administration • DAS28 scores and change from baseline in DAS28 scores following SBT777101 administration
Study Design:	This is a multi-center first-in-human, Phase 1, open-label, dose ranging study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of single ascending doses of SBT777101 administered intravenously (IV) in subjects with active rheumatoid arthritis (RA) and an inadequate response to at least two prior biologic or targeted synthetic disease modifying anti-rheumatic drug (b/tsDMARD) therapies with different mechanisms of action.	
Route of Administration:	Intravenous (IV)	
Number of Participants:	A minimum of 9 and up to a maximum of 36 eligible adult subjects are expected to be treated in the study.	
Replacement of Participants:	Subjects in dose escalation cohorts who have been dosed with SBT777101 and withdraw for reasons other than toxicity or are lost to follow-up before completing the safety evaluation period (up to study Day 28) will be replaced.	
Number of Study Sites:	Approximately 10 sites will be included in the study.	
Duration of Study Participation:	Each subject will participate in the study for approximately 15 months.	
Study Population:	Subjects must have a diagnosis of moderate-to-severe active adult-onset RA as defined by the 2010 ACR/EULAR classification criteria for RA. The study population will comprise males and females, aged ≥18 to ≤70 years, with body mass index (BMI) <35 kg/m^2. Subjects must be eligible for the study as determined by review of medical history, physical examination, vital sign measurements, 12-lead electrocardiogram (ECG), and clinical laboratory tests at screening.	

Safety Assessments:	Safety will be assessed by physical exam, 12-lead ECGs and clinical laboratory tests (clinical chemistry, hematology, urinalysis) at the timepoints described in the schedule of assessments (SoA).
Pharmacokinetic/ Immunogenicity/ Pharmacodynamic Assessments:	Peripheral blood will be analyzed for the presence of circulating SBT777101, synovial tissue and/or fluid will be assessed for the presence of SBT777101, and serum will be analyzed for the presence of SBT777101-specific anti-drug antibodies (ADA) at the timepoints described in the SoA. Peripheral blood will be analyzed for the presence of SBT777101-specific cellular immunogenicity. The pharmacodynamic activity of SBT777101 will be assessed by evaluating inflammatory cells and biomarkers in synovial tissue and/or fluid and peripheral blood as outlined in the SoA.
Statistical Methods:	**Safety:** Safety data will be listed by subject and summarized by dosing level and overall. Clinical and laboratory AEs will be coded using the most current version of MedDRA®. The severity will be graded according to the Common Terminology Criteria for Adverse Events. The number of subjects experiencing treatment emergent adverse events (TEAEs) and number of TEAEs will be summarized by dosing level using frequency counts. Infusion site reactions and SAEs will be tabulated. All safety data will be listed by subject. In addition, a list of AEs leading to discontinuation of study prematurely will be provided. Listings of individual subject laboratory results will be provided. All clinical laboratory results and their change from baseline will be summarized by dosing level and at scheduled visits and for the corresponding change from baseline (Day 1). The incidence of treatment-emergent laboratory abnormalities will be summarized by dosing level. Laboratory abnormalities will also be included in a data listing. **Sample Size:** The sample size in this study was not selected based on statistical considerations but to determine preliminary safety, tolerability, PK, PD, and preliminary clinical activity of SBT777101 subjects with active RA. Up to 18 subjects will be enrolled into dose escalation cohorts. Up to 18 additional subjects may be added in optional backfill cohorts.

1. INTRODUCTION

1.1. Disease Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that primarily affects diarthrodial joints but frequently involves other organs. A major portion of the pathogenesis of RA is mediated by antigen specific effector T cells (T_{eff}) in addition to B cells that produce pathogenic autoantibodies and macrophages that produce pro-inflammatory cytokines. This process contributes to osteoclast activation and proliferation of synoviocytes surrounding the joint that can ultimately expand, resorb cartilage and bone, and present radiographically as erosions. Approximately 1% of the general population is affected worldwide (Firestein and Kelley, 2009), with the peak incidence of onset between the fourth and sixth decades with females being two to three times more likely affected than males (CDC, 2021).

Conventional synthetic disease modifying rheumatic drugs (DMARDs) are the current standard of care in newly diagnosed patients (Fraenkel et al., 2021). In general, conventional synthetic DMARDs (csDMARDs) are effective for patients with mild to moderate disease and who are at low risk of developing erosions. These drugs are typically well tolerated and have a favorable benefit-risk profile (Smolen et al., 2018). However, a significant percentage of patients either don't respond to therapy, have a partial response or are inadequate responders and relapse. Thus, based on current treatment guidelines, these patients are treated with biologic or targeted synthetic DMARDs (b/tsDMARDs) as monotherapy or in combination with csDMARDs. Despite there being therapeutic options for patients with RA, existing therapies may be inadequate for long term disease management. Thus, there is still a significant unmet need for treatment options that are safe, effective, and durable.

1.2. Citrullinated Proteins and RA

Citrullination of proteins is a hallmark of inflammatory diseases and citrullinated proteins can be present in many tissues, including the joints, lungs, lymph nodes, and periodontal tissues (Musaelyan et al., 2018). In patients with RA, citrullinated proteins are present in the inflamed tissue of the synovium (Fox, 2015; Vossenaar et al., 2004). Citrulline is generated via a post-translation conversion of arginine to citrulline by peptidylarginine deiminase enzymes (PADs). While the exact mechanism of pathogenesis is not fully elucidated, it has been established that citrullinated peptide autoantigens can in some individuals induce T-cell-mediated B cell activation (Szili et al., 2014; Sokolove, 2019). This activity leads to anti-citrullinated protein antibody (ACPA) production by hyperreactive B cells and activates pro-inflammatory mediators, which subsequently cause joint inflammation and erosion (Sohrabian et al., 2018).

Citrullinated proteins are highly immunogenic and some patients with RA make ACPA early in the course of their disease (Holers, 2013; Kroot et al., 2000; van der Linden et al., 2009; Renner et al., 2014). ACPA are present in 60-80% of RA patients and can react with a broad range of citrullinated proteins including collagen, filaggrin, histones, fibrinogen, α enolase, and vimentin (Aggarwal et al., 2009). In these patients, the presence of ACPA validate the presence of citrullinated protein, yet citrullination can be detected in synovial tissue independent of ACPA

positivity, (Won et al., 2021) demonstrating that citrullination is part of the pathology of disease and does not necessarily drive ACPA formation.

In addition, ACPA associated immune complexes can activate neutrophils to undergo NETosis (a regulated form of neutrophil cell death that contributes to the host defense against pathogens), releasing intracellular citrullinated antigens into the extracellular spaces. This leads to greater access to citrullinated proteins and further epitope spreading of the autoantibody response, which contribute to increased tissue inflammation and disease progression (Khandpur et al., 2013; Robinson and Sokolove, 2012).

1.3. Background on Regulatory T cells and Targeting of Citrullinated Proteins

Regulatory T cells (T_{regs}) are insufficient in their ability to control disease in patients with RA (Ehrenstein et al., 2004), and the adoptive transfer of T_{reg} cells from mice with inflammatory arthritis has been shown to suppress disease in mice with active induced arthritis (Sun et al., 2018). This suggests that provision of antigen-specific CAR T_{regs} may provide benefit in this patient population. It has been demonstrated that T_{regs} modified to express selective antigen receptors in diseased tissue have increased specific activity and are more efficacious in multiple pre-clinical models. These pre-clinical studies have shown that autologous T_{regs} expressing antigen specific (based on T cell receptor and CAR) receptors can treat systemic inflammation and organ injury (Bluestone and Tang, 2018). T_{regs} can be isolated from subjects with active RA having an inadequate response to at least two previous b/tsDMARDs therapies, transduced with an antigen-specific CAR, expanded over 14 days in culture and shown to suppress T effector cell functional activity in vitro. Therefore, we propose to employ antigen-specific CAR T_{regs} to target diseased tissue in RA patients as a novel approach for the treatment of this autoimmune condition.

Given that citrullinated proteins can be present at high levels in the joints of patients with RA, they present a potential localized antigen source that can be targeted by a CAR on a T_{reg} (Orvain et al., 2021). Citrullinated proteins are present as aggregates in the extracellular matrix allowing for T_{regs} to effectively recognize and be activated by the modified proteins in the inflammatory milieu, which when combined with the ability of T_{reg} to function through bystander suppression (e.g., the localized suppression of inflammatory activities in the near vicinity of T_{reg} activation), leads to inhibition of immune activation and subsequent reduction of inflammation.

Citrullinated vimentin (CV) is one example of an antigen that is found in the extracellular matrix of inflamed synovial tissue of RA patients (Van Steendam et al., 2010). Patients with RA have increased levels of CV in the synovium, including both synovial fluid and tissue as well as elevated levels of a circulating cleavage peptide from CV called citrullinated and matrix metalloproteinase-degraded vimentin (VICM) compared to healthy controls (Drobinski et al., 2020). Clinical studies have reported that decreases in VICM levels correlated with improved ACR50 treatment responses with a significant correlation between VICM reduction and improvement in disease activity scores (DAS28) (Drobinski et al., 2020; Mortensen et al., 2019). It is likely that the majority of patients with moderate to severe disease will be VICM positive and express citrullinated antigens in their synovial fluid and tissue.

Importantly, T_{reg} cells targeting citrullinated proteins, including SBT777101 can be activated in synovial tissue and fluid in inflamed joints. The use of enhanced, antigen specific CAR T_{regs} that can be targeted to sites of joint inflammation represents a promising, innovative approach to the treatment of RA.

1.4. Investigational Product: SBT777101

SBT777101 is a cryopreserved ex vivo expanded autologous $CD4^+CD127^{lo/-}CD25^+$ T_{reg} cell preparation that has been transduced with a lentiviral vector encoding both a CAR that is specific for immunodominant post-translationally modified citrullinated proteins and a modified EGFR tag. The CAR contains an intracellular signalling domain, an intracellular co-stimulatory domain, a transmembrane domain, and an extracellular recognition domain (citrullinated protein-specific single-chain variable fragment [scFv]) to enable specific binding and T_{reg} activation at the site of target expression.

The starting material for SBT777101 is autologous blood cells collected by apheresis from a patient with RA. $FOXP3^+$ expressing T_{reg} cells are then enriched from blood cells in a central manufacturing facility through selection and cell sorting. T_{reg} cells are activated and expanded ex vivo. During activation, the cells are transduced using a lentiviral vector that encodes the SBT777101 CAR and a truncated extracellular membrane portion of the EGFR receptor (EGFR tag). Cells are expanded for 14 days and then harvested, quality controlled and cryopreserved.

Refer to the SBT777101 Investigator's Brochure for further details.

1.5. Study Rationale

Despite there being therapeutic options for patients with RA, a significant unmet medical need still exists. Various studies have been published reporting that even with the current treatment options, existing therapies may be inadequate for long term disease management in many cases as patients fail to respond to treatment or responses to treatment diminish over time (Smolen et al., 2018). A recent study reported that almost three quarters of patients are dissatisfied with their treatments (Radawski et al., 2019) and only 10 to 15% of patients achieve DMARD free remission (Ajeganova and Huizinga, 2017), implying that current therapies fail to produce long-term disease quiescence. Many commonly used approved biologic therapies require chronic administration and are given via frequent infusion or injection, adding to the ongoing disease burden of the patient.

While many patients with early disease can achieve low disease activity with csDMARDs, over time response rates decline and b/tsDMARDs are introduced. Yet about 40-50% of patients treated with a tumor necrosis factor (TNF) inhibitor fail to achieve an improvement of 50% in American College of Rheumatology response criteria (ACR50), a clinically meaningful response, and more patients lose efficacy later during therapy. In fact, patients become inadequate responders to treatment with TNF blockers more rapidly than those who go on to fail earlier lines of treatment standard DMARDs such as methotrexate (MTX) (Aletaha and Smolen, 2018). Further bDMARDs beyond TNF inhibitors have been developed, including those that target IL-6, CD20 and CTLA-4 as well as tsDMARDs including janus kinase (JAK) inhibitors. Response rates with these therapies are poor, with clinical trial data showing that only 10-17% of patients that have failed prior treatment TNF inhibitors are able to achieve an ACR70 response

(Smolen et al., 2018). Even with aggressive goals of treating to remission and guidelines recommending switching rapidly to therapies with alternative mechanisms of action (Fraenkel et al., 2021), response rates continue to decrease with increasing disease duration and multiple drug exposures.

Taken together, the epidemiology studies, coupled with significance relapse rates among patients treated with current therapeutics highlight that there is still significant unmet need for treatment options that are safe, effective, and durable and do not lead to treatment failure.

Infused polyclonal T_{regs} have been shown to be long-lived in patients with autoimmune disease (Bluestone et al., 2015). SBT777101 CAR T_{reg} cell therapy therefore has the potential to provide sustained disease remission, without the need for frequent administration required of many medications that are part of current standard of care for autoimmune diseases. In addition, leveraging the polypharmacy of T_{regs} provides a unique mechanism to suppress multiple mechanisms of inflammation while restoring immune balance.

1.6. Nonclinical Data

SBT777101 is a CAR T_{reg} cell product that was designed to recognize antigens produced in the context of autoimmune disease(s) and exhibit anti-inflammatory activity. The nonclinical studies focused on demonstrating that the SBT777101 CAR specifically recognizes citrullinated proteins known to be present in the inflamed tissue of patients with autoimmune diseases, that the SBT777101 T_{reg} cells exhibit regulatory/immunomodulatory functions, and upon activation SBT777101 does not exhibit proinflammatory activity, and the SBT777101 T_{reg} cells do not exhibit cytotoxic potential, including towards normal cells. The nonclinical safety assessment also includes an evaluation of the risk of lentiviral vector mediated insertional mutagenesis and oncogenesis.

1.6.1. Pharmacology

Several SBT777101 CAR ligands were used to demonstrate antigen-specific activation and proliferation of SBT777101. SBT777101 was incubated with increasing concentrations of platebound citrullinated proteins for 72 hours and upregulation of CD71 was measured as a marker of activation of the CAR T cells and proliferation was assessed by carboxyfluorescein succinimidyl ester (CFSE) fluorescence dilution. There was a dose-dependent increase in CD71 expression and proliferative response in response to CV, and also citrullinated GRP78, citrullinated fibrinogen, and citrullinated GFAP.

Similarly, activation and proliferation of SBT777101 was observed in response to RA patient-derived synovial fluid.

It was demonstrated that the inherent Treg function of T_{regs} isolated from peripheral blood including that from RA patients is maintained in T_{regs} expressing the SBT777101 CAR. Autologous purified T cells were labeled with the CellTrace™ Violet (CTV) tracer dye while T_{regs} were labeled with the CFSE tracer dye. Cells were incubated at various ratios and evaluated for proliferation after incubation with antiCD3/anti-CD28 coated beads used as stimulus. In the presence of increasing amounts of T_{reg} cells, a reduction in proliferation in response to the CD3/CD28-mediated stimulation was observed. SBT777101 inhibited T cell proliferation in

a similar manner to untransduced T_{regs}, demonstrating that the expression of the CAR did not impact inherent T_{reg} function of transduced cell.

SBT777101 cells express a truncated inert version of the EGFR on their cell surface, which can be leveraged to identify and select transduced cells. This tag can be recognized by an anti-EGFR antibody.

1.6.2. Pharmacokinetics

Consistent with ICH S12 (draft version, 2021) (FDA, 2021) indicating that "*in general, biodistribution assessment of ex vivo genetically modified cells of hematopoietic origin is not critical based on expected widespread distribution following systemic administration*." Pharmacokinetic and biodistribution studies with SBT777101 were not conducted.

1.6.3. Safety Pharmacology/Toxicology

The manufacture of SBT777101 involves the transduction of T-lymphocytes with a lentiviral vector. Viral vectors derived from the Retroviridae family are of special interest for introducing modifications to human cells because they can convert their RNA genome into DNA and integrate this DNA into the chromosomes of target cells through reverse transcriptase and integrase enzymes. Lentiviral vectors are attractive technologies for this gene transfer because of the efficient transfer and stable integration of the transgene in the host genome. There are many active clinical studies involving CAR T cell immunotherapies with gene transfer being performed with lentivirus transduction (Holzinger, et al., 2016). A potential risk associated with lentiviral transduction is the insertional mutagenesis caused by the integration of the proviral DNA and viral promotor within or in close proximity to active genes. To address this risk, an insertion site analysis was conducted for SBT777101. This analysis showed a polyclonal integration site profile with no dominant integration site observed.

A theoretical concern associated with engineering T cells is the disruption of normal cell growth control mechanisms. The ability of SBT777101 CAR T_{reg} cells to grow in the absence of IL-2 was therefore evaluated in vitro. SBT777101 cells were plated with or without human IL-2. Untransduced cells were used as a control. Cell counts and viability were followed for 14 days after IL-2 withdrawal. A steady decrease in cell counts was observed over 14 days in the absence of IL-2, indicating a lack of unexpected cell growth after transduction.

The polyclonal integration site profile of the SBT777101 lentiviral vector and the lack of abnormal growth of SBT777101 in the absence of IL-2 are consistent with the demonstrated safety profile of lentiviral vectors broadly used in therapeutic settings (Milone and O'Doherty, 2018).

A cell microarray technology was used to screen for potential off-target binding interactions of a human Fc fusion protein that contains the scFv contained in the SBT777101 CAR fused to a human IgG1 Fc. This study demonstrated that the SBT777101 scFv did not bind to off-target proteins aside from binding to Fc gamma receptors via its IgG1-Fc component. It can therefore be concluded that the SBT777101 CAR is not associated with off-target binding activity.

1.7. Clinical Development

This Phase 1 study is the first in human study for SBT777101.

1.8. Benefit/Risk Assessment

There has been no prior clinical experience with SBT777101. The objectives for this first in human study are to evaluate the safety, tolerability, PK, PD, and preliminary clinical efficacy of a single dose of SBT777101 in patients with RA, and to inform dose selection for subsequent studies of SBT777101 in RA and other autoimmune diseases.

SBT777101 has not been tested in humans and so the actual risks are unknown. The rationale for evaluating CAR T_{reg} therapy in RA is driven by the potential for this therapy to reduce the signs and symptoms of RA as well as ameliorate disease within the tissue by restoring normal immune balance. Clinical studies and case reports with polyclonal T_{regs} in patients with autoimmune conditions and T_{regs} selected for alloantigen specificity showed that these cells were well tolerated at doses up to and exceeding those proposed in this study. SBT777101 is a regulatory CAR T therapy, not an effector CAR T therapy. As such, the safety profile is expected to reflect more closely that seen in the polyclonal T_{reg} trials rather than that from the CAR T_{eff} trials in patients with oncological diseases.

Overall, the nonclinical data (see Section 1.6) for SBT777101 support this Phase 1 trial in subjects with RA. The potential safety issues associated with administration of study drug are expected to be clinically monitorable and manageable, and measures will be taken to avoid or minimize such toxicities in this trial, as described in Section 7.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, tolerability, PK, PD, and preliminary clinical activity of a single intravenous (IV) infusion of SBT777101 in adult subjects with RA that have failed two or more prior b/tsDMARDs. Specific objectives and corresponding endpoints of this study are described below.

Objectives	Endpoints
Primary	
To evaluate and characterize the safety and tolerability of SBT777101	• Incidence, nature, and severity of adverse events • Incidence and nature of dose-limiting toxicities (DLTs) • Change from baseline in targeted vital signs, clinical laboratory tests and ECG parameters
Exploratory	
To assess and characterize SBT777101 pharmacokinetic profile in peripheral blood and synovium	• Peripheral blood CAR transgene PK parameters including, but not limited to, T_{max}, C_{max}, AUC_{0-28}, and C_{last}

	• Presence of SBT777101 in synovial tissue and/or fluid
To assess and characterize SBT777101 mechanism of action and pharmacodynamic parameters in peripheral blood and synovium	• Levels of inflammatory cells and biomarkers in synovial tissue and/or fluid pre-dose and following SBT777101 administration • Levels of systemic markers of inflammation in peripheral blood, including but not limited to TNFα, CRP, and IL-6, at baseline and following SBT777101 administration • Change from baseline in phenotypic and molecular signatures in T cells and other immune cell subsets in peripheral blood and synovial tissue and/or fluid following SBT777101 administration
To assess immunogenicity of SBT777101	• Presence of circulating anti-drug antibodies (ADA) pre-dose and following SBT777101 administration • Detection of cellular immunogenicity pre-dose and following SBT777101 administration
To evaluate the preliminary efficacy of SBT777101	• ACR20, ACR50 and ACR70 response rates following SBT777101 administration • DAS28 scores and change from baseline in DAS28 scores following SBT777101 administration

3. STUDY DESIGN

3.1. Description of the Study

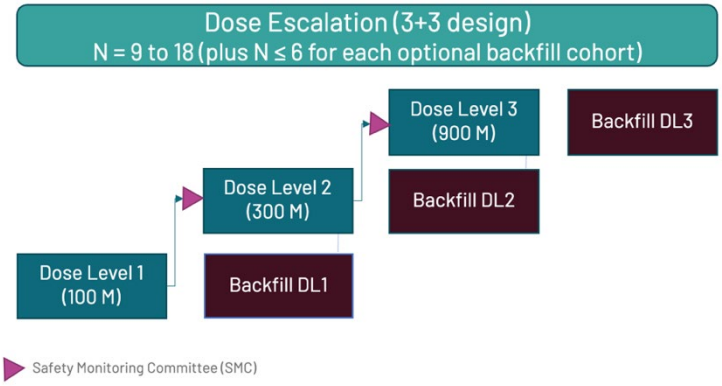
3.1.1. Overall Study Design

This is a Phase 1, open-label, study to evaluate the safety, tolerability, PK, PD, and preliminary clinical activity of single ascending doses of SBT777101 in patients with active RA.

Following screening, eligible subjects will undergo apheresis, and SBT777101 drug product will be manufactured for each subject. Each subject will receive a single dose of SBT777101 intravenously (IV) on study Day 1. Subject safety will be monitored acutely post dosing and throughout the study for 1 year. After one year and due to the use of lentivirus vector in SBT777101, all subjects will be encouraged to participate in a long-term safety follow-up (observational) study that will be conducted under a separate protocol in accordance with current FDA guidance.

The overall study design is displayed in Figure 1. A schedule of assessments (SoA) is provided in Appendix A and Appendix B.

Figure 1: Study Design



Dose Escalation Cohorts

The study will be open-label and employ a "3+3 Dose Escalation" design. Initially three eligible subjects will be evaluated in each cohort, enrolled for a safety monitoring period at least 14 days apart. Subjects will be monitored for dose limiting toxicities (DLTs) for at least 28 days following enrollment of the third or sixth subject.

- If a DLT is not seen in the first three subjects, then escalation to the next dose level may occur.
- If a DLT is seen in 1 of the first 3 subjects in any dose cohort, the cohort size will be expanded to six subjects. These additional subjects will be dosed at least 14 days apart and have a safety monitoring period of at least 28 days.
- If more than one DLT occurs in ≤6 subjects in a dose cohort, dose escalation will not occur, and this dose level will be identified as the non-tolerated dose. Otherwise, dose escalation may occur.

See Section 3.3 for definitions of DLTs and details of dose escalation rules.

Additional subjects may be screened and undergo apheresis at risk prior to the previous subject within a dose escalation cohort being dosed or completing their post dose safety monitoring period. These additional subjects will not receive treatment with SBT777101 until the safety monitoring period has been completed for the prior subject.

Dose escalation will be overseen by the study Safety Monitoring Committee (SMC; see Section 3.3).

Backfill Cohorts

At the Sponsor's discretion, additional eligible subjects (e.g., those beyond the initial 3 or 6 subjects initially treated as described above) may be enrolled into optional protocol-defined dose level "backfill" cohorts. Each backfill cohort will contain up to six subjects dosed at least 14 days apart. Backfill cohorts will not be opened until the dose escalation cohort at that dose level has been completed. Doses will not exceed the last cleared dose from the initial dose escalation cohorts.

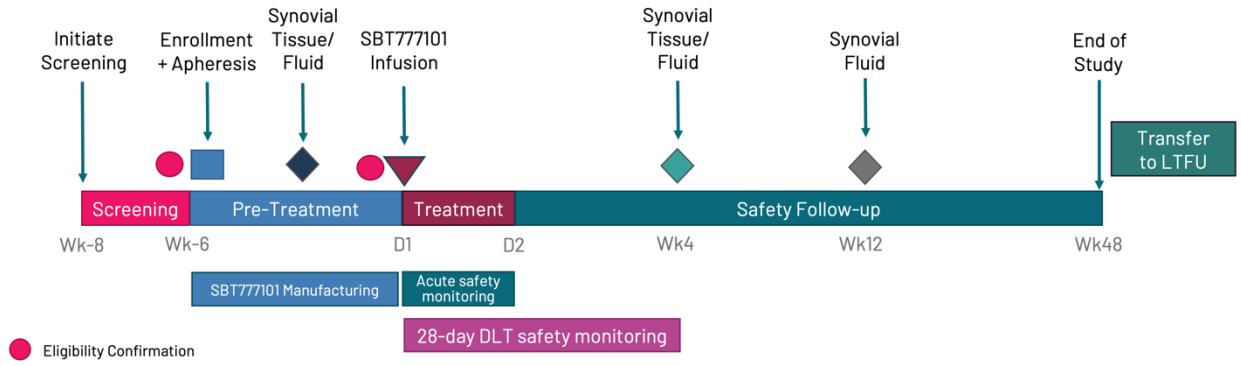
Additional subjects may be enrolled at the Sponsor's discretion under the following conditions:

- Inability to manufacture the required dose of SBT777101 for any given subject, wherein the number of CAR positive T_{reg} cells is in the final drug product is insufficient for the assigned dose level. In this case, the subject may be enrolled into a backfill cohort at the highest possible cleared dose level (e.g., a subject intended for dose level 2 may be enrolled in dose level 1 backfill).
- Evaluation of PK, PD and biomarker data from a dose cohort indicates that additional data may better aid interpretation of preliminary PK and PD data and to guide future dose selection. Subjects may be added provided that the SMC does not indicate that doing so will present additional safety risks.

3.1.2. Subject Flow

The overall subject flow is displayed in Figure 2. Details of study assessments required during each study period are provided in the SoA (see Appendix A and Appendix B).

Figure 2: Subject Flow



DLT = Dose Limiting Toxicity; LTFU = long-term follow up; Wk = week
Timing of the synovial biopsy and/or fluid collection for backfill cohorts may change based on evaluation of data from dose escalation cohorts

The study will consist of Screening, Pre-Treatment, Treatment and Safety Follow-Up periods. Details on study visits are provided in Section 7.1 and details on study assessments are provided in Section 7.2.

3.1.3. Starting dose and dose levels

Eligible subjects will be enrolled into sequential dose-level cohorts and will receive a single dose of SBT777101 by IV administration. Planned dose levels are shown in Table 1. Selection of dose levels for cohorts 2 and 3 will be overseen by the SMC in collaboration with the Sponsor.

Table 1: Planned Dosed During Dose Escalation

Planned dose	Total CAR^+ T cells (noted by EGFR expression)
1 (Starting dose)	100×10^6
2	300×10^6
3 (Maximum dose)	900×10^6

If a dose limiting safety event is observed the Sponsor may choose to enroll subjects into a cohort at a dose lower than 100×10^6 cells. Dose selection and initiation of this cohort would be overseen by the SMC.

Although three dose level cohorts are planned, fewer or additional cohorts may be included based on safety observations and/or study product manufacturing limitations. These additional dose levels will be lower than the maximum planned dose of 900×10^6 transduced cells. Determination of dose levels for additional cohorts will be overseen by the SMC in collaboration with the Sponsor.

3.2. Rationale for Study Design

3.2.1. Rationale for Study Population

Subjects with active RA have been chosen for this first in human study to assess the safety of SBT777101, a CAR T_{reg} specific for citrullinated proteins. Patients rather than healthy volunteers will be enrolled in this study as there is a clear potential for benefit of the drug treatment based on the known pathophysiology of the T_{regs} in this disease as demonstrated by previous clinical and preclinical data. Furthermore, healthy volunteers typically do not have chronic inflammation and are unlikely to have significant levels of citrullinated antigens that can activate SBT777101, limiting a full safety assessment of the cell product.

Eligible subjects will have active RA that is uncontrolled by FDA approved therapies and will have received prior treatment with at least two mechanistically different classes of b/tsDMARDs before being considered for inclusion. These are the patients with the greatest unmet need since they represent a treatment-refractory group. As such, SBT777101 treatment offers a novel option with the potential for treatment benefit.

The study will be open-label and employ a "3+3 Dose Escalation" design, with optional backfill cohorts. The open-label design will provide all subjects with the opportunity to receive active treatment with SBT777101 rather than placebo.

SBT777101 has been designed to target citrullinated proteins including vimentin, which can be further degraded to form the circulating peptide VICM. VICM levels are elevated in RA patients with active disease and are increased in patients with systemic inflammation as evidenced by elevated CRP (Drobinski et al., 2021; Mortensen et al., 2019). Taking this into consideration, this study has been designed to only enroll patients with active disease and all patients are required to have DAS28>3.1 (calculated using CRP) to be eligible. The relationship between levels of citrullinated proteins in the inflamed synovium and other biomarkers associated with local or systemic inflammation, including CRP and VICM, will be evaluated longitudinally in this trial to help inform inclusion criteria for future studies.

3.2.2. Rationale for Dose Selection and Escalation

3.2.2.1. Starting Dose

Given the lack of direct translatability to in vivo models, it is not possible to use a no observed adverse effect level (NOAEL) approach from nonclinical studies to determine the starting dose or an expected maximum dose level. The planned starting dose for the initial cohort in the Phase 1 study is 100 x10^6 CAR^+ T cells (noted by EGFR expression) administered by IV infusion. This low dose level is similar to the starting dose level administered to subjects in multiple clinical trials and case reports using polyclonal autologous and alloantigen-specific T_{reg} cellular therapy in disease indications including type 1 diabetes, graft versus host disease, kidney and liver transplantation, lupus and Crohn's disease (Bluestone et al., 2015; Chandran et al., 2017; Dall'Era et al., 2019; Desreumaux et al., 2012; Marek-Trzonkowska et al., 2014; Mathew et al., 2018; Roemhild et al., 2020).

Unlike prior T_{reg} products, SBT777101 includes addition of a CAR. While this introduces a modification to the cell, addition of the CAR to the T_{regs} is not expected to negatively alter the benefit-risk compared to untransduced cells. This is supported by data from studies with allo-antigen specific T_{regs}, where the potency of the allo-antigen T_{regs} is increased over that for polyclonal T_{regs} (Jiang et al., 2006; Golshayan et al., 2007). The increase in specificity of the T_{reg} via the T cell receptor did not lead to a change in safety profile compared to polyclonal T_{reg} therapies in clinical studies and the doses administered were within range of the proposed starting dose and were well tolerated. The starting dose level is also consistent with the doses of allo-antigen T_{reg} therapy previously given to transplant patients (Brunstein et al., 2011; Todo et al., 2016; Trzonkowski et al., 2009; NCT02474199, 2022).

3.2.2.2. Maximum Dose

The proposed maximum dose is 900 x 10^6 CAR^+ T cells (noted by EGFR expression) administered by IV infusion. The total number of T_{regs} to be given will be up to approximately 2.7 x 10^9 total T_{reg} cells, assuming a 30% CAR transduction efficiency rate. This is aligned with the maximum dose evaluated in polyclonal T_{reg} T1D study (2.6 x 10^9 total cells; (Bluestone et al., 2015) and below that tested in the kidney transplant study (5.0 x 10^9 total cells); (Mathew et al., 2018), both of which were well tolerated in these patient populations. This level of T_{regs} represents approximately 17% of the total T_{reg} pool in a human (Tang and Lee, 2012). A small fraction (approximately 2%) of T_{regs} can be found in the bloodstream, with most cells being sequestered in the lymph nodes, intestine and bone marrow. It is therefore appropriate to dose up to the proposed level to ensure that sufficient study drug is present in the circulation to be able to traffic to the site of inflammation and reach the CAR target antigen within the synovial tissue.

3.2.2.3. Dose Escalation

Dose escalation to the next dose level will occur at least 28 days after the last subject in that cohort has been dosed.

The dose selected for the next cohort will be no more than 3-fold higher than that administered in the cleared cohort. This aligns with the dose escalation regimen utilized in other T_{reg} studies (Bluestone et al., 2015; Brunstein et al., 2011; Mathew et al., 2018; Roemhild et al., 2020).

3.2.3. Rationale for Pharmacokinetic and Immunogenicity Sampling Schedule

The frequent sampling schedule that follows the dosing of SBT777101 is designed to capture data at a sufficient number of timepoints to provide a detailed profile of the kinetics of SBT777101 in peripheral blood and to assess the presence of SBT777101- specific anti-drug antibodies (ADA) and their potential impact on kinetics and/or pharmacodynamic (PD) activity. Less frequent sampling will suffice to explore the induction of SBT777101-specific cellular immunogenicity (see Appendix A, Appendix B, and Appendix C).

3.2.4. Rationale for Pharmacodynamic and Biomarker Assessments

Peripheral blood and serum samples will be collected pre- and post-SBT777101 infusion as outlined in the SoA (Appendix A and Appendix B) to evaluate changes in systemic markers of inflammation, including measurements of cytokines, biochemical markers of inflammation and immunophenotyping of circulation cells, including both drug product and cells from subjects. Cytokine levels will be collected frequently over the first month following infusion to permit a thorough evaluation of SBT777101 dosing on inflammation and to aid understanding of the clinical and pathophysiologic impact of CAR T_{reg} cell therapy administration. Samples will be collected out to one year to permit evaluation of the longer-term effects of SBT777101 on PD biomarkers.

3.2.5. Rationale for Synovial Biopsy and Synovial Fluid Assessments

A synovial biopsy will be collected to inform on synovial pathotype and presence of citrullinated protein in the synovial tissue and/or fluid prior to dosing with SBT777101. Additional analyses will be performed on the biopsy sample and synovial fluid to compare pre- and post-treatment levels of citrullinated proteins and other inflammatory biomarkers. The presence of SBT777101 cells within the synovium will also be evaluated at the post-dose time point to determine the extent of CAR T_{reg} trafficking and persistence.

3.3. Dose Escalation Rules

Determination of dosing within a cohort will be overseen by the SMC. Dosing may be temporarily withheld, modified (expansion of cohort size from three to six subjects) or stopped (with no further subject enrollment into the cohort) if any event or series of events occurs that suggests that there is a significant safety risk to subjects, or a clinically significant pattern of toxicity occurs in several subjects.

Dose-Limiting Toxicity Definition

A dose-limiting toxicity (DLT) is defined as any treatment-emergent CTCAE ≥Grade 3 AE considered related to study drug, except Grade 3 infusion reactions that are rapidly reversible with supportive care and that do not recur following re-initiation of the study drug infusion.

If 1 of the first 3 subjects experiences a DLT during the first 28 days after SBT777101 administration, an additional three subjects will be enrolled into the cohort, for a total of 6 subjects. Subjects who discontinue from the study prior to Week 4 for reasons unrelated to study treatment will be considered non-evaluable for dose escalation decisions and will be replaced with another subject at that same dose (see Section 7.4.3).

If 0 of 3 or ≤ 1 of 6 subjects experience a DLT during the 28-day DLT evaluation period, and cumulative safety data support tolerability of the dose level as determined by the SMC, escalation to the next higher dose level will be initiated. If ≥2 subjects in a cohort experience a DLT during the first 28 days or if cumulative safety data suggest an overall unacceptable toxicity profile, dose escalation will be discontinued and either the prior dose level will be considered the maximum tolerated dose (MTD) or an intermediate dose level will be evaluated.

In addition, dose escalation will be temporarily halted if any of the following occur:

- One subject in a cohort experiences a potentially life-threatening AE considered related to study drug
- Two or more subjects experience similar SAEs considered related to study drug

The SMC review of safety data will serve as the basis on which the Sponsor will determine whether dosing can be resumed. Further details may be found in the SMC Charter.

3.4. Safety Monitoring Committee

An SMC will regularly assess the safety of SBT777101. The SMC will provide their assessment of safety and recommendations for dose escalation and ongoing study conduct (see SMC Charter for further details).

The SMC will consist of at least the Principal Investigators, the Sponsor's Medical Monitor, an independent physician with expertise in RA, and an independent physician with expertise in CAR T therapy. Dose escalation decisions will be made by the SMC in collaboration with the study Investigators.

The SMC will convene approximately four weeks after the first subject has been dosed in each dose escalation cohort. They will then reconvene on a regular basis during the study to review available clinical study data or on an ad hoc basis if a DLT occurs.

Based on ongoing assessment of benefit and risk, the SMC may recommend dose escalation, stop dose escalation before the maximum proposed dose is reached or stop dosing completely.

3.5. Study Stopping Rules

The study will be paused, and the risk to other subjects evaluated, prior to a decision as to whether to terminate the study if any of the following criteria are met:

- A decision to stop dose escalation or study activities has been recommended by the SMC in two cohorts for safety concerns
- The SMC determines that a pattern of adverse events would preclude evaluation of any further dose cohorts or place subjects already in the study at increased safety risk

Alternatively, the SMC may determine that dose escalation may be delayed, paused, or modified as deemed appropriate.

3.6. End of Study Definition

Up to 36 eligible adult subjects will be enrolled in the study; up to 18 subjects will be enrolled in dose escalation cohorts and an additional 18 subjects may be included in optional backfill cohorts. Each subject will participate in the study for approximately 15 months. The study duration is expected to be approximately 24 months.

A subject is considered to have completed the study if they have completed all periods of the study including the final safety follow-up or early termination visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

In addition, the Sponsor may decide to terminate the study at any time.

All subjects that receive SBT777101 will be encouraged to participate in a long-term follow-up trial under a separate protocol.

4. STUDY POPULATION

4.1. Inclusion Criteria

All subjects must meet all of the following inclusion criteria:

1. Age ≥18 and ≤70 at the time of signing the informed consent
2. Body mass index (BMI) <35 kg/m^2, inclusive

RA Characteristics

3. Diagnosis of adult-onset RA as defined by the 2010 ACR/EULAR classification criteria for RA
4. Moderate-to-severe active disease defined by DAS28 >3.1 (calculated using CRP)
5. Must have at least one joint that can be used for synovial biopsy
6. Clinical and/or ultrasound evidence of synovitis
7. Have had an inadequate response to prior treatment with available therapies, including at least two prior treatment options with differing mechanisms of action
    - Prior treatment options include approved therapies or biosimilars that target TNF (e.g., adalimumab, golimumab, etanercept, infliximab), IL-6 (e.g., tocilizumab, sarilumab), IL-1 (e.g., anakinra), T cells (e.g., abatacept), CD20 (e.g., rituximab), or JAK (e.g., baricitinib, filgotinib, tofacitinib)
8. Doses of medications for RA (or biosimilar equivalents) including methotrexate, hydroxychloroquine, adalimumab, golimumab, infliximab, certolizumab, etanercept, anakinra, tocilizumab or sarilumab must be stable for 30 days prior to the screening visit

Contraceptive/Barrier Requirements

9. Women of childbearing potential must agree to use two methods of contraceptive for at least one year post SBT777101 administration. One method must be considered a highly effective

method of contraception, while the second method may be a barrier method (refer to Appendix D).

10. Women of childbearing potential must have a negative urine pregnancy test before the administration of study drug performed on the day of study drug administration
11. Males who are sexually active with women of childbearing potential must agree to use one method of contraception for one year post SBT777101 administration (refer to Appendix D).
12. Male subjects must refrain from donating sperm for one year post SBT777101 administration

Other Inclusions

13. Ability to comply with all the requirements of the study, in the Investigator's opinion
14. Adequate vascular access, in the opinion of the Investigator, for apheresis procedure
15. Willing to undergo repeat synovial biopsies to obtain tissue and synovial fluid collections during the study
16. Willing to comply with study specific safety monitoring requirements (see Section 8.1)
17. Willing and able to provide signed informed consent

4.2. Exclusion Criteria

Subjects that meet any of the following exclusion criteria will be excluded from participating in the study:

General

1. Major surgery (including joint surgery) within 12 weeks prior to screening or planned within 12 months after dosing

Medical Conditions

2. History of or current inflammatory joint disease other than RA or other autoimmune or inflammatory disease that may confound clinical assessments or increase subject risk in the study
3. Current or previous (within the past two years) evidence of serious uncontrolled concomitant cardiovascular, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus) or gastrointestinal disease
4. Active current infection or history of recurrent bacterial, viral, fungal, mycobacterial or other infections, including but not limited to tuberculosis and atypical mycobacterial disease, hepatitis B and C, and herpes zoster (>2 episodes within the previous 12 months)
5. Any major episode of infection requiring hospitalization or treatment with IV antibiotics within four weeks of screening or oral antibiotics/anti-infectives within two weeks prior to screening
6. Active tuberculosis requiring treatment within three years prior to screening
7. Latent tuberculosis diagnosed during screening that has not been appropriately treated

8. Primary or secondary immunodeficiency (history of or currently active), including a history of HIV positivity
9. Prior diagnosis with diverticulitis requiring antibiotic treatment
10. Females who are pregnant or breastfeeding or planning to become pregnant within 12 months from start on study
11. History of malignancy within five years from the time of screening (including squamous cell carcinoma of the skin or cervix or carcinoma-in-situ), except adequately treated basal cell carcinoma
12. History of epilepsy or other seizure disorder, stroke, dementia or other central nervous system disorder
13. Known history of drug or alcohol abuse within one year of screening
14. Any medical or psychological condition that in the judgment of the Principal Investigator would interfere with the conduct of the study or may confound the interpretation of the study results
15. Any out-of-range electrocardiogram (ECG) parameter(s) or abnormal finding(s) considered clinically significant by the Investigator including if the QTc calculated using Fridericia's formula (QTcF) is:
    - >450 ms in males or >470 ms in females

Excluded previous or concomitant therapy

16. Prior treatment with cell or gene therapy
17. Treatment with an investigational agent within 30 days or five half-lives, whichever is longer prior to screening
18. Treatment with intravenous, intra-articular or intramuscular glucocorticoids within 14 days of the screening visit
19. Treatment with azathioprine, cyclophosphamide, cyclosporine, leflunomide, and sulfasalazine within 4 weeks of the screening visit:
    - Subjects previously on leflunomide must have either discontinued ≥8 weeks prior to screening or discontinued with the following elimination procedure at least 4 weeks prior screening

      Cholestyramine or activated charcoal should be taken at standard doses for a minimum of 6 days but ideally for the standard 11 days (Arava ® U.S. Package Insert, 2011)
20. Treatment with abatacept or rituximab within 3 months of the screening visit

Prior/Concurrent Clinical Study Involvement

21. Is currently participating in another trial of an investigational or marketed drug or medical device

Allergies/Anaphylaxis

22. Any confirmed clinically significant drug allergy and/or known hypersensitivity to protein therapeutics or formulation components or a related drug

23. Known allergy to heparin, fresh frozen plasma (FFP) or replacement colloid/albumin

Specific Laboratory Assessments

24. Laboratory tests, if abnormal, may be repeated once during the screening period. Clinically significant abnormalities in laboratory test results that would exclude a subject from study participation include:

    a) AST or ALT >2 × the upper limit of normal (ULN)

    b) Total and direct bilirubin >1.5 x ULN

    c) EGFR <45 ml/min/m^2 (2021 CKD-EPI criteria; (Delgado, et al., 2022)

    d) Absolute neutrophil count <1.0 x 10^9/L

    e) Platelet count <100 x 10^9/L

    f) Hemoglobin <9 g/dL

    g) Positive hepatitis BsAg or hepatitis C antibody

       Note: In the event of a potential false positive hepatitis C antibody test result, PCR testing for HCV RNA may be performed; subjects who are negative for HCV RNA by PCR are not excluded

Other Exclusions

25. Donation of blood or clinically significant loss of blood, in the opinion of the Investigator, within three months prior to date of consent

26. Subjects under judicial supervision or guardianship

4.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Subjects may be rescreened up to two times, if deemed appropriate by the Principal Investigator. All screening assessments that led to screen failure must be repeated for rescreening.

During the course of screening if a lab result is not available for technical reasons (e.g., blood sample hemolysis), this evaluation may be repeated, and this will not be considered a rescreen. A lab result (other than those specified in the exclusion criteria) outside the normal range will be considered as a reason to screen fail if it is deemed clinically significant, in the opinion of the Investigator.

5. CONCOMITANT THERAPY

Concomitant therapy consists of any general medication used by a subject in addition to SBT777101 from 30 days prior to screening to the end of the study/early termination visit.

Prior and current therapies used by a subject for the treatment of RA must be reported from the time of diagnosis through to the end of the study/early termination visit, where available. This includes DMARDs and corticosteroids. Pain medications used to manage signs and symptoms of RA are considered general medications and must be recorded for the 30 days prior to screening.

Please contact the Medical Monitor for guidance on management of concomitant medications, including medications for RA and rescue therapy.

5.1. General Medications

Standard medications are permitted for the treatment of general medical conditions during the screening, pre-treatment and treatment periods of the study.

- Medications should be kept at stable doses from 30 days prior to screening throughout the study where possible.
- Receipt of new medications required for synovial biopsy, synovial fluid collection, apheresis and infusion are permitted.
- If corticosteroids are required for reasons other than RA, appropriate doses should be administered (e.g., ≤10 mg/day PO prednisone or equivalent) for no more than two weeks and should be tapered down to the previous level as rapidly as medically possible.

5.1.1. Vaccines

- Subjects who have received a vaccine should have completed their vaccination schedule at least two weeks prior to dosing
- Live vaccines are not permitted during the study
- COVID-19 vaccination including at least one booster is recommended

5.2. Medications for RA

Certain concomitant medications for the treatment of RA are permitted or prohibited. Details on medication types, doses and management of treatments are provided in the sections below.

5.2.1. Permitted Medications for RA

Details of the potential impact of permitted concomitant medications for RA with SBT777101 are provided in Appendix H.

The following medications are permitted during the study up to Week 48. Guidance on doses and routes of administration are provided below:

- NSAIDs (see Table 2 for guidance)
- Pain relief medications (see Table 2 for guidance)
- Oral corticosteroids (see Table 2 for guidance)
- csDMARDs (see Table 2 and Table 3 for guidance)

- Methotrexate (≤25 mg SC, PO or IM QW)
- Hydroxychloroquine (200 mg PO BID or 400 mg PO QD)

- bDMARDs (and biosimilar equivalents) (see Table 2 and Table 3 for guidance
  - Adalimumab (40 mg SC QW or Q2W)
  - Golimumab (50 mg SC once monthly)
  - Infliximab (3-10 mg/kg IV Q4W - Q8W)
  - Certolizumab pegol (200 or 400 mg SC Q2W)
  - Etanercept (50 mg SC QW)
  - Anakinra (100 mg SC QD)
  - Tocilizumab (162 mg SC QW or Q2W; 4 or 8 mg/kg IV Q4W)
  - Sarilumab (200 mg SC Q2W)

5.2.2. Prohibited Medications for RA

Details of the potential impact of prohibited concomitant medications for RA on SBT777101 are provided in Appendix I.

Use of the following medications is prohibited during the study from screening to Week 48:

- Intramuscular corticosteroids
- Intravenous corticosteroids
- Intraarticular corticosteroids
- csDMARDs
  - Azathioprine
  - Cyclophosphamide
  - Cyclosporin
  - Leflunomide
  - Sulfasalazine
- bDMARDs (and biosimilar equivalents)
  - Abatacept
  - Rituximab

tsDMARDs must be discontinued at least 7 days prior to the subject undergoing apheresis and are prohibited to Week 48.

- tsDMARDs
  - Baricitinib
  - Filgotinib

- Tofacitinib
- Upadacitinib

5.2.3. Guidelines for the Management of Medications for RA

It is important that doses of medications taken for the treatment of RA remain stable throughout the study where possible. If clinically required for safety reasons or to manage disease activity, modifications to the treatments are allowed and are described in Table 2 below.

Table 2: Guidelines for Use of Certain Medications for RA During the Study

Medication	Guidance
Screening (first study visit through enrollment)	
DMARDs	Doses must remain stable during screening Subjects should not start a new DMARD or switch to a different type of DMARD at any time
Oral corticosteroids	Subjects may receive background treatment (≤10 mg/day prednisone or equivalent) If changes in dose are required, the increased dose must be no higher than 20 mg/day and must be tapered quickly, returning to the previous dose level within 2 weeks
NSAIDs	NSAIDs (e.g., ibuprofen and naproxen) are permitted
Pain relief medications	Short courses of pain relief medications (e.g., opioids and acetaminophen) are permitted.
Pre-treatment period (apheresis through study drug administration)	
DMARDs	Doses must remain stable during pre-treatment up to study Day 1 Subjects should not start a new DMARD or switch to a different type of DMARD at any time
Oral corticosteroids	Subjects may receive background treatment (≤10 mg/day prednisone or equivalent) The dose must remain stable for at least 1 week before the synovial biopsy procedure and/or synovial fluid collection. If changes in dose are required, the subject must return to the previous dose level within 2 weeks and remain at that stable dose for at least 7 days before the study Day 1 visit can occur.
NSAIDs	NSAIDs (e.g., ibuprofen and naproxen) are permitted but should not be used in the 7 days prior to the synovial biopsy collection where possible
Pain relief medications	Short courses of pain relief medications (e.g., opioids and acetaminophen) are permitted.

Table 2: Guidelines for Use of Certain Medications for RA During the Study (Continued)

Medication	Guidance
Safety follow-up period (Day 1 through Week 48)	
DMARDs	Doses must remain stable during the safety follow-up period Subjects should not start a new DMARD or switch to a different type of DMARD
Oral corticosteroids	Subjects may receive background treatment of corticosteroids (≤10 mg/day prednisone or equivalent) The dose must remain stable for at least 1 week before the synovial biopsy procedure and/or synovial fluid collection and the Week 12 study visit If changes in dose are required, the increased dose must be no higher than 20 mg/day and must be tapered quickly, returning to the previous dose level within 2 weeks
NSAIDs	NSAIDs (e.g., ibuprofen and naproxen) are permitted but should not be used in the 7 days prior to the post dose synovial tissue collection where possible.
Pain relief medications	Short courses of pain relief medications (e.g., opioids and acetaminophen) are permitted.

5.2.4. Rescue Therapy

Certain concomitant medications are permitted as rescue therapy for the treatment of RA flares. Rescue therapy is permitted if a subject experiences ≥30% worsening in TJC and/or SJC compared to study Day -10 to -4 according to the guidance provided in Table 3 below. Rescue therapy must not be given until all assessments have been completed at a study visit.

Table 3: Rescue Therapy Guidelines

Medication	Guidance
DMARDs	Increase doses of existing permitted DMARD to a higher approved dose after Week 12 Start a new DMARD or switch to a different type of DMARD after Week 12
Oral corticosteroids	Increases in corticosteroid dose up to 20 mg/day are permitted after Week 12. The dose must be tapered, returning to the previous dose level, within 4 weeks
Intraarticular corticosteroids	May be used in a limited fashion as treatment for severe RA flares after Week 12.

5.2.5. Use of Prohibited Medication

Use of prohibited medication is not allowed during the study from screening to Week 12 (see Section 5.2.2 for details of prohibited medications). However, if a subject does take a prohibited medication or receives rescue therapy outside of permitted guidelines they should remain in the study and continue to attend visits and complete study assessments as described in the SoA (Appendix B).

6. STUDY DRUG

6.1. Description of Study Drug

SBT777101 is a suspension of autologous human regulatory T cells (T_{regs}) expressing a CAR transmembrane protein, which targets citrullinated proteins including CV in the extracellular domain of subjects with inflammatory diseases.

Peripheral blood cells are removed from an RA patient through apheresis. The apheresis product is enriched for $CD25^+$ cells through cell selection followed by cell sorting for $CD4^+CD127^{lo/-}CD25^+$ cells using a microfluidics chip-based cell sorter. After cell selection and sorting, the cells are placed into in vitro culture and activated using anti-CD3/CD28 magnetic beads. Following activation and cell recovery, a lentiviral vector encoding the construct for the citrullinated protein-specific CAR, is added to the culture, and cells are subsequently expanded in serum free media containing IL-2. The cells are restimulated on Day 9 with anti-CD3/CD28 beads and expanded until Day 14. The cells are then harvested, washed and formulated in a cryopreservation solution with a targeted cell density of 30 x 10^6 cells/mL. Upon formulation, cells are filled into cryobags and cryopreserved using a controlled-rate freezer. The Drug Product (in bags) is shipped under qualified conditions to the clinical site and thawed prior to administration to the patient.

Procedures will be in place to address product tracking requirements, including collection of the apheresis product, receipt of the apheresis product for manufacturing, SBT777101 manufacturing and testing, labeling, and packaging for shipment. The identity of the product will be checked and verified at each step of the cell apheresis, manufacturing, shipping, and administration process.

6.2. Product Labeling

Each SBT777101 infusion bag label will contain, at a minimum, the following information:

- Subject name (first and last)
- Subject date of birth
- Protocol Number
- Unique sponsor assigned product order tracking number
- Unique Subject Identifying Number (Subject ID)

These identifiers listed above are maintained throughout order management/scheduling, apheresis collection procedure, the manufacturing process and at infusion and are documented on the final product labels prior to cryopreservation.

6.3. Storage and Shipping

The cryopreserved SBT777101 final product will be stored in a continuously monitored vapor-phase liquid nitrogen freezer designed to maintain a temperature of ≤-150°C. The final product will be transported in a qualified liquid nitrogen dry vapor shipper, which is designed to maintain temperature for at least 10 days. The product will be shipped via a sponsor managed and qualified courier with continuous data loggers, monitoring, and chain of custody documentation.

Details on storage, handling, and preparation of SBT777101 are provided in the Investigational Product Manual.

6.4. Drug Accountability

In accordance with GCP, the study site will account for all supplies of product SBT777101. Details of receipt, storage, assembly, infusion, and destruction or return are provided within Investigational Product Manual.

The Principal Investigator or their representative will account for drug product provided by the Sponsor. All drug products are required to be stored at the site in a secure and locked location. The Principal Investigator shall maintain adequate records of the disposition of the drug product including dates, quantity and use by subjects.

6.5. Drug Disposal and Destruction

Any unused product that remains in the unopened shipper and is still within the product stability window may be returned to the Sponsor (e.g for research purposes). Return of product to the manufacturing site should be coordinated with the Sponsor.

Any used or unused product that has exceeded the product stability window and all unused administration supplies must be disposed of in accordance with the policy at the clinical site.

6.6. Dosing Regimen

A single dose of SBT777101 study drug will be administered to the subject by intravenous infusion (see Table 1 for planned doses).

6.7. SBT777101 Preparation and Cell Thaw

The SBT777101 shipping container must be opened, and the thaw commenced on a date prior to the packaging expiration date on the shipper.

The product is removed from LN2 shipping container and visually inspected to ensure that there is no leakage or damage and identity of the product verified for the intended Subject.

SBT777101 is supplied in sealed cryobags; the number of bags supplied for each subject will differ depending on the dose level and the number of transduced cells present in the product. The Sponsor will provide the exact volume of study drug to be infused for each individual subject.

Please refer to the Investigational Product Manual for details on preparation and thaw of SBT777101.

6.8. SBT777101 Administration

Prior to administration, the drug product should be visually inspected. SBT777101 should only be administered by trained and qualified study staff in a setting equipped for the safe administration of a cell therapy product.

A calculated volume of SBT777101 based on dose assignment will be administered to the subject. Prior to infusion, the identity of the subject should be confirmed and cross checked against the subject identifiers on the study drug packaging. SBT777101 will be infused intravenously. The subject must be continually monitored during the infusion.

Please see Section 8.1 for details and guidance on the management of potential and theoretical adverse events for SBT777101.

Please refer to the Investigational Product Manual for details on administration of SBT777101.

6.9. Continued Access to Study Drug After the End of the Study

SBT777101 will not be provided to subjects after they complete the treatment period.

6.10. Overdose or Medication Error

For this study, any dose of SBT777101 greater than that designated in the cohort the subject was assigned to will be considered an overdose.

In the event of an overdose, the study site Investigator should:

- Treat all symptoms, as appropriate, and provide supportive care
- Contact the medical monitor immediately
- Closely monitor the subject for any AE/SAE and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdose
- Obtain a serum sample for PK analysis as soon as practicable

Subjects who receive an overdose or for whom there is a medication error should remain in the study and continue to complete the study assessments.

6.11. Method of Treatment Assignment and Blinding

This is an open-label study; all subjects will be treated with SBT777101. After a subject has provided informed consent, they will be provided with a unique screening number.

The Investigator, study site personnel, the laboratories assigned to analyze PK, PD, and ADA samples and all subjects will know the treatment allocation during the study. The Sponsor and designees will also know the treatment and dose that each subject receives.

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (see Appendix A and Appendix B). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if any action is required.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Repeat or unscheduled blood samples may be taken for safety reasons or if technical issues occur (e.g., blood sample hemolysis) at any study visit.

7.1. Study Visits

All study assessments will be performed as described in the SoA (Appendix A and Appendix B).

7.1.1. Screening

The screening period for a subject commences at the point at which they sign the informed consent form (ICF). The subject must sign and date the ICF before any screening procedures or study-specific tests can be performed.

All consenting subjects will be given a unique subject ID number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject.

Subjects will be screened for study eligibility according to the assessments described in the SoA. Select data obtained during screening will be evaluated by the Sponsor to confirm study eligibility. Once full eligibility has been confirmed the subject may be enrolled into the study.

Screening is expected to last approximately 2 weeks.

7.1.2. Pre-treatment

Upon enrollment, subjects will enter the pre-treatment phase of the study. The apheresis procedure, SBT777101 manufacturing, synovial biopsy and/or fluid collection and pre-infusion eligibility checks will take place during this study period.

The pre-treatment phase is expected to last approximately 6-8 weeks.

7.1.2.1. Apheresis

An apheresis procedure will be performed on each subject to collect peripheral blood mononuclear cells (PBMCs) required for the manufacturing of SBT777101.

The collection will be performed according to Apheresis Collection Manual using standard collection procedures at a Sponsor qualified collection center and utilizing FDA approved equipment for the collection of mononuclear cells. The apheresis product should be handled per local institutional policies and procedures, in accordance with applicable regulations (including but not limited to 21 CFR 1271.145) and Occupational Safety and Health Administration (OSHA) Universal Precautions. Please refer to local site guidance for the details of criteria that need to be met before a subject can undergo apheresis.

The apheresis product will be packaged and shipped as described in the Apheresis Collection Manual.

Should technical issues arise during the apheresis procedure or during the manufacturing of SBT777101, the subject may undergo a second collection procedure with Sponsor approval. Subjects must repeat the pre-apheresis assessments to confirm that they are eligible to undergo a second apheresis procedure.

7.1.2.2. SBT777101 Manufacturing

SBT777101 study drug product will be manufactured according to the Sponsor defined process.

7.1.2.3. Synovial Biopsy and Fluid Collection

The biopsy to collect synovial tissue and/or synovial fluid prior to infusion will take place after the subject has undergone enrollment into the study. This procedure must be completed at least one week prior to the planned dosing date.

Ultrasound evaluation of joints (e.g., knees, wrists and ankles) may be performed at the same time as the synovial biopsy procedure/synovial fluid collection to assess baseline condition and pathophysiological changes following dosing with SBT777101.

7.1.2.4. Pre-Infusion Eligibility Confirmation

Subject eligibility must be reconfirmed between study Days -10 and -4 to confirm that it is safe and appropriate that the subject receives study drug.

If any of the eligibility criteria are not met the subject must not be dosed with SBT777101. In this case, the subject remains enrolled but will need to be reassessed according to the pre-infusion eligibility criteria before dosing. Subjects can be reassessed for up to 6 months after enrollment. A subject that is not dosed within 6 months of being enrolled will be withdrawn from the study. A second apheresis is not required for subjects who qualify for infusion upon reassessment and have an available SBT777101 cell product that met the release criteria.

Subjects with active infections during the pre-treatment period should not be dosed until at least four weeks after completion of IV antibiotics and two weeks after completion of treatment with oral antibiotics/anti-infectives.

7.1.3. SBT777101 Administration

Subjects will receive SBT777101 by IV infusion on study Day 1.

Subjects will be closely monitored for acute safety events at the site under direct supervision of medical staff post administration of study drug. See Section 8.1 for details of safety monitoring requirements.

7.1.4. Safety Follow-Up

Subjects will attend study visits up to Week 48 and complete study assessments as described in the protocol.

7.1.5. Unscheduled Evaluations

The subject may be requested to come to the site for an unscheduled visit if the Investigator determines that a subject needs to be evaluated at a time other than the protocol specified visits.

Results from any unscheduled assessments, including laboratory assessments, should be captured in the appropriate eCRF.

7.1.6. End of Study Visit

An end of study visit will take place at Week 48.

If a subject withdraws from the study prior to Week 48, an end of study visit will be scheduled as soon as possible, and the assessments listed for the end of study visit will be performed. The reason for early withdrawal will be captured in the eCRF.

Following completion of the end of study visits, subjects should be encouraged to enroll in a long-term follow-up study under a separate protocol for further safety evaluation.

7.2. Study Assessments

Planned timepoints for all study assessments are provided in the Schedule of Assessments (SoA) (see Appendix A and Appendix B).

The preferred order of assessments is presented in Section 7.3.

7.2.1. Demographics

Data collected will include but is not limited to age (date of birth), gender, and self-reported race/ethnicity (see Section 9.6).

7.2.2. Medical History

Medical history will include but is not limited to clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), inflammatory/autoimmune disease, smoking history, use of alcohol and drugs of abuse within the previous year. Medical conditions that are a result of side effects from concomitant medications should be clearly defined and entered into the eCRF.

Any medical condition present at study Day 1 should be followed during the study and a change in status (intensity or frequency) should be reported as an adverse event if deemed clinically significant by the Principal Investigator.

7.2.3. Concomitant Medications

All standard concomitant medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the subject within 30 days prior to the Screening visit should be entered on the Concomitant Medications eCRF.

Prior and current therapies used by a subject for the treatment of RA must be reported from the time of diagnosis through to the end of the study/early termination visit, where available. This includes DMARDs and corticosteroids.

A start date should be entered for all medication items entered into the Concomitant Medications eCRF, including those medications used chronically.

7.2.4. Safety Assessments

7.2.4.1. Physical Examinations

A complete physical examination or a symptom directed physical examinations will be performed.

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. A genitourinary or breast examination is not required unless clinically indicated, in the opinion of the Investigator assessing the subject. Height and weight will also be measured and recorded.
- A symptom directed physical examination will include those organs, body sites required to assess the symptoms and associated findings.

7.2.4.2. Electrocardiograms

Triplicate 12-lead electrocardiograms (ECGs) will be obtained at specific timepoints during the study.

- ECGs should be performed after the subject has been at rest for at least five minutes, and whilst in a supine position.
- At a minimum, the following ECG parameters will be collected in the eCRF: HR, PR-interval, RR interval, QTc, QTcF, QRS width.
- The three ECG recordings should be performed within a five-minute period and at least 1 minute apart. If any abnormal findings are measured, then the ECGs will be repeated in triplicate (within five minutes; at least one minute apart).

7.2.4.3. Vital Signs

Vital sign assessments will be performed at specific timepoints during the study.

- Will include oral body temperature, systolic and diastolic blood pressure, and pulse and respiratory rate. Height and weight will be recorded at screening only.

- Blood pressure and heart rate measurements will be assessed after the subject has been rested for at least 5 minutes, in a quiet setting if possible, and in a supine or semi-reclined position.
- Oxygen saturation will be measured at screening, during apheresis and during infusion of study drug.

7.2.4.4. Chest X-Ray

A standard posterior-anterior and lateral chest x-ray will be obtained. All clinically significant abnormalities noted prior to SBT777101 administration should be noted on the medical history eCRF.

7.2.5. Synovial Tissue and Fluid

All subjects will undergo collection of synovial tissue and fluid pre- and post-dose for evaluation of CAR-antigen reactivity, and characterization of local inflammatory microenvironment, including the number and phenotype of T cell and other immune cell subtypes.

The presence of SBT777101 will be evaluated in the synovial fluid and tissue (if sampling is clinically feasible). Synovial biopsy should be performed in the same joint pre- and post-dose where possible.

Sites using ultrasound evaluation of joints (e.g., knees, wrists and ankles) as part of the synovial biopsy/synovial fluid collection procedure will collect ultrasound images to assess pathophysiological changes following dosing with SBT777101.

Details of procedure requirements and sample processing are provided in the Biopsy Manual.

7.2.6. Laboratory Assessments

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

7.2.6.1. Clinical Laboratory Tests

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Additional laboratory tests may be performed at the Investigator's discretion for the purpose of planning treatment administration, following AEs, or as clinically indicated.

For all females, a serum pregnancy test will be performed at the Screening and Pre-Infusion visits. Urine pregnancy tests will be done at all other study visits.

Details of laboratory tests are described in Appendix C.

7.2.6.2. Replication Competent Lentivirus

Blood samples will be collected to monitor for replication competent lentivirus (RCL) per FDA guidance (FDA, 2020) using VSV-G qPCR.

7.2.6.3. PK and Immunogenicity Assessments

Whole blood and serum samples will be collected to evaluate the pharmacokinetics and immunogenicity of SBT777101. This will include:

- Whole blood samples for PK analysis
- Serum samples for immunogenicity analysis will be collected to measure ADAs against the extracellular domain of the CAR and the EGFR tag.
- PBMCs will be collected to measure cellular immunogenicity against CAR-derived and EGFR tag-derived peptides.

In addition, the Sponsor may collect synovial tissue and fluid for analysis of presence of SBT777101.

The Sponsor may store samples for up to 15 years after the end of the study to achieve study objectives.

7.2.6.4. Pharmacodynamic and Biomarker Assessments

Whole blood and serum samples as well as synovial tissue and fluid will be collected to evaluate the pharmacodynamics of SBT777101 and for exploratory biomarker analysis.

The Sponsor may store samples for up to 15 years after the end of the study to achieve study objectives. Additionally, with subjects' consent, samples may be used for further research by Sponsor or others such as universities or other companies to contribute to the understanding of RA or other diseases, the development of related or new treatments, or research methods.

7.2.6.4.1. Pharmacodynamic Biomarkers

Pharmacodynamic (PD) effects of SBT777101 will be evaluated by measurement of relevant inflammatory cytokines (including but not limited to: IL-1, IL-6, IL-10, IL-15, IL-17, TNFα and interferon-gamma (IFNγ)) and chemokines, as well as measurement of levels of C-reactive protein (CRP) and ACPA pre-dose and after dosing.

7.2.6.4.2. Exploratory Biomarkers

Exploratory biomarkers will include but are not limited to enumeration and phenotyping of CAR T_{reg} cells in peripheral blood by flow cytometry, immunophenotyping of peripheral blood T cell and other immune cell subsets by flow cytometry, and molecular profiling studies using samples collected pre- and post SBT777101 treatment. These studies will inform and enable discovery of potential new biomarkers of response to treatment.

7.2.7. Clinical Assessments

7.2.7.1. Synovitis Assessment

Physical examination and/or ultrasound will be performed to confirm presence of synovitis in the joint considered for synovial biopsy according to local clinical practice. Synovitis of the joint selected for biopsy will also be assessed using these techniques during the study.

7.2.7.2. Efficacy Assessments

ACR and DAS28 response rates will be used to evaluate efficacy responses. Joint count assessments should be performed by the same assessor throughout the study where possible.

The components of these efficacy instruments include evaluation of:

- Swollen and tender joint count (includes assessment of 28 and 66 swollen joints and/or 28 and 68 tender joints)
- Subject's assessment of arthritis pain (using a 100 mm visual analogue scale (VAS))
- Subject's global assessment of arthritis (using a 100 mm VAS)
- Physician's global assessment of arthritis (using a 100 mm VAS)
- Health Assessment Questionnaire-Disability Index (HAQ-DI) to assess subject's physical functioning.

Fatigue will also be measured using the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) score.

7.3. Order of Study Assessments

The preferred order of assessments for study visits is as follows:

- Safety assessments (ECG must be performed first, followed by vital signs, where required)
- Demographics, medical history and concomitant medication review
- Clinical assessments (PROs must be performed prior to any interventional assessments including lab draws)
- Clinical laboratory tests
- Labs for RCL
- Labs for PK and immunogenicity
- Labs for PD
- Labs for exploratory biomarkers
- Study drug administration
- Synovial biopsy and/or synovial fluid collection and ultrasound evaluation of joints

Unscheduled safety assessments should take priority over any scheduled clinical or PK assessments.

7.4. Subject Discontinuation / Withdrawal and Replacement

7.4.1. Subject Discontinuation/ Withdrawal from the Study

Subjects may discontinue the study for any of the following reasons:

- Subject withdraws consent
- The study is terminated
- May be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons
- The subject requires medical treatment prohibited by the protocol
- Failure to generate a SBT777101 dose that meets the required quality control (QC) and release criteria as defined by the Sponsor

If a subject takes a prohibited medication or receives rescue therapy outside of permitted guidelines, they should remain in the study and continue to attend visits and complete study assessments as described in the SoA (Appendix B).

7.4.1.1. Data Collected for Subjects Withdrawn from the Study

If a subject chooses to withdraw from the study after enrollment but prior to study Day 1, SBT777101 will not be administered. All subjects that are dosed with SBT777101 and withdraw from the study will be encouraged to enroll in the long term follow-up study at the time of withdrawal.

The date and reason for study withdrawal, if available, must be recorded in the subject's eCRF. An Early Termination (ET) visit (see Appendix B) will be conducted unless consent to do so is withdrawn.

- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested to prevent future testing. The Investigator must document this in the site study records.
- Any data already generated from samples collected up to the point of withdrawal of consent will not be removed from the study database.

7.4.2. Lost to Follow-Up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, [3] telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.4.3. Subject Replacement

Subjects in dose escalation cohorts who have been dosed with SBT777101 and withdraw for reasons other than toxicity or are lost to follow-up before completing the safety evaluation period (up to study Day 28) will be replaced.

Additionally, a replacement subject may be enrolled in the study at the discretion of the Sponsor if one or more enrolled subjects are not fully evaluable for purposes of complete safety, PK or PD determination. These replacement subjects may be enrolled while the cohort is still ongoing or concurrently with subsequent cohorts.

Subjects in backfill cohorts that withdraw from the study will not be replaced.

7.5. Early Discontinuation of the Study or Study Site

The Sponsor has the right to terminate this study at any time for any reason. Reasons for terminating the study or study site may include, but are not limited to:

- Incidence or severity of adverse events in this or other studies indicating a potential health hazard to subjects
- Unsatisfactory subject recruitment, e.g., excessively slow
- Poor protocol adherence
- Incomplete or inaccurate data recording
- Poor compliance with the protocol, the requirements of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or local health authorities, the Sponsor's procedures, or the International Council for Conference Harmonisation Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP)

In any instance of early discontinuation of the study or study site, the Sponsor will notify, in writing, the Investigators, regulatory authorities and ethics committees, and will specify the reason(s) for termination.

8. ASSESSMENT OF SAFETY

8.1. Safety Plan

This is the first study in which SBT777101 will be administered to humans. As such, the actual risks are unknown. The anticipated potential and theoretical safety risks for subjects are detailed in the sections below. Please refer to the Investigator Brochure for SBT777101 for a complete summary of safety information.

Measures will be taken to ensure the safety of subjects participating in this study, including the use of stringent inclusion and exclusion criteria (see Section 4), and rigorous monitoring

assessments as detailed in Section 8.1.1. As described in Section 3.1.1, all subjects receiving SBT777101 in dose escalation cohorts will be dosed at least 14 days apart and monitored for onset of DLTs for at least 28 days prior to dose escalation. In addition, subjects in backfill cohorts will be dosed 14 days apart. Dosing of subsequent subjects within cohorts and dose escalation decisions will be made by a SMC in collaboration with the study Investigators (see Section 3.3).

All subjects will be monitored closely for toxicity. Administration of SBT777101 will be performed in a setting with available emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Subjects will be closely monitored for acute safety events at the site under direct supervision of medical staff post administration of study drug. Safety monitoring should be performed as described below:

- Subjects should remain in a supine or semi-reclined position prior to and for the duration of the infusion. Vital signs must be measured approximately 15 minutes prior to infusion, and approximately every 15 minutes during the infusion.
- Subjects must remain at the study site/medical facility under medical supervision for at least 24 hours from the start of the Day 1 study drug infusion through completion of procedures at the Day 2 study visit.
- Subjects will be contacted by study staff on Days 3-7 to check for adverse events and provide reminders for temperature monitoring. Check-in may occur by phone call, text, or other method.
- The Sponsor recommends the following from study Day 2 to Day 28:
    - Subjects should stay within approximately 1 hour travel time to the study site from Day 2 through completion of procedures at the Day 7 study visit.
    - The subject remains under the care of a responsible adult in case of the onset of unexpected adverse medical events
    - The subject does not drive or operate heavy machinery

Subjects will be assessed clinically for adverse events during the conduct of this study using the CTCAE Grading Scale (Appendix E). All adverse events and serious adverse events will be recorded and reported as described in Section 8.2 and Appendix E.

8.1.1. Potential Risks

Risks potentially associated with SBT777101 treatment are described in the sections below. Please contact the Medical Monitor in case of questions on potential risks.

8.1.1.1. Infusion Related Reactions

Infusion related reactions are considered a potential risk for autologous cell therapies such as SBT777101. Pre-treatment with an antipyretic (e.g., acetaminophen 650 mg PO) and/or an antihistamine (e.g., diphenhydramine 25-50 mg PO or IV) is not required but may be administered as clinically indicated and at the discretion of the treating physician. Any infusion related adverse events will be reported in the eCRF and treatment given according to standard of care.

A blood sample for potential analyses of infusion reaction mediators (e.g., histamine, tryptase) should be collected at the time of an infusion related reaction AE.

The following guidelines should be followed for the management of infusion reactions:

- For mild reactions (Grade 1) with onset during an IV infusion, continue infusion of study drug at the same rate. Supportive care (e.g., antipyretics and/or antihistamines) may be administered as clinically indicated.
- For reactions of Grade 2 severity, pause SBT777101 infusion and administer supportive care. Study drug infusion may be re-initiated at a reduced rate (50%).
- For reactions of Grade 3 severity, pause SBT777101 infusion and administer supportive care. If symptoms resolve to ≤ Grade 2, study drug infusion may be re-initiated at a reduced rate (50%). If symptoms recur or worsen, discontinue infusion of study drug.
- For reactions of Grade 4, discontinue infusion of study drug.
- For reactions occurring after an IV infusion, apply supportive care as necessary.

Of note, SBT777101 is stable for 3 hours at room temperature; therefore, the time post-thawing should be monitored in the event that study drug infusion is paused, or the rate of administration is reduced.

8.1.1.2. Infections

Physicians should exercise caution when considering use of SBT777101 in subjects with a history of opportunistic and/or recurrent infections or those with underlying conditions that may predispose them to infections (e.g., diabetes). SBT777101 should not be administered to a subject with an active infection.

Close monitoring of subjects for signs of infection is recommended since they may be receiving concomitant therapy that could lessen the signs and symptoms of acute infections due to suppression of the acute phase response. Subjects should be instructed to monitor their temperature daily and to contact their physician immediately if experiencing symptoms that suggest infection in order to ensure rapid evaluation and appropriate treatment. All subjects with a fever (temperature >38°C or 100.4°F) should be evaluated for an infectious etiology.

See Section 7.1.2.4 for guidance on management of infections during the pre-treatment period of the study.

8.1.1.3. Viral Reactivation

While reactivation of viral (e.g., EBV) or other serious infections has been observed with biologic therapies for RA, the potential for this to occur with SBT777101 is unknown. Reactivation of latent viral infections is considered a potential risk for SBT777101 (Brunstein et al., 2013; Zhang et al., 2018). However, it should be noted that there has been no evidence of reactivation of viral or other serious infections observed in clinical trials in other autoimmune diseases using polyclonal T_{reg} adoptive immunotherapy. One subject in a Type 1 diabetes study developed grade 2 pharyngitis and had transient low-copy number cytomegalovirus (CMV), but

this was presumed to be due to a new infection with CMV occurring before receiving autologous polyclonal T_{reg} cells (Brunstein et al., 2011; Bluestone et al., 2015).

Subjects must be monitored closely for signs and symptoms suggesting potential reactivation of viruses and treated according to standard of care.

8.1.2. Theoretical Risks

Risks theoretically associated with SBT777101 treatment are described in the sections below.

8.1.2.1. Cytokine Release Syndrome

Cytokine Release Syndrome (CRS) is thought to result from a high level of immune activation of effector lymphocytes, macrophages and/or myeloid cells with subsequent massive release of proinflammatory cytokines. CRS is associated with markedly increased levels of IL-6, IL-10, TNFα and INFγ, and the sequelae may be severe or life-threatening. Administration of CAR T_{eff} therapy is associated with CRS, with symptoms typically appearing within 14 days of CAR T_{eff} administration (Chou and Turtle , 2020), with the overwhelming majority developing within 1-2 days.

Although the precise risk of CRS with SBT777101 is unknown, CRS was not observed in studies of polyclonal T_{regs} in patients with autoimmune indications (see SBT777101 Investigator Brochure). Therefore, it is important to closely monitor subjects for signs and symptoms of onset of CRS despite this low risk.

CRS may be associated with one or more of the following signs and symptoms:

- High fever (>39°C)
- Fatigue
- Nausea
- Headache
- Dyspnea
- Tachycardia
- Peripheral and/or pulmonary edema
- Coagulopathy
- Electrolyte abnormalities (e.g., hypophosphatemia, hypokalemia, hyponatremia)
- Rigors
- Fluid-refractory hypotension
- Respiratory failure/hypoxia
- Myalgia/arthralgia
- Anorexia
- Neurological abnormalities

The diagnosis of CRS requires a fever (temperature of ≥38°C or 100.4°F). All subjects will be provided with infrared thermometers for at-home temperature evaluations and instructed to seek medical attention if they develop a temperature of ≥38°C (100.4°F). *It is critical to exclude potential infections during the initial evaluation of any subject presenting with a fever.*

Laboratory studies for the evaluation of possible CRS should include markers of inflammation, especially IL-6 and IFNγ when available. Although C-reactive protein (CRP) is frequently elevated in CRS, it is often elevated in patients with RA in general. Therefore, a diagnosis of CRS should not rely solely on a finding of abnormal CRP.

Subjects should be treated according to site protocols for the management of CRS or standard clinical practice.

See Appendix F for guidance on grading CRS adverse events according to the ASTCT scale.

8.1.2.2. Neurotoxicity

CAR T_{eff} cell therapy has been shown to be associated with neurological toxicities, also known as CAR T-Cell Related Encephalopathy (CRES) or Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) that may correlate with high cytokine levels. The risk of neurotoxicity with SBT777101 treatment is unknown given the difference in mechanism of action from CAR T_{eff} therapies used in the oncology setting. However, CRES was not observed in studies of polyclonal T_{regs} in patients with autoimmune indications (see SBT777101 Investigator Brochure).

Neurotoxicity can be characterized by the following signs and symptoms (Siegler and Kenderian, 2020):

- Confusion
- Aphasia
- Tremor
- Word finding difficulty
- Lethargy
- Obtundation
- Stupor
- Seizures
- Coma
- Myoclonus

In general, onset of neurologic symptoms has been seen to begin five to seven days after CAR T_{eff} therapy administration.

Subjects receiving SBT777101 should be monitored closely for signs and symptoms of neurotoxicity. Management of neurologic toxicity should occur according to site protocols or standard clinical practice.

See Appendix G for guidance on grading neurotoxicity adverse events according to the ICANS scale.

8.1.2.3. Malignancies

Risks of cell therapy using a lentivirus include insertional mutagenesis. There have been no reports of long-term toxicities associated with retroviral vector-mediated gene transfer into mature T cells and an insertion site analysis conducted for SBT777101 showed a polyclonal integration site profile with no dominant integration site (Milone and O'Doherty, 2018). Subjects will be monitored for 1 year in this study and longer term in a safety follow-up protocol as per current FDA guidelines.

8.2. Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events, performing protocol-specified safety laboratory assessments, measuring

protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 8.2.2.

8.2.1. Adverse Events (AEs) Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix E.

AEs will be reported by the subject.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious or considered related to the study intervention or study procedures.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix E.

8.2.2. Time Period and Frequency for Collecting AE and SAE Information

All SAEs plus any AE that is the result of a protocol specified procedure or intervention will be collected from the signing of the ICF until study drug administration.

All AEs will be collected from the time of first study drug administration until the final safety follow-up visit.

Medical occurrences that begin before study drug administration but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix E. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.2.3. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.2.4. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4.2). Further information on follow-up procedures is provided in Appendix E.

8.2.5. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.2.6. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of study intervention and until completion of final safety follow-up visit.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female subject or female partner of male subject (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Appendix E. While the Investigator is not obligated to actively seek this information in former study subjects/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

9. STATISTICAL CONSIDERATIONS

9.1. Determination of Sample Size

The sample size in this study was not selected based on statistical considerations but to determine preliminary safety, tolerability, PK, PD, and preliminary clinical activity of SBT777101 subjects with active RA.

This study will enroll up to 36 eligible adult subjects with RA. Up to 18 eligible adult subjects will be enrolled in escalation cohorts and an additional 18 subjects may be included in optional backfill cohorts.

9.2. Blinding and Randomization

This clinical study is open-label, and all subjects enrolled will be treated with SBT777101.

9.3. Analysis Datasets

The following populations will be considered in the analysis of data for this study.

- Safety population: All subjects who received any portion of an infusion of study drug will be included in the safety population. The safety population will be used for both the safety and efficacy analyses.
- PK/PD population: will include all subjects in the safety analysis set with the necessary pre- and post-dose measurement to provide interpretable results for the specific parameter of interest. Subjects will be excluded from the PK/PD analysis if they have protocol deviation or any important event that would affect the interpretation and integrity of the concentration data.

9.4. Endpoints

9.4.1. Primary Endpoint

To evaluate and characterize the safety and tolerability of SBT777101:

- Incidence, nature and severity of AEs
- Incidence and nature of DLTs
- Changes from baseline in clinical laboratory tests, 12-lead ECG parameters and targeted vital signs

9.4.2. Exploratory Endpoints

9.4.2.1. PK Endpoints

To assess and characterize SBT777101 pharamcokinetic profile in peripheral blood and synovium:

- The determination of PK parameters including but not limited to T_{max}, C_{max}, $AUC_{0\text{-}28,}$ C_{last} by the evaluation of CAR transgene levels in peripheral blood

- Presence and levels of SBT777101 in the synovial tissue and/or fluid

9.4.2.2. Mechanism of action and PD Endpoints

To assess and characterize SBT777101 mechanism of action and pharmacodynamic parameters in peripheral blood and the synovium:

- Levels of systemic markers of inflammation in peripheral blood including but not limited to TNFα, CRP, IL-6 pre-dose and following SBT777101 administration
- Levels of inflammatory cells and biomarkers in synovial tissue and/or synovial fluid pre-dose and following SBT777101 administration
- Change from baseline in phenotypic and molecular signatures in T cells and other immune subsets in peripheral blood and synovial tissue and/or fluid following SBT777101 administration

9.4.2.3. Immunogenicity Endpoints

To assess the immunogenicity of SBT777101:

- Presence of anti-drug antibodies in serum at baseline and following SBT777101 administration
- Detection of cellular immunogenicity pre-dose and following SBT777101 administration

9.4.2.4. Efficacy Endpoints

To assess the preliminary efficacy of SBT777101:

- ACR20, ACR50 and ACR70 response rates following SBT777101 administration
- DAS28 scores and change from baseline in DAS28 scores following SBT777101 administration

9.5. Data Handling Convention

Descriptive statistics on continuous data will include means, medians, Q1, Q3, standard deviations, and ranges. Categorical data will be summarized using frequency counts and percentages.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit plus or minus one significant digit, respectively (e.g., if the result of a continuous laboratory test is <10, a value of 9 will be assigned).

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed. However, a missing pre-treatment laboratory result would be treated as normal (e.g., no toxicity grade) for the laboratory abnormality summary.

All analyses and summaries will be presented by dose level and overall.

9.6. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive statistics. Demographic summaries will include but will not be limited to sex, race, ethnicity (Hispanic or non-Hispanic), age (at baseline), disease duration, RF and ACPA status. Baseline data will include a summary of screening body height and weight.

9.7. Safety Analysis

Safety analysis will be conducted based on the safety population. All safety data collected on or after the date that SBT777101 was first dosed will be summarized by dose level and overall. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. No inferential statistics will be done on safety assessments. In addition to safety analysis for SMC (see SMC charter for further details), a final safety analysis will occur after all enrolled patients have completed Week 48 visit. Full details for safety analysis will be provided in the SAP.

9.7.1. Adverse Events

Clinical and laboratory AEs will be coded using the most current version of MedDRA®. The severity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The number of subjects experiencing treatment emergent adverse events (TEAEs) and number of TEAEs will be summarized by dosing level using frequency counts. Injection site reactions and SAEs will be tabulated. All safety data will be listed by subject. In addition, a list of AEs leading to discontinuation of study prematurely will be provided.

9.7.2. Laboratory Evaluation

Graded laboratory abnormalities will be defined according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. All clinical laboratory results and their change from baseline will be summarized by dosing level and at scheduled visits. Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline will be summarized by dosing level. Laboratory abnormalities will also be included in a data listing. A shift table describing out-of-normal range shifts may be provided for clinical laboratory results.

9.7.3. Other Safety Evaluations

Descriptive statistic will be generated to summarize data for physical examination findings, concomitant medications, and medical history. Concomitant medications will be coded using MedDRA® Version 24.1. The number and percentage of patients taking concomitant medication will be summarized.

12-lead ECGs and vital signs measurements will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistical summaries (eg, n, mean, SD, median, Q1, Q3, minimum, and maximum), as appropriate.

9.7.4. PK and Immunogenicity Analysis

SBT77701 CAR transgene level in peripheral blood and PK parameters will be listed and summarized using descriptive statistics. Relevant PK parameters (T_{max}, C_{max}, $AUC_{0-28,}$ C_{last}) will be determined using standard non-compartmental methods.

Immunogenicity data will be listed by subject. The proportion of subjects with a positive anti-drug antibody result will be summarized over time and by dosing level. Proportion of subjects with at least one positive result post dosing will be summarized.

9.7.5. Exploratory Biomarker Analysis

Exploratory analyses may be performed to enhance the understanding of the biological effects, the mechanism of action, or safety of SBT77701. Exploratory analyses will include but will not be limited to the evaluation of the association of each biomarker or combination of biomarkers with clinical outcomes, the identification of molecular and/or phenotypic signatures associated with CAR signaling pathways and assessment of the CAR T_{reg} immunophenotype following dosing with SBT77701.

10. REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

10.1. Ethical Considerations

It is the responsibility of the Principal Investigator to assure that the study is conducted in accordance with the study protocol, FDA regulations, ICH-GCP guidelines, applicable laws and regulations, and the Declaration of Helsinki.

10.2. Institutional Review Board (IRB) and Regulatory Approval

The Principal Investigator must inform, and obtain approval from, the IRB for the conduct of the study at the study site, the protocol, the ICF, any other written information that will be provided to the subjects and any advertisements that will be used. The Sponsor must approve the ICF and all subject recruitment materials before they are submitted to the IRB for approval. Written approval of the protocol and the ICF by the IRB must be obtained prior to recruitment of subjects into the study and shipment of study drug. The written approval of the IRB will be retained as part of the study file, and a copy will be provided to Sponsor.

Any change to the protocol requires a written protocol amendment. Proposed amendments to the protocol or any of the other aforementioned documents must be discussed with the Sponsor, and then submitted to the IRB/IEC for approval. Amendments may be implemented only after a copy of the local IRB approval letter has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or IRB approval. However, in this case, the Sponsor's medical monitor and the IRB must be notified immediately, and IRB approval must be obtained as soon as possible after implementation.

The Principal Investigator will be responsible for ensuring that an annual update is sent to the IRB to facilitate its continuing review of the study and that the IRB is informed of the end of the

study. Copies of the update, subsequent approvals and the final notification letter must be sent to the Sponsor.

10.3. Institutional Biosafety Committee (IBC)

The Principal Investigator will be responsible for ensuring that the appropriate Institutional Biosafety Committee (IBC) has reviewed and approved the protocol and any other required materials prior to initiating the study if required per institutional policy.

An institution must follow the NIH Guidelines if it receives any funding from the NIH for research involving recombinant or synthetic nucleic acid molecules. Although the Sponsor does not receive any NIH funding for research involving recombinant or synthetic nucleic acid molecules; nonetheless, the Sponsor chooses voluntarily to comply. The Sponsor recognizes that following the NIH Guidelines promotes the safe and responsible practice of this research and gives the public confidence that the Sponsor is attending to important safety matters.

10.4. Insurance and Financial Disclosure

The Sponsor has obtained an insurance policy covering, in its terms and provisions, its legal liability for certain injuries caused to subjects arising out of this research performed strictly in accordance with the study protocol as well as with applicable law and professional standards.

Financial Disclosure statements for study personnel listed on the Form FDA 1572 will be handled in a separate agreement apart from the protocol, kept on file and submitted as applicable with any subsequent license application.

10.5. Essential Documentation Requirements

The Sponsor will collect from the study site the required essential regulatory documents per FDA regulations and ICH guidance prior to shipment of the study drug to the site.

10.6. Informed Consent

It is the Principal Investigator's responsibility to obtain written informed consent from each subject after adequate explanation of the objectives, methods, anticipated benefits, and potential risks of the study and before any study procedures are commenced. The subject should be given a copy of the ICF in their native language. The informed consent process should be recorded in the source documentation. The original copy of the signed and dated ICF must be retained in the study site's records and is subject to inspection by representatives of the Sponsor, contract research organization (CRO), or representatives from regulatory agencies.

10.7. Subject Privacy

The Principal Investigator must ensure that each subject's privacy is maintained. On the CRF or other documents submitted to the Sponsor, subjects will be identified by a subject study number only. Documents that are not submitted to the Sponsor (eg, ICFs) should be kept in a strictly confidential file by the Principal Investigator.

The Principal Investigator shall permit representatives of the Sponsor, CRO, regulatory agencies and IRB/IECs to review and audit the portion of the subject's medical record that is directly

related to the study. As part of the required content of informed consent, the subject must be informed that his/her records will be reviewed in this manner.

10.8. Study Record Retention and Storage

The Principal Investigator must retain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by representatives of the Sponsor, CRO, IRB/IEC, and regulatory authorities.

The Principal Investigator will retain all records required to be maintained under 21 CFR § 312.62 for a period of 2 years following the date a marketing application is approved for SBT777101 for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Principal Investigator will retain these records until 2 years after the investigation is discontinued and the US FDA or applicable regulatory authorities are notified.

The Principal Investigator must retain the protocol, amendments, IRB approvals, copies of the Form FDA 1572, signed and dated ICFs, medical records, original reports of test results, all other source data, eCRFs, drug accountability records, all correspondence and any other documents pertaining to the conduct of the study.

Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Principal Investigator. If the Principal Investigator moves, withdraws from the study or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor. Further, should the Principal Investigator wish to move the study records to another location, prior written agreement must be obtained from the Sponsor.

10.9. Disclosure of Information

The contents of this protocol, information concerning the study, patent applications, processes, scientific data obtained during the study, and other pertinent information is Sponsor's confidential information and remains the property of the Sponsor. The Principal Investigator may use this information for the purposes of the study only and will not disclose such information without the Sponsor's written consent.

It is understood by the Investigator that the Sponsor will use information developed in this clinical study in connection with the development of SBT777101 and, therefore, may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands their obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with the prior written consent of the Sponsor.

10.10. Publication

The Sponsor plans to publish the results of the study as a whole once all subjects have completed the study and the study has been analyzed.

The Principal Investigator may not submit the data or results of the study for publication or present such data or results without the prior written consent of the Sponsor. Detailed obligations regarding the publication or presentation of any results, data, or other information generated or created in relation to the study shall be set out in the agreement between the study site and the Sponsor, as appropriate.

The Clinical Trial Agreement will detail the procedures for publications. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

11. ADMINISTRATIVE OBLIGATIONS

11.1. Source Data

Original documents, data, records (eg, clinic records, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study) and all relevant sections of the subject's medical records and all other data collection made specific to this study constitute source documents.

The completed eCRF is not a source document. The Principal Investigator/study site will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection by providing direct access to source documents.

11.2. Data Collection

The Principal Investigator will be responsible for maintaining accurate and adequate case records (source documents) from which data will be electronically transcribed (or if electronically captured [EDC] source data, transferred) to eCRFs designed to record data pertinent to this study and transferred to the Sponsor. All relevant observations and data related to the study will be so recorded. This will include medical and medication history, physical examinations, a checklist of inclusion and exclusion criteria, investigational treatment administration, and a record of sample collection, clinical assessments, AEs, and final evaluation. The clinical site Clinical Research Associate (CRA), site monitor or equivalent, will review all eCRFs and compare data to that contained in clinic notes and subjects' source documents/medical records.

Data collected regarding each subject will be entered into the eCRF. The Investigator will be responsible for the timeliness, completeness, and accuracy of the information and data entered into the eCRFs.

11.3. Monitoring

It is understood that CRAs, monitors, and any authorized personnel contracted by Sponsor may contact and visit the Principal Investigator and the study site, and that they will be allowed to inspect the various records of the study on request (eCRFs and other pertinent data), provided that subject confidentiality is maintained, and that the inspection is conducted in accordance with local regulations.

It is the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to GCP guidelines.

The Principal Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

11.4. Quality Control and Quality Assurance

The Sponsor or its designee will perform quality control and quality assurance checks of all clinical studies that it sponsors according to its internal procedures. Before the enrollment of any subject in this study, the Sponsor personnel will review and provide training as needed to the Investigator, Sub-Investigators, and study site personnel regarding the following: protocol, IB, CRFs and procedures for their completion, informed consent process, and procedures for reporting SAEs. Site visits will be performed by Sponsor's CRA or designee periodically throughout the study. During these visits, information recorded on the CRFs will be reviewed against source documents, and requests for clarification or correction may be made. The CRFs will be reviewed by the CRA for safety information, completeness, accuracy, and logical consistency. Requests for clarification or correction will be sent to Investigators via data queries.

A Safety Monitoring Committee will periodically review safety data (e.g., AEs and SAEs, laboratory data) as the clinical trial is ongoing. A Quality Assurance representative of the Sponsor may audit the study. All necessary data and documents will be made available for inspection.

11.5. Site Audits and Regulatory Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC or an IRB about an inspection.

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13. APPENDICES

APPENDIX A. SCHEDULE OF ASSESSMENTS: SCREENING AND PRE-TREATMENT PERIODS

	Screening	Pre-Treatment	
Study Week	**-8 to -7**	**-6 to -1**	
Study Day (visit window)			**-10 to -4**
Procedure			
Informed consent	●		
Assign Allocation Number (Subject ID)	●		
Eligibility criteria	●		●
Demographics	●		
Medical history	●	●	●
Prior/Concomitant medications	●	●	●
Vital signs	●	●	●
Full physical exam	●		
Directed physical exam			●
Height	●		
Weight	●		●
12-lead triplicate ECG	●		
Chest X-ray	●		
Assessment of synovitis (clinical and/or ultrasound)	●	●	●
Joint evaluation for biopsy	●		
Synovial biopsy for tissue [a]		●	
Synovial fluid collection [a]		●	
Vein assessment	●		
Apheresis		● [b]	
Infectious disease serology [c]	●		
TB screening [c]	●		
Serum pregnancy test	●		●
Lipid tests [c]			●
Coagulation [c]	●		●
Hematology [c]	●		●
Clinical chemistry [c]	●		●
Urinalysis [c]	●		●
Markers of inflammation			●
CRP	●		●
Joint count assessment (28 SJC and 28 TJC)			●
Joint count assessment (66 SJC and 68 TJC)	●		
Physician VAS	●		●
Subject VAS (global and assessment of pain)	●		●
HAQ-DI	●		●
FACIT-F			●

	Screening	Pre-Treatment	
Study Week	**-8 to -7**	**-6 to -1**	
Study Day (visit window)			**-10 to -4**
Procedure			
Blood samples for PK (ddPCR)			●
Blood sample for cellular immunogenicity			●
Blood sample for ADA			●
Blood sample for exploratory inflammatory markers			●
Blood sample for ACPA/RF			●
Blood sample for VICM			●
Blood samples for exploratory biomarkers			●
Blood samples for RCL			●
Adverse events [d]	●	●	●

ACPA = anti-citrullinated protein antibody; ADA = anti-drug antibody; APH = apheresis; CRP = C-reactive protein; ddPCR = droplet digital polymerase chain reaction; ECG = electrocardiogram; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = health assessment questionnaire disability index; PK = pharmacokinetic; RCL = replication competent lentivirus; RF = rheumatoid factor; SJC = swollen joint count; TB = tuberculosis; TJC = tender joint count; UV = unscheduled visit; VAS= visual analogue score
VICM = citrullinated and MMP degraded vimentin fragment

[a] Synovial biopsy and/or synovial fluid collection during the Pre-treatment period should be performed after enrollment and at least one week prior to the planned dosing visit.
[b] Apheresis should be scheduled and performed as soon as possible once screening eligibility is confirmed and the subject enters the Pre-Treatment period. The synovial biopsy should be done after apheresis.
[c] Tests included in laboratory assessments are described in protocol Appendix C. Fasting glucose should be collected at the pre-treatment visit and as clinically indicated.
[d] After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported.

APPENDIX B. SCHEDULE OF ASSESSMENTS: BASELINE AND SAFETY FOLLOW-UP PERIOD

	Safety Follow Up															UV	ET
Study Week	1				2		3	4	6	8	10	12	24	36	48/ES		
Study Day (visit window)	1	2	4 or 5	7 ±1	11 ±1	14 ±2	21 ±2	28 ±2	42 ±2	56 ±2	70 ±2	84 ±3	168 ±7	252 ±7	336 ±7		
Procedure																	
SBT777101 administration	●																
Overnight stay/acute safety monitoring	●																
Patient self-temperature monitoring	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Patient check-in (phone call, text etc) [a]		●	●	●													
Vital signs [b]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Adverse events [c]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Prior/Concomitant medications	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Full physical exam				●				●		●					●		●
Directed physical exam	●	●	●		●	●	●		●		●	●	●	●		●	
Weight										●					●		●
12-lead triplicate ECG				●		●									●	●	●
Synovial biopsy for tissue								●[d,e]									●[e]
Synovial fluid collection								●[d,e]				●[d,e,f]					●[e]
Assessment of synovitis (clinical and/or ultrasound)								●				●					●
Urine pregnancy test	●											●	●		●		●
Lipid tests [g]															●		
Coagulation [g]													●		●		
Hematology [g]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Clinical chemistry [g]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Urinalysis [g]										●				●	●		●
Markers of inflammation [h]																●	
CRP		●		●		●	●	●	●	●	●	●	●	●	●	●	●
Joint count assessment (28 SJC/28 TJC)						●		●		●			●		●		●
Joint count assessment (66 SJC/68 TJC)												●					
Physician VAS						●		●		●		●	●		●		●
Subject VAS (global and assessment of pain)						●		●		●		●	●		●		●
HAQ-DI						●		●		●		●	●		●		●
FACIT-F													●		●		●
Blood samples for PK (ddPCR) [i]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood sample for cellular immunogenicity												●			●	●	●

	Safety Follow Up															UV	ET
Study Week	**1**				**2**		**3**	**4**	**6**	**8**	**10**	**12**	**24**	**36**	**48/ES**		
Study Day (visit window)	**1**	**2**	**4 or 5**	**7 ±1**	**11 ±1**	**14 ±2**	**21 ±2**	**28 ±2**	**42 ±2**	**56 ±2**	**70 ±2**	**84 ±3**	**168 ±7**	**252 ±7**	**336 ±7**		
Procedure																	
Blood sample for ADA										●					●	●	●
Blood sample for exploratory inflammatory markers		●		●		●	●	●	●	●	●	●	●	●	●	●	●
Blood sample for ACPA/RF						●	●	●	●	●	●	●	●	●	●		●
Blood sample for VICM				●		●	●	●	●	●	●	●	●	●	●		●
Blood samples for exploratory biomarkers		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood samples for RCL												●	●		●		

ACPA = anti-citrullinated protein antibody; ADA = anti-drug antibody; CRP = C-reactive protein; ddPCR = droplet digital polymerase chain reaction; ECG = electrocardiogram; ES = End of Study; ET = early termination; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = health assessment questionnaire disability index; PK = pharmacokinetic; RCL = replication competent lentivirus; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count; UV = unscheduled visit; VAS= visual analogue score VICM = citrullinated and MMP degraded vimentin fragment

Note: On Day 1, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Subjects should be contacted daily by the site (e.g by phone or text) following discharge through Day 7.

[b] Vital signs must be measured approximately 15 minutes prior to infusion, then approximately every 15 minutes during the infusion.

[c] After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs will be reported until the end of the study. After this period, the Sponsor should be notified if the investigator becomes aware of any SAE that is believed to be related to prior study drug treatment

[d] The synovial biopsy/fluid collection can be performed at or up to 1 week after the scheduled assessment visit.

[e] The timing of the synovial biopsy and/or synovial fluid collection in may be changed based on evaluation of data from the first dose escalation cohort.

[f] The synovial biopsy sample/fluid collection at Week 12 and at the ET visit is optional.

[g] Tests included in laboratory assessments are described in protocol Appendix C.

[h] A sample to test for markers of inflammation should be collected within 30 minutes of the onset of a suspected adverse event of infection or CRS.

[i] The PK sample collected on study Day 2 should be collected at approximately the same time of day that the infusion of study drug took place on study Day 1 (+/- 1 hour). An unscheduled PK sample should be collected within 30 minutes of a suspected infusion related reaction adverse event.

APPENDIX C. CLINICAL LABORATORY TESTS

The tests detailed in Table 4 will be performed at the times specified in the SoA (Appendix A and Appendix B).

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 4: Protocol-Required Safety Laboratory Tests

Laboratory Tests	**Parameters**			
Hematology (CBC with diff, RBC indices)	Platelet count	RBC indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Red blood cell (RBC) count			
	Hemoglobin			
	Hematocrit			
Clinical chemistry (comprehensive metabolic panel including transaminases and bilirubin)	Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT)	Total protein
	Glucose (fasting at the pre-treatment visit and as clinically indicated)	Calcium	Alkaline phosphatase	HbA1c (only for subjects with a history of glucose intolerance, pre-diabetes or diabetes)
	Chloride	Bicarbonate	Albumin	
Lipid tests	LDL		Total cholesterol	

Table 4: Protocol-Required Safety Laboratory Tests (Continued)

Laboratory Tests	**Parameters**	
Serology	Hepatitis B surface antigen [HbsAg],	Hepatitis C virus antibody
Tuberculosis screening	Quantiferon Gold	
Coagulation	PT	INR
	aPTT	
Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, by dipstick Microscopic examination (if blood or protein is abnormal)	
Pregnancy testing	Highly sensitive [serum or urine] human chorionic gonadotropin (hCG) pregnancy test (for women of childbearing potential)	
Other screening tests	Follicle-stimulating hormone (FSH) and estradiol (as needed in women reported as post-menopausal)	

Investigators must document their review of each laboratory safety report.

APPENDIX D. CONTRACEPTION GUIDANCE

For Female subjects:

- Woman of Childbearing Potential (WOCBP)
  - A woman is considered to be of childbearing potential following menarche and until becoming postmenopausal, unless permanently sterile (see below). If fertility is unclear (e.g., amenorrhea in athletes) and a menstrual cycle cannot be confirmed before study drug administration, the subject should be managed as a WOCBP.
  - All WOCBP must agree to use two methods of contraception for at least one year post SBT777101 administration. One method must be considered a highly effective method of contraception, while the second method may be a barrier method, as outlined here:

CONTRACEPTION GUIDANCE
Highly Effective Methods with Low User Dependency *Failure rate of <1% per year when used consistently and correctly*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner. *Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* • For men only: history of vasectomy with documented confirmation of the absence of sperm.
Highly Effective Methods that Are User Dependent *Failure rate of <1% per year when used consistently and correctly*
• Combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal, or injectable) associated with inhibition of ovulation • Progestogen-only hormone contraception (oral or injectable) associated with inhibition of ovulation • Sexual abstinence. *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*

CONTRACEPTION GUIDANCE
Barrier Methods
• Female condom with spermicide foam • Diaphragm • Cervical cap • Sponge • Film • Male condom (for partner)

- Women in the following categories are *not* considered WOCBP and are exempt from the contraceptives requirement:
  - Premenopausal woman with documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy.
  - Postmenopausal woman. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
    - Women using HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status prior to enrollment.

  For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

For male subjects:

- Males who are sexually active with WOCBP must agree to use a single acceptable method of contraception (e.g. condom) for one year post SBT777101 administration (not required for men with history of vasectomy with documented confirmation of the absence of sperm).

APPENDIX E. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS - DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

AE Definition
An AE is any untoward and/or unfavorable sign, symptom, disease event, or lab abnormality in a clinical study participant, temporally associated with the use of study drug or a study intervention, whether or not considered related to the study drug or study intervention.
Events Meeting the AE Definition
• In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs is considered an AE. This includes any side effect, injury, toxicity or sensitivity reaction. • Increase in severity of a previously identified on-study AE, including an increase in frequency and/or intensity of the AE. • Only clinically significant, in the medical opinion of the Investigator, laboratory test abnormalities that require active management (eg, abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, increased alkaline phosphatase and bilirubin associated with cholecystitis), only the diagnosis (eg, cholecystitis) is recorded as an AE.
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant *was at risk of death at the time of the event*. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event that does not meet any of the above criteria

- May be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient
- May require medical or surgical intervention to prevent one of the outcomes listed above (a to e)
- This also includes a suspected transmission of any infectious agent via an authorized medicinal product

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the database.
- In the instance where medical records/information for individual participants is sent by the site and/or requested by the Sponsor the site will follow their standard procedures, which include redaction of all participant identifiers, with the exception of the participant number.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The severity of an event describes the degree of impact upon the participant and/or the need for medical care necessary to treat the event. The Investigator will make an assessment of severity for each AE and SAE reported during the study using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0

For AEs not adequately addressed in the NCI-CTCAE Version 5.0, the criteria in Table 5 should be used.

Table 5: Grading for Adverse Events Not Covered in the NCI-CTCAE

Severity	Description
Grade 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 – Moderate	Minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL)
Grade 3 – Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4 – Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5 – Fatal	Death

ADL = activities of daily living; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events

Assessment of Causality

- The Investigator will assess the relationship between study intervention and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- An AE/SAE may be considered as not related, possibly or probably related, or related to study drug. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The Investigator will also consult the Investigator's Brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the database that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, the Investigator should always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

SAE Reporting to the Sponsor

- The primary mechanism for formally reporting an SAE to the Sponsor will be via EDC entry. The site will enter the SAE data into the EDC system as soon as it becomes available.
- If it is not possible to access the EDC system, then the site will send an email to Medpace Safety at Medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace within 24 hours of awareness.

Initial notification via email, telephone, or fax does not replace the need for the SAE information to be entered in EDC. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

- If the site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or to the Sponsor's medical director by telephone.
- The Sponsor/designee is responsible for submitting the necessary documents to regulatory authorities as required.

Safety Contact Information:
Medpace Clinical Safety Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: Medpace-safetynotification@medpace.com

APPENDIX F. ASTCT CRS CONSENSUS GRADING

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or[b]				
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Source: Lee et al., 2019

[a] Fever is defined as temperature 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Note: Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

APPENDIX G. ASTCT ICANS CONSENSUS GRADING FOR ADULTS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Source: Lee, et al., 2019

[a]A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[c]Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Abbreviations: N/A indicates not applicable.

NOTE: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

APPENDIX H. GUIDANCE ON PERMITTED CONCOMITANT MEDICATIONS FOR RA

Certain medications used for the treatment of RA may impact the functioning of T_{regs}. Details for each medication class and mechanism of action (MOA) and potential for interaction with T_{regs} is summarized in the table below.

See Section 5 for details of permitted medications for RA (with guidelines on doses and frequency).

Permitted Medications

Class	Examples of Drugs in this Class/MOA	Potential for T_{reg} Interaction
Non-Steroidal Anti-Inflammatory Drugs		
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen, naproxen, aspirin (inhibit prostaglandin production via COX1/2)	• Potentially reduce T_{reg} activity, given evidence for reduced Treg expansion in IVIG via COX2-dependent PGE2 (Trinath, et al., 2013) • Unknown effect on T_{regs} in RA • Inhibit platelet COX, blocking formation of thromboxane A2 necessary for platelet aggregation for hemostasis
Corticosteroids		
Oral corticosteroids (CS)	Prednisone [bind glucocorticoid receptor (GCR), translocate to nucleus and inhibit NFkB-mediated transcription of inflammatory genes, also can uncouple TCR signaling]	• Potential for direct interaction, GCR expressed by all cells • Have inhibitory effects on T_{effs}, but may amplify T_{reg} responses directly through increased FOXP3 expression and working with IL-2 to facilitate T_{reg} expansion (Furukawa, et al., 2016, Karagiannidis, et al., 2004, Chen, et al., 2006) • May also facilitate T_{reg} suppression through modulation of inflammatory environment • Mouse studies suggest CS effect on T_{reg} in cell-intrinsic manner is necessary for anti-inflammatory role (Kim, et al., 2020, Rocamora-Reverte, et al., 2019) • T_{regs} less sensitive to CS-induced apoptosis (Prenek, et al., 2020) • Some conflicting reports of an impact on T_{regs}, though most point to positive correlation between CS therapy and T_{reg} numbers in autoimmune setting (Cari, et al., 2019, Kim, et al., 2020)

Class	Examples of Drugs in this Class/MOA	Potential for T_{reg} Interaction
Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)		
Hydroxychloroquine	Increase pH within phagolysozomes inhibiting antigen presentation	• Decreased DC activation should be beneficial to T_{regs} • In SLE patient PBMCs, HCQ led to increased T_{regs} (Zhang, et al., 2013)
Methotrexate	• Suppression of: purine and pyrimidine synthesis, transmethylation reactions, translocation of nuclear factor-κB (NF-κB) to the nucleus, signaling via the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, and nitric oxide production • Promotion of: adenosine release and expression of certain long non-coding RNAs	• May increase T_{regs} numbers or function (Avdeeva, et al., 2020) • MTX responsiveness has been linked to CD39 expression on T_{regs} (Peres, et al., 2015)
Biologic DMARDs (bDMARDs)		
TNF inhibitor	Adalimumab, golimumab, infliximab (blocks binding of TNFα to TNFR1/R2); certolizumab (pegylated Fab, blocks binding of TNFα to TNFR1/R2); etanercept (TNFR-Fc, binds to TNFα and TNFβ, blocks binding to TNFR1/R2);	• Adalimumab, Golimumab, Infliximab: Low likelihood for depletion of T_{regs} by ADCC/CDC via mTNF binding, modulation of TNFR1/2 signaling in T_{reg} • Certolizumab: No likelihood for ADCC/CDC, modulation of TNFR1/2 signaling in T_{reg} • Etanercept: Very low likelihood for depletion of T_{regs} by ADCC/CDC via mTNF binding, modulation of TNFR1/2 signaling in T_{reg} • All: decrease in TNFR2 signaling theoretically a negative impact on T_{regs} but not supported by clinical data in RA
IL-1 inhibitor	Anakinra (recombinant IL-1RA inhibits IL-1a and IL-1b through IL-1R binding)	• Reports of higher T_{regs} following treatment with anakinra plus MTX (Niu, et al., 2011) • T_{regs} express IL-1R, but also high IL-1RA and no difference between suppression of IL-1R+/- T_{regs} (Mercer, et al., 2010) • May prevent formation of osteoclastogenic T_{regs} (Levescot, et al., 2021)

Class	**Examples of Drugs in this Class/MOA**	**Potential for T_{reg} Interaction**
IL-6 inhibitor	Tocilizumab, sarilumab (anti-IL-6R mAb, blocks IL-6 mediated activity)	May promote T_{reg} polarization away from Th17 and stabilize T_{reg} phenotype (Furukawa, et al., 2016

APPENDIX I. GUIDANCE ON PROHIBITED CONCOMITANT MEDICATIONS FOR RA

Certain medications used for the treatment of RA may impact the functioning of T_{regs}. Details for each medication class and mechanism of action (MOA) and potential for interaction with T_{regs} is summarized in the table below.

See Section 5 for details prohibited medications for RA.

Prohibited Medications

Class	Examples of Drugs in this Class/MOA	Potential for T_{reg} Interaction
Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)		
Azathioprine	Inhibits purine synthesis	• May decrease FOXP3 expression in T_{reg} and slightly decreased proportion of T_{reg} in PBMC from Graves disease patients (Hu, et al., 2012) • Also reported reductions in FOXP3+ cells in IBD and autoimmune hepatitis patients treated with drug regimens containing AZA (Taubert, et al., 2014, Verdonk, et al., 2007) • Another study showed no effect on T_{regs} in IBD patients given thiopurines (Lord, et al., 2017)
Cyclophosphamide	DNA alkylation and protein synthesis inhibition via DNA/RNA cross-linking	• Human T_{reg} are more sensitive to cyclophosphamide at low doses compared to T_{eff} and are depleted in humans in vivo in oncology setting (Heylmann, et al., 2013, Noordam, et al., 2018, Scurr, et al., 2017)
Cyclosporine	Inhibits calcineurin signaling including synthesis of interleukins such as IL-2	• Cyclosporine A reduced T_{reg} activity and proliferation in vitro (Miroux, et al., 2009,Bocian, et al., 2010). • IL-2 therapy may restore reduction in T_{reg} numbers by calcineurin inhibitors to rescue tolerance (Whitehouse, et al., 2017)
Leflunomide	• Inhibits pyrimidine synthesis • Augments the immunosuppressive cytokine TGFβ1 • Suppresses the immunostimulatory cytokine IL-2	Human in vitro data: • Significantly reduced anti-proliferative T_{reg} function • Reduced expression of FOXP3 mRNA in T_{regs} Animal in vivo data: • No effect on T_{reg} number in mouse CIA model (Zhu, et al., 2014) • Increased T_{regs} in rat CIA model(Wang, et al., 2010)

Sulfasalazine	Not fully understood but possibly: • Inhibits NFkB, thereby suppressing pro-inflammatory genes [e.g. tumor necrosis factor (TNF)α] • Inhibits osteoclast formation by suppressing receptor activator of NFkB ligand (RANKL) Induces conversion to adenosine, and consequently increases adenosine-dependent, NFkB/prostaglandin-independent inhibition of leukocyte accumulation	Human in vitro data: • Significantly reduced anti-proliferative T_{reg} function • Reduced expression of FOXP3 mRNA in T_{regs} Other study showed no suppression of IFNg production of immobilized anti-CD3 stimulated CD4+ T cells (not specifically T_{regs}) (Choi, 2021)
Biologic DMARDs (bDMARDs)		
CD28 inhibitor	Abatacept (CTLA4-Ig binds to CD80, CD86 and blocks co-stimulatory interactions with CD28)	• Mixed results on T_{reg} effect (enhanced vs inhibit) but could interfere with CTLA4-mediated suppression by T_{regs}. CTLA4 is expressed by T_{regs} and a primary means of suppression
CD20 inhibitor	Rituximab (Anti-CD20, depletes CD20+ cells primarily through ADCC, but also CDC and possibly ADP or direct signaling)	• No direct interaction
Targeted synthetic DMARDs (tsDMARDs)		
JAK inhibitor	Baricitinib (JAK1/2); filgotinib (JAK1); tofacitinib (JAK1/3+/-2); upadacitinib (JAK1); all inhibit cytokine receptor signaling by decreased STAT phosphorylation	Can directly inhibit cytokine signaling in T_{regs} (Palmroth, et al., 2021, van Gurp, et al., 2009, Sewgobind, et al., 2010, Tanaka, et al., 2018, Meyer, et al., 2021, Choi, et al., 2018, Yao, et al., 2021; Tarrant et al., 2020)

APPENDIX J. ABBREVIATIONS

Abbreviation	Definition
ACPA	anti-citrullinated protein antibodies
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADL	activities of daily living
AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice per day
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
C_{max}	maximum concentration
CRA	clinical research associate
CRO	contract research organization
CTCAE	common terminology criteria for adverse events
CV%	coefficient of variation
ECG	electrocardiogram
ECM	extracellular matrix
eCRF	electronic case report form
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV Ab	hepatitis C antibody
HED	human equivalent dose

Abbreviation	Definition
HIV Ab	human immunodeficiency virus antibody
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IM	intramuscular
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LFA-3	leukocyte function-associated antigen 3
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MRSD	maximum recommended starting dose
MTX	methotrexate MTX
NCI	National Cancer Institute
NET	neutrophil extracellular traps
NETosis	a regulated form of neutrophil cell death that contributes to the host defense against pathogens
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamic(s)
PI	Principal Investigator
PK	pharmacokinetic(s)
PO	by mouth
QD	daily
QTcF	QTc calculated using Fridericia's formula
QW	once per week

Abbreviation	Definition
RBC	red blood cell
SAD	single ascending dose(s)
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SoA	schedule of assessments
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
T1D	type 1 diabetes mellitus
TBD	to be determined
T_{CM}	central memory T cell
TEAE	treatment-emergent adverse event
T_{eff}	effector T cell
T_{EM}	effector memory T cell
THC	tetrahydrocannabinol
T_{max}	time to maximum concentration
$T_{naïve}$	naïve T cell
T_{reg}	regulatory T cell
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization