CLINICAL STUDY PROTOCOL

Protocol Number:	SBT777101-02
Study Title:	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Activity of Single Ascending Doses of SBT777101 in Subjects with Hidradenitis Suppurativa
Investigational Product:	SBT777101
IND Number:	30047
Sponsor Name:	Sonoma Biotherapeutics, Inc.
Legal Registered Address:	201 Haskins Way, Suite 203 South San Francisco, CA 94080
Sponsor's Medical Director	Mei-Lun Wang, MD Senior VP, Clinical Development Sonoma Biotherapeutics
Medical Monitor	Same as above
Version Number / Approval Date:	3.0 / May 01, 2025

Sponsor Signatory:

Signed by:
Mei-Lun Wan
D652F03F99D546C...

5/9/2025

Mei-Lun Wang, MD
Senior VP, Clinical Development

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 Hidradenitis Suppurativa

Protocol Number: SBT777101-02

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 Harmonisation 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 Hidradenitis Suppurativa	
Protocol No.:	SBT777101-02	
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	• Peripheral blood chimeric antigen receptor (CAR) transgene PK parameters including, but not limited to, T_{max}, C_{max}, AUC_{0-28}, and C_{last} • Presence of SBT777101 in lesional skin
	To assess and characterize SBT777101 mechanism of action and pharmacodynamic parameters	• Levels of inflammatory cells and biomarkers in peripheral blood and lesional skin, 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 lesional skin 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 clinical activity of SBT777101	• Hidradenitis Suppurativa Clinical Response (HiSCR) 50, 75 and 90 at Week 4 and Week 12 following SBT777101 administration • International Hidradenitis Suppurativa Severity Score System (IHS4) and IHS4-55

		at Week 4 and Week 12 following SBT777101 administration • Number of inflammatory nodules, abscesses, and tunnels at Week 4 and Week 12 following SBT777101 administration • Hidradenitis Suppurativa Quality of Life (HiSQOL) score and pain numerical rating score (NRS30) following SBT777101 administration
Study Design:	This is a multicenter Phase 1, open-label, dose-ranging study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of single ascending doses of SBT777101 administered intravenously (IV) in subjects with active hidradenitis suppurativa (HS) who have had an inadequate response to conventional systemic therapy.	
Route of Administration:	Intravenous (IV)	
Number of Subjects:	Up to 28 eligible adult subjects are expected to be treated in the study.	
Replacement of Subjects:	Subjects who receive <85% of the planned dose of study drug or withdraw for reasons other than toxicity or are lost to follow-up before completing the dose-limiting toxicity (DLT) evaluation period (up to study Day 28) will be replaced. The replacement of subjects is contingent on approval by the independent SMC.	
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 14 months.	
Study Population:	The study population will comprise adults aged ≥18 to ≤70 years, with body mass index (BMI) ≤50 kg/m^2. Subjects must have a diagnosis of clinically active moderate-to-severe HS Hurley Stage 2 or 3), with signs and symptoms consistent with HS for at least 6 months; Documented history of inadequate response (e.g., based on HiSCR50 or equivalent clinical assessment) to at least a 3-month course of at least 1 conventional systemic therapy such as antibiotics and 1 biologic drug (e.g., adalimumab, infliximab, secukinumab, and/or bimekizumab) or demonstrated intolerance or contraindication to conventional systemic or biologic treatments for their HS, or demonstrated intolerance to, or have a contraindication to, a conventional systemic therapy for treatment of HS; Total abscess or inflammatory nodule (AN) count of ≥5, affecting at least 2 distinct anatomic regions, with at least 1 accessible AN of adequate size for biopsy (diameter >1.5 cm); and total draining tunnel (dT) count of ≤20. 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.	
Safety Assessments:	Safety will be assessed by physical exam including vital signs, 12-lead ECGs, clinical laboratory tests (clinical chemistry, hematology, coagulation factors, lipid panel, urinalysis, infectious tests, and where relevant, pregnancy testing) and	

	adverse event reporting at the timepoints described in the schedule of assessments (SoA).
Pharmacokinetic/ Pharmacodynamic Assessments:	Peripheral blood will be analyzed for the levels of circulating SBT777101; skin 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 peripheral blood and skin. All assessments will be conducted at the timepoints described 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. Cytokine release syndrome and neurotoxicity AEs will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) criteria. 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, clinically significant 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 in subjects with active HS. Up to 18 subjects will be enrolled into dose escalation cohorts and up to a total of 10 additional subjects may be enrolled to further characterize preliminary efficacy, PK, and PD properties of SBT777101.

1. INTRODUCTION

1.1. Disease Background

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition characterized by recurrent painful lesions, including inflammatory nodules (N), abscesses (A), and purulent draining tunnels or fistulae (dT), in the axillae, buttocks, groin, and anogenital region (Sellheyer and Krahl, 2005; Alikhan et al., 2019a; Sabat et al., 2020). While the underlying mechanisms of disease are not completely understood, it is hypothesized that skin lesions are formed from occlusion and rupture of hair follicles, possibly due to the formation of epithelial tendrils in the follicle, which initiates a chronic cutaneous feed-forward inflammatory response mediated by dysregulated innate and adaptive immune pathways, ultimately leading to more follicular occlusion and subsequent inflammation (Fletcher et al., 2020; Moran et al., 2017; Sabat et al., 2020; Frew, 2020; Dunstan et al., 2020; Navrazhina et al., 2021). Recent data suggests that there is a significant role of immunopathogenesis in the disease manifested by dysfunction of Type 2 conventional dendritic cells, relatively reduced regulatory T cells, an influx of memory T cells and a plasma cell/plasmablast infiltrate in the skin of HS patients (Lowe et al., 2023; Gudjohnsson et al., 2021). In addition, data suggests that in HS there are tertiary lymphoid structures in which B and T cells are primed and actively undergo maturation which suggests that the disease has a significant underlying immune mechanism (Lowe et al., 2023). While HS is not an infectious disease, there may also be an infectious component because occluded hair follicles can act as a site for bacterial colonization, leading to additional immune activation (Wolk et al., 2020).

HS typically affects individuals starting in their late teens, with peak incidence in the 4th and 5th decades (Garg et al., 2017; Naik et al., 2019). Estimates of the global prevalence of HS vary, ranging from 0.05% to 4% (Shahi et al., 2014; Jfri et al., 2021; Garg et al., 2017). Increased prevalence is seen in patients who are female (Garg et al., 2017), of African descent (Garg et al., 2017), of lower socioeconomic status (Deckers et al., 2016), or who have comorbid obesity and a history of cigarette smoking (Kaleta et al., 2022; Fletcher et al., 2020; Kromann et al., 2014).

Treatment for HS includes both local and systemic interventions. Local management of disease includes topical or intralesional corticosteroids, topical antibiotics or retinoids, laser or light therapies, and in severe and extensive refractory cases, surgery (Gracia Cazana et al., 2020; Ravi et al., 2022; Alikhan et al., 2019b). Systemic treatments include oral medications, such as corticosteroids, antibiotics, retinoids, and agents with antiandrogenic effects, as well as biologics, including but not limited to subcutaneous adalimumab, intravenous (IV) infliximab, secukinumab, and bimekizumab (Orenstein et al., 2020; Alikhan et al., 2019a). Despite the therapeutic options available for patients with HS, existing therapies may be inadequate for long-term disease management, and a significant percentage of patients do not respond to the available medical options, achieving HiSCR50 at Week 12 of 42–59% (vs 26-28% on placebo) (Kimball et al., 2016), and thereby potentially requiring surgery. Thus, there is significant unmet medical need for additional treatment options that are safe, effective, and durable.

1.2. Citrullinated Proteins and HS

Citrulline is generated via a post-translational conversion of arginine to citrulline by peptidylarginine deiminase (PAD) enzymes. Inflammation leads to the citrullination of proteins, which accumulate at sites of cell activation, injury and turnover. Citrullination of proteins is a hallmark of inflammatory diseases, and can be present in many tissues, including skin, joints, lungs, and lymph nodes (Musaelyan et al., 2018). In patients with HS, citrullinated proteins (Cit-Prot) are present at increased levels in inflammatory skin lesions (Byrd et al., 2019; Carmona-Rivera et al., 2022), even though they are also part of the process of normal skin keratinization (Baka et al., 2012; György et al., 2006). These citrullinated peptide autoantigens can induce T-cell-mediated B cell activation and production of anti-citrullinated protein antibodies (ACPAs), which form antigen-antibody complexes that contribute to complement activation and stromal remodeling (Frew et al., 2020; Byrd et al., 2019). ACPAs can react with different Cit-Prot, including citrullinated fibrinogen, myeloperoxidase, nucleosome, histone H4, and dsDNA. Clustering of autoantibodies to specific Cit-Prot has been shown to be associated with specific Hurley stages of HS disease severity (Byrd et al., 2019).

There is also increased expression of PAD enzymes in activated neutrophils in inflamed skin lesions, which are essential for the formation of neutrophil extracellular traps (NETs) (Rohrbach et al., 2012; Byrd et al., 2019). 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 into the extracellular spaces both intracellular citrullinated antigens such as citrullinated vimentin (CV) and citrullinated fibrinogen and other immunostimulatory molecules such as damage-associated molecular patterns (DAMPs), which are implicated in driving HS pathogenesis (Byrd et al., 2019; Wolk et al., 2020; Carmona-Rivera et al., 2022).

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

Multiple studies have demonstrated that patients with HS have an increase in effector T cells (Teff) leading to an imbalance between effector T helper cells and regulatory T cells (Tregs). In particular, there are abnormally increased ratios of Th17 to Tregs and Th1 to Tregs. This suggests reduced ability of Tregs to suppress these highly active Teffs (Moran et al., 2017; Lowe et al., 2023; Melnik et al., 2018). This is further supported by single cell RNA data from HS lesions demonstrating a lack of IL-10 and TGFβ expression in HS Treg cells (Kim et al., 2023). It is unclear whether HS Treg dysfunction influences Treg-T17 plasticity as described in RA and IBD models (Komatsu et al., 2014; Omenetti and Pizarro, 2015) and whether chimeric antigen receptor (CAR) Tregs (SBT777101) can overcome the HS Treg defect.

Dermal fibrosis is a prominent feature of late-stage HS lesions and likely sequela of chronic inflammation. Such chronic inflammation and an overabundance of Teff cells shift the immune balance, resulting in existing Tregs being ineffective or outnumbered in controlling the inflammatory consequences of autoimmune and autoinflammatory diseases such as HS. Tregs have been shown to localize to hair follicles (Chow et al., 2013; Ali et al., 2017), and have recently been reported to play a role in suppressing dermal fibrosis (Kalekar et al., 2019). Thus, the ability of therapeutic Tregs to normalize these ratios has the potential to ameliorate immune dysregulation and restore immune tolerance in HS.

Citrullinated proteins (Cit-Prot) are present in the skin and serum of patients with HS, and thus represent antigens that can be targeted by a chimeric antigen receptor (CAR) engineered-Treg (Orvain et al., 2021). Cit-Prot are present as aggregates in the extracellular matrix, allowing Cit-Prot specific Tregs to recognize and be activated by these antigens that are present in the inflammatory milieu. When combined with the ability of Tregs to function through bystander suppression (ie, the localized suppression of inflammatory activities in the vicinity of Treg activation), this is hypothesized to lead to activation of the resident Treg and subsequently reduce localized areas of inflammation, such as the inflammatory skin lesions observed in HS. Enhanced antigen-specific Tregs targeting Cit-Prot to treat patients with demonstrated presence of antigen at the sites of inflammation thus presents a novel approach to the treatment of HS. Moreover, inclusion of the CAR in the Treg drug product, SBT777101, is designed to promote its activation directly at the sites of inflammation, specifically the skin lesions of HS patients where Cit-Prot are enriched. In principle, the SBT777101 CAR Tregs will increase the local activity of the treatment and lead to a specific and effective suppression of disease activity at the inflamed site.

1.4. Investigational Product: SBT777101

SBT777101 is a cryopreserved ex vivo expanded autologous $CD4^+CD127^{lo/-}CD25^+$ Treg cell preparation that has been transduced with a lentiviral vector encoding both a CAR that is specific for immunodominant post-translationally modified Cit-Prot and a truncated (nonfunctional) epidermal growth factor receptor (EGFRt) tag protein. The CAR contains an intracellular signalling domain, an intracellular costimulatory domain, a transmembrane domain, and an extracellular recognition domain (Cit-Prot-specific single-chain variable fragment [scFv]).

The starting material for SBT777101 is autologous blood cells collected by apheresis from the patient to be treated. $FOXP3^+$ expressing Treg cells are then enriched from blood cells in a central manufacturing facility through selection and cell sorting. Treg 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 approximately 14 days and then harvested, quality controlled, and cryopreserved.

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

1.5. Rationale for SBT777101 in HS

HS is a disease with a significant unmet clinical need. Currently, there are limited therapeutic options and the following biological agents are approved as of December, 2024: adalimumab, infliximab, secukinumab, and bimekizumab. Only 41.8% to 58.9% of patients receiving weekly adalimumab reached HS Clinical Response (HiSCR) 50 at 12 weeks after administration, compared to 26-28% on placebo treatment. HiSCR50 is at least a 50% reduction in the abscess and inflammatory nodule (AN) count, without any increases in counts of abscesses or draining tunnels (dTs) (Kimball et al., 2016). Existing therapies are inadequate for long-term disease management in most cases, and many patients experience a high disease burden, which has a negative impact on their quality of life (QOL), including physical and mental health (Ingram et al., 2022; Kouris et al., 2016; Marvel et al., 2019; Matusiak, 2020).

A recent global survey evaluating patients' unmet needs in HS found that many patients are dissatisfied with available medical or procedural treatments (Garg et al., 2020). Patients experience flares often (23.0% daily, 29.8% weekly, and 31.1% monthly), and 12.5% of patients had visited the hospital at least 5 times due to their HS, incurring significant financial burden. Greater than 60% of patients rated their recent HS-related pain as moderate or higher, while 4.5% described it as the worst possible. Extreme impact on life was reported by 43.3%, and 14.5% were classed as disabled, as measured by the HS Quality of Life instrument (HiSQOL), a validated patient-reported HS-specific QOL scale generated by the HS Core Outcomes Set International Collaboration (HISTORIC) Delphi study (Zouboulis et al., 2021). Current treatments have limited QOL improvement, low treatment effectiveness, and inadequate pain control (Willems et al., 2022).

In patients with HS, citrullinated proteins (Cit-Prot) are present at increased levels in inflammatory skin lesions (Carmona-Rivera et al., 2022). SBT777101 is an engineered CAR Treg cell therapy specific for Cit-Prot and 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, Tregs provide a unique mechanism to suppress multiple mechanisms of inflammation while restoring immune balance.

1.6. Nonclinical Data

SBT777101 is a regulatory CAR T cell therapy product that was designed to recognize antigens produced in the context of autoimmune disease(s) and exhibit anti-inflammatory activity. The nonclinical studies documented the regulatory T cell phenotype of SBT777101 via FOXP3 Treg-specific demethylated region (TSDR) analysis. When SBT777101 was manufactured using whole blood samples from patients with HS, cells were transduced efficiently and exhibited the same phenotype post transduction as cells from healthy donors. Studies also demonstrated that the SBT777101 CAR specifically recognizes Cit-Prot and does not exhibit off-target binding. SBT777101 exhibits regulatory/immunomodulatory functions in vitro. An immunohistochemistry-based tissue cross reactivity study showed that the SBT777101 CAR mostly stains cytoplasmic and nuclear elements in multiple cell types and that it is associated with membranous staining only in rare epithelial and mononuclear leukocytes in various tissues. Staining of extracellular material was also observed in various tissues, as further detailed below. The nonclinical assessment of SBT777101 has also demonstrated in vivo that SBT777101 does not cause adverse events towards normal tissues including under proinflammatory conditions, that SBT777101 is not activated in vivo within normal tissues, that SBT777101 exhibits a stable Treg phenotype under pro-inflammatory conditions, and that SBT777101 exhibits an immunoregulatory activity in vivo that is similar to the activity of untransduced polyclonal Tregs. An evaluation of the risk of lentiviral vector mediated insertional mutagenesis showed a multi-site integration profile with no dominant integration site which is consistent with numerous published studies of third generation lentiviral vectors, similar to that used in the SBT777101 vector, and no abnormal impact of the transduction of Tregs on cell growth activity.

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 plate-

bound Cit-Prot for 72 hours, 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 proliferation in response to Cit-Prot.

SBT777101 exhibits a Treg phenotype that is similar to natural Tregs (ie, Tregs freshly isolated from peripheral blood based on $CD4^{+}CD127^{lo/-}CD25^{+}$ phenotype) based on FOXP3 expression, cytokine production profile, and FOXP3 Treg-specific demethylated region (TSDR) status.

It was demonstrated that the inherent function of Tregs isolated from peripheral blood including that from HS patients is maintained in Tregs expressing the SBT777101 CAR. Autologous purified T cells were labeled with the CellTrace™ Violet (CTV) tracer dye while SBT777101 Tregs were labeled with the CFSE tracer dye. Both cell populations were incubated at various ratios and CTV-labeled cells were evaluated for proliferation after incubation with anti-CD3/anti-CD28 coated beads used as stimulus. In the presence of increasing amounts of Treg cells, a reduction in proliferation was observed. SBT777101 inhibited T cell proliferation in a similar manner to untransduced Tregs, demonstrating that the expression of the CAR did not impact inherent Treg function of transduced cells. The same inhibitory effects of SBT777101 were observed following activation by CV.

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*," a formal biodistribution study with SBT777101 was 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 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 close 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.

A theoretical concern associated with engineering T cells is the disruption of normal cell growth control mechanisms. The ability of SBT777101 CAR Treg cells to grow in the absence of IL-2 was therefore evaluated in vitro. The survival of SBT777101 was evaluated in the absence and

presence of IL-2 in vitro over 28 days. Cell numbers and percent survival decreased over time with and without IL-2 and were consistently lower in the absence of IL-2. These data indicate that SBT777101 does not exhibit abnormal growth after being thawed in the absence of CAR stimulation, with or without addition of IL-2.

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 CAR is not associated with off-target binding activity.

In vitro studies showed that SBT777101 does not exhibit cytotoxicity towards any of a variety of human cell types from major organs (eg, brain, heart, liver, lung, kidney).

In vivo studies were conducted in triple immunodeficient NOD-Prkdc^{em26CD52}Il2rgem^{26Cd22}/NjuCrl (NCG) mice whose unique phenotype decreases the immune-mediated rejection of human transplanted cells. Intravenous administration of SBT777101 to NCG mice at a dose of 5.0 x 10^6 cells per animal was well tolerated with no adverse effects observed based on clinical observations, body weight, gross necropsy, and light microscopic examination of tissues.

Please see the Investigator's Brochure for additional information.

1.7. Clinical Development

This is a Phase 1 study for SBT777101 in moderate-to-severe HS with inadequate response to conventional systemic therapy.

1.8. Benefit/Risk Assessment

HS represents a significant unmet clinical need, as affected patients have limited therapeutic options, most of which provide symptom relief without long-term disease control. Adalimumab, infliximab, secukinumab, and bimekizumab are approved by the FDA for use in patients with moderate to severe HS. However, not all patients respond initially or have a long-term duration in response to these agents.

Given therapeutic challenges and limitations, HS remains difficult to treat. Individuals with moderate-to-severe disease may therefore experience a significant negative impact on health-related QOL, including but not limited to pain, pruritus, malodor, low self-esteem, sleep problems, sexual dysfunction, and poor mental health. New therapeutic options with unique mechanisms of action are needed for this challenging patient population.

SBT777101, a novel CAR Treg cell therapy, is currently being developed for patients with refractory rheumatoid arthritis. This approach may represent a powerful new tool to treat autoimmune diseases. This builds on evidence that polyclonal Tregs and Tregs selected for allo- and autoantigen specificity used to treat patients with autoimmune conditions were well tolerated

at doses up to and exceeding those proposed in this study (Dall'Era et al., 2019). While SBT777101 has not been tested in humans and so the actual risks are unknown, the safety profile of SBT777101 is expected to reflect that seen in the polyclonal Treg studies (see Table 2 in Section 3.2.1), rather than that from the CAR Teff studies.

Overall, the nonclinical data (see Section 1.6) for SBT777101 support this Phase 1 study in subjects with HS. The potential safety issues associated with administration of SBT777101 will be carefully monitored. If adverse events do occur, measures will be taken to avoid or minimize serious toxicities as described in Section 8.1.

Given the significant unmet clinical needs and burden of disease in patients with HS, the benefit/risk assessment weighs strongly in favor of developing SBT777101 for patients with this disease.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, tolerability, PK, PD, and preliminary clinical activity of a single IV infusion of SBT777101 in adult subjects with clinically active moderate-to-severe HS, global Hurley Stage 2 or 3. 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	• 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 lesional skin
To assess and characterize SBT777101 mechanism of action and pharmacodynamic parameters	• Levels of inflammatory cells and biomarkers in peripheral blood and lesional skin, 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 lesional skin 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 clinical activity of SBT777101	• Hidradenitis suppurativa clinical response (HiSCR) 50, 75 and 90 at Week 4 and Week 12 following SBT777101 administration • International Hidradenitis Suppurativa Severity Score System (IHS4) and IHS4-55 at Week 4 and Week 12 following SBT777101 administration • Number of inflammatory nodules, abscesses, and tunnels at Week 4 and Week 12 following SBT777101 administration • Hidradenitis Suppurativa Quality of Life (HiSQOL) score and pain numerical rating score (NRS30) following SBT777101 administration

3. STUDY DESIGN

3.1. Description of the Study

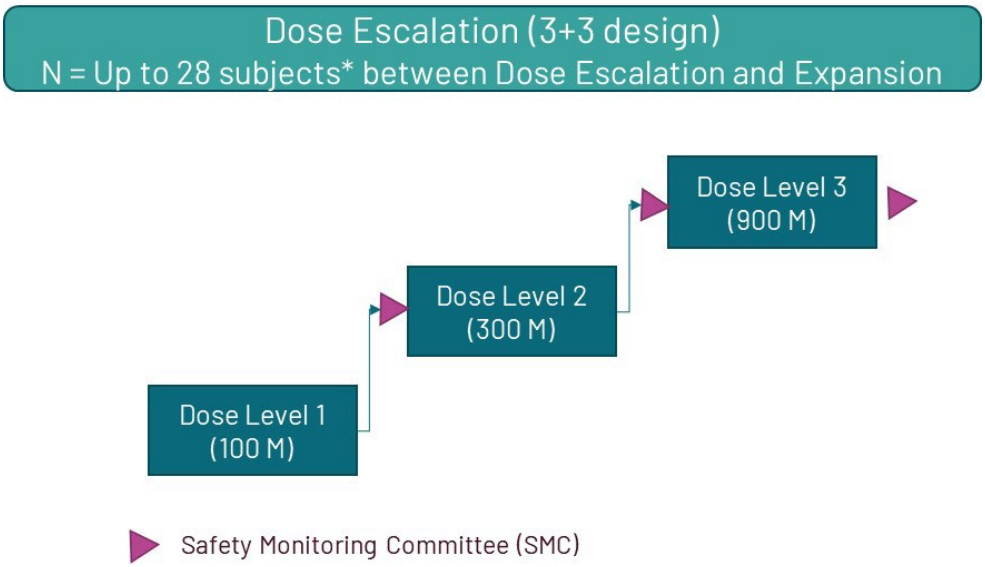
3.1.1. Overall Study Design

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 subjects with active HS.

Following screening, eligible subjects will undergo apheresis, and SBT777101 drug product will be manufactured for each subject. Each subject will undergo a skin biopsy prior to dosing (pretreatment = baseline biopsy) before receiving a single dose of SBT777101 intravenously (IV) on study Day 1. There is an option to add a skin biopsy during the screening period. Subject safety will be monitored acutely post dosing (ie, as an inpatient for the first 24 hours) and then periodically throughout the study for 1 year. After 1 year and due to the use of lentivirus vector in SBT777101, all subjects will be required to participate in a long-term safety follow-up (observational) study for up to 15 years that will be conducted under a separate protocol in accordance with the 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



M = millions of CAR^+ T cells

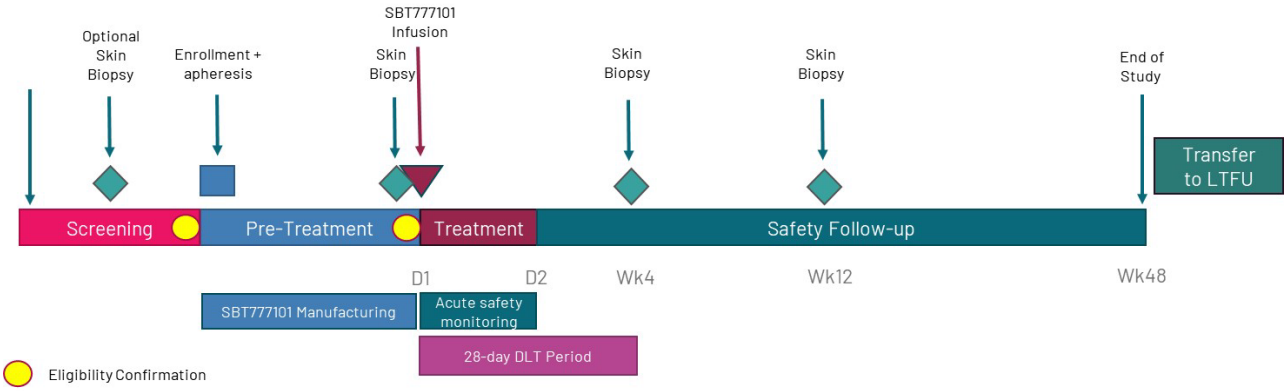
3.1.1.1. Dose Escalation Cohorts

The study will be open-label and employ a "3+3 Dose Escalation" design. Initially, 3 eligible subjects will be evaluated in each cohort. Treatment of the first 3 subjects of each cohort will be staggered by at least 28 days in order to fully assess the safety of the product in the acute setting. Thereafter, the treatment of subjects can be staggered by 14 days between subjects. All subjects will be monitored for dose-limiting toxicities (DLTs) for at least 28 days following SBT777101 administration. See Section 3.3 for definitions of DLTs and details of dose escalation rules. Dose escalation will be overseen by the Safety Monitoring Committee (SMC; see Section 3.4).

3.1.2. Subject Flow

The overall subject flow is displayed in Figure 2. Details of study assessments required during each study period will be 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

The study will consist of Screening, Pretreatment, 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 Dose Levels During Dose Escalation

Cohort/Dose Level	Total CAR^+ T cells
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 discontinue the study or to enroll subjects into a cohort at a lower dose. Dose selection and initiation of this cohort would be overseen by the SMC.

Although 3 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 x 10^6 transduced cells. Determination of dose levels for additional cohorts will be overseen by the SMC in collaboration with the Sponsor.

In the case of inability to manufacture the planned dose of SBT777101 for any given subject, wherein the number of CAR-positive cells is insufficient for the assigned dose level, the subject may receive treatment at a lower dose level that was previously determined to be safe by the SMC (eg, a subject intended for dose level 2 may receive treatment at dose level 1).

Dose escalation rules are described in Section 3.3.2. In the event that a dose limiting toxicity (DLT, see Section 3.3.1) is observed in one of the first 3 subjects in any dose cohort, the cohort size will be expanded to a total of 6 subjects.

The Sponsor may enroll additional subjects (up to a total of 10) at any dose levels determined safe by the SMC, to gain additional characterization data.

3.2. Rationale for Study Design

3.2.1. Rationale for Dose Selection and Escalation

3.2.1.1. 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) or minimal observed biologic effect level (MABEL) approach from nonclinical studies to determine the starting dose. Therefore, the doses of similar cellular therapies administered to subjects in multiple other clinical studies and case reports were used to estimate a starting dose level of Treg cells that would be expected to be safe (Table 2).

The planned starting dose for the initial cohort in this Phase 1 study is 100 x10^6 CAR^+ T cells administered by IV infusion. This low dose level is within the range of dose levels administered to subjects in multiple clinical studies and case reports of similar Treg therapies, outlined in Table 2. The majority of these reports describe polyclonal autologous Treg cellular therapy in multiple disease indications including type 1 diabetes, kidney transplantation, and lupus (Mathew et al., 2018; Dall'Era et al., 2019; Chandran et al., 2017; Bluestone et al., 2015). In addition, the proposed starting dose is also within the range of doses for autologous cell therapies enriched for antigen-specific Tregs in the setting of Crohn's Disease and post-liver transplantation (Desreumaux et al., 2012; Todo et al., 2016), as well as for non-autologous Treg therapy in the setting of bone marrow or umbilical cord blood cell transplantation to treat graft-vs-host disease (Trzonkowski et al., 2009; Brunstein et al., 2011). Importantly, the cell therapies administered in these clinical studies were considered to be well tolerated at all dose levels tested. Furthermore, reports of treatment-related adverse events were infrequent and did not demonstrate dose dependence.

Table 2: Cellular Therapy Studies Used to Estimate SBT777101 Starting Dose

Infusion Product Description	Indication	Doses Administered
Autologous polyclonal Tregs Mathew et al., 2018	Post-kidney transplant recipients	500, 1000, 5000 x 10^6 Tregs (total) @ ~ 80% FOXP3+
Autologous polyclonal Tregs Dall'Era et al., 2019	Systemic Lupus Erythematosus (single subject)	100 x 10^6 Treg (total)
Autologous polyclonal Tregs Chandran et al., 2017	Post-kidney transplant recipients	319, 321, 363 x 10^6 Tregs
Autologous polyclonal Tregs Bluestone et al., 2015	Type 1 Diabetes	5 – 2900 x 10^6 Treg Treg purity: 92% FOXP3+ Treg (average). Range = 76-97%
Autologous cell therapy, enriched for antigen-specific Tregs Desreumaux et al., 2012	Crohn's Disease	1-1000 x 10^6 Tregs
Autologous polyclonal natural Tregs Roemhild et al., 2020	Post-kidney transplant recipients	0.5, 1.0, or 2.6-3.0 x 10^6 cells/kg (>90% CD4+ CD25+ FOXP3+). Note: weight-based dosing
Autologous polyclonal Tregs Marek-Trzonkowska et al., 2014	Type 1 Diabetes (Pediatric)	10, 20 x 10^6 Tregs/kg in a single dose; 30 x 10^6 Tregs/kg in separate infusions (6-to 9-month interval between infusions). Note: weight-based dosing
Autologous cell therapy, enriched for allo-antigen-reactive Tregs Todo et al., 2016	Post-liver transplant recipients	Mean number of infused CD4+ CD25+ FOXP3+ cells: 3.39 x 10^6/kg. Dose range: 0.24 x 10^6/kg to 6.37 x 10^6/kg Note: weight-based dosing
HLA-matched non-autologous Treg cell therapy Trzonkowski et al., 2009	Post-bone marrow transplant GvHD (single acute GvHD subject)	60 x 10^6 Tregs per infusion (3 infusions total, ~ 10 days apart, total dose 180 x 10^6 Tregs)
Partially HLA-matched umbilical cord blood enriched for Tregs Brunstein et al., 2011	Post-double umbilical cord blood transplant recipients with hematologic malignancies	Target dose: 3 x 10^6 Tregs/kg Dose range: 0.1 x 10^6 Tregs/kg to 3 x 10^6 Tregs/kg Note: 6 subjects received two doses of 3 x 10^6 Tregs/kg for a total of 6 x 10^6 Tregs/kg Note: weight-based dosing

Unlike prior Treg therapies, SBT777101 includes addition of a CAR and thus confers antigen specificity. While this introduces a modification to the cell, addition of the CAR to the Tregs is not expected to negatively alter the benefit-risk ratio compared to untransduced Treg cells. This is supported by data from studies with allo-antigen specific Tregs, where the potency of the allo-antigen Tregs is increased over that for polyclonal Tregs (Jiang et al., 2006; Golshayan et al., 2007). The increase in specificity of the Treg via the T cell receptor did not lead to a change in safety profile compared to polyclonal Treg therapies in clinical studies and the doses administered were within range of the proposed starting dose and were well tolerated.

3.2.1.2. Highest Planned Dose

The highest planned dose is 900 x 10^6 CAR^+ T cells administered by IV infusion. It is hypothesized that a small fraction (approximately 2%) of Tregs will be found in the bloodstream, with most cells being sequestered in the lymph nodes, bone marrow, and epithelial tissue. 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 inflammatory skin lesion.

3.2.1.3. Dose Escalation Rationale

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 Treg studies (Bluestone et al., 2015; Brunstein et al., 2011; Mathew et al., 2018; Roemhild et al., 2020).

3.2.2. 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/or cellular immunogenicity and their potential impact on kinetics and/or pharmacodynamic (PD) activity.

3.2.3. 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 Treg cell therapy administration. Samples will be collected out to 1 year to permit evaluation of the longer-term effects of SBT777101 on PD biomarkers.

3.2.4. Rationale for Skin Biopsy

Skin biopsy samples will be collected before and after treatment to compare pre- and post-treatment levels of biomarkers. The presence of SBT777101 cells within the skin will also be evaluated at the post-dose time points to determine the extent of CAR Treg presence in the target tissue.

3.3. Dose Escalation

Determination of dosing within a cohort will be overseen by the SMC. Dosing may be temporarily withheld, modified (expansion of cohort size from 3 to 6 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.

3.3.1. Dose-Limiting Toxicity Definition

A dose-limiting toxicity (DLT) is defined as any of the following occurring within 28 days after infusion of SBT777101:

1. Death
2. Grade 4 cytokine release syndrome (CRS, see Appendix F) of any duration
3. Grade 3 CRS that does not improve to Grade ≤2 within 72 hours following adequate therapy
4. Grade 1-2 CRS that does not resolve within 7 days
5. Grade ≥3 immune effector cell-associated neurotoxicity syndrome (ICANS, see Appendix G) of any duration
6. Any Grade 1-2 ICANS event that does not completely resolve after 14 days
7. Any Grade ≥3 toxicity involving vital organs (eg, cardiac, pulmonary)
8. Any Grade 3 toxicity of a non-vital organ that does not resolve to Grade ≤2 within 14 days
9. Any Grade 4 hematological toxicity that does not improve to Grade ≤2
10. Any Grade ≥3 infections
11. Any instance of HLH/MAS
12. Any Grade 3 infusion-related reaction that does not resolve to ≤2 within 24 hours
13. Any Grade 4 infusion-related reaction
14. Any anaphylaxis event that meets Sampson's criteria (Sampson et al., 2006)

3.3.2. Dose Escalation Rules

If a DLT is not seen in the first 3 subjects, then escalation to the next dose level may occur. Dose escalation will be temporarily halted if any of the following occur:

- If a DLT is seen in 1 of the first 3 subjects in any dose cohort, the cohort size will be expanded to a total of 6 subjects.
- If more than 1 DLT occurs in ≤6 subjects in a dose cohort, any of the study stopping rules are met (see Section 3.5), 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 or lower dose level may be evaluated. Otherwise, dose escalation may occur.

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).

The SMC review of safety data will serve as the basis on which the Sponsor will determine whether dosing can be resumed. See Section 3.4; further details may be found in the SMC Charter.

3.4. Safety Monitoring Committee

An independent 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 independent SMC will consist of a facilitator, at least 1 independent physician with expertise in HS, and 1 physician with CAR T cell therapy expertise. The Principal Investigator and Medical Monitor will operate solely as external experts, providing pertinent data as requested by the SMC. The SMC will convene on a regular basis during the study to review available clinical study data, to make dose escalation decisions, or on an ad hoc basis if a DLT occurs.

The SMC may meet at any time during the study to review available clinical study data. Based on ongoing assessment of benefit and risk, the SMC may recommend dose escalation, stop dose escalation before the maximum proposed dose is reached, dose reduction, any possible additional doses, or stop dosing completely. Based on the SMC's recommendation following review of all available safety data, the SMC will provide the Sponsor with a recommendation. The Sponsor will make final dose escalation and dose level decisions.

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:

- Death from any cause
- Diagnosis of a malignancy of T cell origin in any subject who has received SBT777101, until insertional mutagenesis is ruled out
- Any of the following events regardless of duration and occurring at any study timepoint:
    - Grade ≥3 CRS
    - Any Grade ≥3 toxicity involving vital organs (eg, cardiac, pulmonary)
    - Grade ≥3 ICANS
    - Any Grade ≥3 non-hematologic adverse events
    - Grade ≥3 infection (other than skin infection)
    - Grade >3 skin infection
    - Any Grade 4 hematologic toxicity
    - Any anaphylaxis event that meets Sampson's criteria (Sampson et al., 2006)
    - Any instance of hemophagocytic lymphohistiocytosis (HLH) / macrophage activating syndrome (MAS)
- A decision to stop dose escalation or study activities has been recommended by the SMC in 2 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 recommend that dose escalation may be delayed, paused, or modified as deemed appropriate.

3.6. End of Study Definition

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

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 who receive SBT777101 will be required to participate in a long-term follow-up study of up to 15 years 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 years old at the time of signing the informed consent
2. Body mass index (BMI) ≤50 kg/m^2, inclusive

HS Characteristics

3. Diagnosis of clinically active moderate-to-severe HS (Hurley Stage 2 or 3), with patient-reported signs and symptoms consistent with HS for at least 6 months prior to the screening visit
4. Total abscess or inflammatory nodule (AN) count of ≥5, affecting at least 2 distinct anatomic regions, with at least 1 accessible AN of adequate size for biopsy (diameter >1.5 cm)
5. Total draining tunnel (dT) count of ≤20
6. Documented history of inadequate response (e.g., based on HiSCR50 or equivalent clinical assessment) to at least a 3-month course of at least 1 conventional systemic therapy such as antibiotics and 1 biologic drug (e.g., adalimumab, infliximab, secukinumab, and/or bimekizumab) or demonstrated intolerance or contraindication to conventional systemic or biologic treatments for their HS, or demonstrated intolerance to, or have a contraindication to, a conventional systemic therapy for treatment of their HS
7. Doses of medications for HS must be stable for at least 5 weeks prior to study drug administration (refer to Section 5 for details)

Contraceptive/Barrier Requirements

8. Persons of childbearing potential must agree to use 2 methods of contraception for at least 1 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)

9. 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
10. Individuals who are sexually active with women of childbearing potential must agree to use one method of contraception for 1 year post SBT777101 administration (refer to Appendix D)
11. Subjects must refrain from donating sperm for 1 year post SBT777101 administration

Other Inclusions

12. Subjects receiving systemic estrogen replacement therapy must agree to discontinue use at least 1 week or 5 half-lives prior to study treatment
13. Ability to comply with all the requirements of the study, in the Principal Investigator's opinion
14. Adequate vascular access, in the opinion of the Principal Investigator, for apheresis procedure and SBT777101 administration
15. Willing to undergo repeat skin biopsies 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 within 12 weeks prior to screening or planned within 12 months after dosing.

Medical Conditions

2. History of or current inflammatory or other autoimmune disease
3. Complex presentations of HS, including but not limited to PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne), PASH (pyoderma gangrenosum, acne, and suppurative hidradenitis), PAPASH (pyogenic arthritis, acne, pyoderma gangrenosum, and suppurative hidradenitis), and PG (pyoderma gangrenosum)
4. Skin disease other than HS that may confound clinical assessments or increase subject risk in the study
5. Current or previous (within the past 2 years) evidence of serious uncontrolled (in the opinion of the investigator) concomitant cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disease
6. Active current infection or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections not associated with HS, including but not limited to tuberculosis and atypical

mycobacterial disease, hepatitis B and C, and herpes zoster (>2 episodes within the previous 12 months)

7. Uncontrolled diabetes (HbA1C > 9%)
8. Any major episode of infection requiring hospitalization or treatment with IV antimicrobials within 5 weeks prior to study drug administration. The timing of study drug treatment and the pretreatment biopsy may be adjusted if the subject has received one of these drugs after apheresis
9. Active tuberculosis requiring treatment within 3 years prior to screening
10. Latent tuberculosis diagnosed during screening that has not completed appropriate treatment
11. History of Crohn's disease
12. Primary or secondary immunodeficiency (history of or currently active), including a history of HIV positivity
13. Any known significantly increased risk of hypercoagulability or personal or family history of thromboembolic disease
14. Females who are pregnant or breastfeeding or planning to become pregnant within 12 months from start on study
15. History of malignancy within 5 years from the time of screening (including squamous cell carcinoma of the skin or cervix or carcinoma-in situ)
16. History of epilepsy or other seizure disorder, stroke, dementia or other central nervous system disorder
17. Known history of drug or alcohol abuse within 1 year of screening
18. 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
19. Any out-of-range electrocardiogram (ECG) parameter(s) or abnormal finding(s) considered clinically significant by the Principal Investigator including if the QTc calculated using Fridericia's formula (QTcF) is >480 ms

Excluded previous or concomitant therapy

20. Prior treatment with cell or gene therapy
21. Treatment within 4 weeks prior to apheresis with corticosteroids at a dose of >10 mg of prednisone equivalent QD. Of note, low dose daily inhaled corticosteroids for asthma or COPD is permitted (maximum of fluticasone propionate 250 mcg (or equivalent) . The timing of study drug treatment and the pretreatment biopsy may be adjusted if the subject has this therapy after apheresis.
22. Treatment with a JAK inhibitor within 7 days prior to apheresis
23. Treatment with mycophenolate mofetil (MMF) within 4 weeks prior to apheresis
24. Treatment with cyclosporine or tacrolimus within 4 weeks prior to apheresis

25. Treatment with an investigational agent within 4 weeks or 5 half-lives, whichever is longer, prior to date of apheresis
26. Treatment with a biologic therapy (other than anti-TNF or anti-IL-17 agents) within 5 weeks prior to study drug administration. The timing of study drug treatment and the pretreatment biopsy may be adjusted if the subject has received one of these drugs after apheresis.
27. Treatment with intralesional corticosteroids within 5 weeks prior to study drug administration or plans to receive intralesional corticosteroids in any lesion during the study period. The timing of study drug treatment and the pretreatment biopsy may be adjusted if the subject has this therapy after apheresis.
28. Laser treatment within 5 weeks prior to study drug administration. The timing of study drug treatment and the pretreatment biopsy may be adjusted if the subject has laser treatment after apheresis.
29. Incision and drainage procedure within 5 weeks prior to study drug administration. The timing of study drug treatment and the pretreatment biopsy may be adjusted if the subject has this procedure after apheresis.

Prior/Concurrent Clinical Study Involvement

30. Is currently participating in another study of an investigational or marketed drug or medical device

Allergies/Anaphylaxis

31. Any confirmed clinically significant drug allergy and/or known hypersensitivity to protein therapeutics or formulation components or a related drug
32. Known allergy to heparin, fresh frozen plasma (FFP) or replacement colloid/albumin

Specific Laboratory Assessments

33. 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 x 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
34. Positive HIV, hepatitis BsAg or hepatitis C antibody at screening
    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

35. 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 2 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 (eg, 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 a reason to screen fail if it is deemed clinically significant, in the opinion of the Principal 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 HS must be reported from the time of diagnosis through to the end of the study/early termination visit, where available. This includes biologics, corticosteroids (both oral and intralesional), medications with antiandrogenic effects, antibiotics, retinoids, light/laser therapy, and surgery. Pain and anti-pruritic medications, and wound dressings used to manage HS or post-biopsy symptom relief are considered general medications and must be recorded.

Please contact the Medical Monitor for guidance on management of concomitant medications, including any contemplated changes in medications for HS as well as rescue therapy.

5.1. General Medications

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

- Short courses of pain relief medications (eg, opioids and acetaminophen) are permitted
- NSAIDs (eg, ibuprofen and naproxen) are permitted but should not be used in the 7 days prior to each skin biopsy collection
- Systemic estrogen replacement therapy is prohibited from 1 week (or 5-half-lives) prior to study treatment
- Receipt of new medications required for skin biopsy, apheresis, and infusion is permitted

5.1.1. Vaccines

- Subjects who have received a vaccine should have completed their vaccination schedule at least 2 weeks prior to study drug administration
- Live vaccines are not permitted during the study

- COVID-19 vaccination, including at least one booster, and non-live influenza vaccination are recommended

5.2. Therapeutic Modalities for HS

Certain concomitant medications and other therapeutic modalities for the treatment of HS are permitted or prohibited. It is important that doses of medications taken for the treatment of HS remain stable throughout the study where possible. To maintain stability of subjects' disease, replacement of prohibited HS medications with treatments that are permitted on study is strongly encouraged. If the investigator chooses to institute a new HS treatment regimen after discontinuing prohibited medications, the regimen must be stable for at least 5 weeks prior to study drug administration per inclusion criterion 7. The medical monitor should be consulted for any questions regarding concomitant treatments.

A list of permitted and prohibited HS medications and discontinuation times, if applicable, is presented in Table 3.

Table 3: Prohibited and Allowed HS Treatments

Prohibited Treatments	**Discontinuation Time**
JAK inhibitors	7 days prior to apheresis
Systemic corticosteroids (IV or oral) regardless of route of administration (>10 mg oral prednisone equivalent QD)	4 weeks prior to apheresis *Note: Following apheresis corticosteroids may be resumed, but corticosteroid (if at a dose of >10 mg prednisone equivalent QD) must be either discontinued 5 weeks prior to dosing or reduced to ≤10 mg QD oral prednisone equivalent for 5 weeks prior to study drug administration.*
Mycophenolate mofetil (MMF)	4 weeks prior to apheresis
Cyclosporine; tacrolimus	4 weeks prior to apheresis
Investigational agents	4 weeks or 5 half-lives prior to apheresis (whichever is longer)
Biologics (other than anti-TNF and anti-IL-17 agents)	5 weeks prior to study drug administration
Intralesional corticosteroids	5 weeks prior to study drug administration
IV antibiotics	5 weeks prior to study drug administration
Laser treatment	5 weeks prior to study drug administration [a]
Incision and drainage	5 weeks prior to study drug administration [b]
Permitted Treatments	**Treatment Rules**
Anti-TNF agents	Stable dose for 5 weeks prior to study drug administration
Anti-IL-17 agents	Stable dose for 5 weeks prior to study drug administration
Oral corticosteroids	Stable dose ≤10 mg QD prednisone equivalent for 5 weeks prior to study drug administration [c]
Oral antibiotics	Stable dose for 5 weeks prior to study drug administration [c]
Topical ointments, including topical steroids	Stable regimen for 5 weeks prior to study drug administration [c]
Other treatments (eg, retinoids, antipruritics, antiandrogenics, methotrexate, apremilast) and long-acting pain medications	Stable dose for 5 weeks prior to study drug administration [c]

a. May not biopsy lesion that received laser treatment in last 12 months
b. May not biopsy a lesion that was surgically treated within the last 2 years
c. Treatment of exacerbations with oral corticosteroids >10 mg prednisone equivalent or intralesional corticosteroids is permitted up to 5 weeks prior to study drug dosing; oral antibiotics are permitted up to 5 weeks prior to study drug dosing. Dosing may be delayed to accommodate the timing of the treatment of exacerbations.

5.2.1. Rescue Therapy

Treatment of severe acute HS exacerbations during the study is at the discretion of the Principal Investigator, following discussion with the Sponsor medical monitor, and will depend on clinical severity, duration, subject's overall clinical status, and response to NSAIDs and general pain medications, etc. Rescue therapy should be considered if a subject experiences a sustained

increase between consecutive study visits in the number and severity of HS lesions. Guidelines for rescue therapy are presented in Table 4. Note, if lesions require either intralesional injections or surgical treatment, these lesions should not be biopsied after the treatment has been administered. Whenever possible, rescue therapy should be initiated after all assessments have been completed at a study visit. If it is deemed appropriate by the Investigator, the subject's inflamed lesion(s) will be cultured and analyzed. An unscheduled study visit may be done if rescue therapy is needed between scheduled study visits.

Subjects may receive up to 2 courses of rescue therapy as outlined in Table 4. Subjects who receive greater than 2 courses of rescue therapy will be considered treatment failures. In addition, subjects who require increasing the dose of an existing biologic or begin treatment with a new biologic will be considered treatment failures. Subjects who are considered treatment failures will remain on study for all assessments through Week 48. For each HS exacerbation, please record, at minimum, the date of the exacerbation, the medication/intervention used to treat the exacerbation, and the dates of treatment for the exacerbation in the eCRF.

Table 4: Rescue Therapy Guidelines

Medication/Intervention	Guidance
Intralesional corticosteroids	Limit the dose to <40 µg/kg/month if possible
Abscess drainage	Incision and drainage OR punch drainage
Systemic corticosteroids	Doses >10 mg QD prednisone equivalent for up to 14 days
Oral antibiotics	Up to 14 day course

6. STUDY DRUG

6.1. Description of Study Drug

SBT777101 is a suspension of autologous human regulatory T cells (Tregs) expressing a CAR transmembrane protein, which targets Cit-Prot including citrullinated vimentin (CV) in the extracellular space of subjects with inflammatory diseases, and a truncated EGFR protein.

Peripheral blood cells are removed from an HS subject 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 the cells are subsequently expanded and restimulated. The cells are then harvested, washed, and formulated in a cryopreservation solution. 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 subject.

Written 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 ≤ −135°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 (eg, 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.

Once the product is removed from LN2 shipping container, a visual inspection will 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. On the Certificate of Release for Infusion, 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. 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.

Please see Section 8.1 for details and guidance on the medical 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 only be given once and 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 that is 15% 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 Principal 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 (ie, receiving a dose that is 15% greater than or less than the intended dose) 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 dosed with SBT777101. After a subject has provided informed consent, they will be provided with a unique screening number.

The Principal Investigator, study site personnel, the laboratories assigned to analyze PK, PD, and immunogenicity 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 Principal 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 (eg, 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. An option to perform a skin biopsy is included during the screening visit (see Section 7.2.5).

Select data obtained during screening will be evaluated by the Sponsor to confirm study eligibility. Once full eligibility has been confirmed, the subject is enrolled into the study and enters the pretreatment phase. The date that full eligibility has been confirmed will be recorded as the enrollment date.

7.1.2. Pretreatment

The pretreatment phase of the study begins upon enrollment and entails the apheresis procedure, SBT777101 manufacturing, pre-infusion eligibility checks, and a pretreatment skin biopsy. Subjects are required to have discontinued from some HS medications prior to the pretreatment biopsy; refer to Table 3 for washout requirements.

The pretreatment phase is expected to last approximately 6 weeks (but up to the date of drug product expiry is permitted).

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. For the manufacturing of SBT777101, a standard apheresis procedure is to be performed. The procedure is, more specifically, leukapheresis without the use of any stem cell mobilization agents.

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 additional collection procedure(s) with Sponsor approval. Subjects must repeat the pre-apheresis assessments (e.g. washout periods and local apheresis requirements) to confirm that they are eligible to undergo additional apheresis procedure(s). These subjects remain enrolled in the study and will be classified as enrolled but not dosed until study drug infusion is complete or withdrawal of consent.

7.1.2.2. SBT777101 Manufacturing

SBT777101 study drug product will be manufactured in accordance with Good Manufacturing Practice by the Sponsor defined process.

7.1.2.3. Pre-Infusion Eligibility Confirmation

Subject eligibility must be reconfirmed between study Days -10 and -4 to confirm that it is safe and appropriate for the subject to receive the study drug. If any of the eligibility criteria (with the exception of inclusion criteria 4 and 5) 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 and dosed until study drug product expiration and they will remain enrolled in the study during this time. A subject not dosed by the time of study drug product expiration, 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 meets the release criteria.

7.1.2.4. Pretreatment (Baseline) Biopsy

A baseline skin biopsy must be performed after the pre-infusion eligibility confirmation and prior to dosing (see Section 7.2.5). The biopsy can be performed up to 7 days prior to dosing.

7.1.3. Treatment Phase

7.1.3.1. SBT777101 Administration

Once subjects are deemed eligible, they 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 for post administration of study drug for approximately 24 hours. See Section 8.1 for details of safety monitoring requirements.

7.1.3.2. Safety Follow-Up

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

7.1.3.3. Unscheduled Evaluations

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

Assessments (which may include but are not limited to safety labs, ECG, ICE assessment, PK, ADA, cellular immunogenicity, RCL, biomarker sample collection, and skin biopsy) should be performed as clinically indicated.

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

7.1.3.4. End of Study Visit

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

If a subject withdraws from the study prior to Week 48, an early termination (ET) visit (see Section 7.4 and Appendix B) will be scheduled as soon as possible as the EOS visit for that

subject, and the assessments listed for the EOS visit will be performed. The reason for early withdrawal will be captured in the eCRF.

Subjects will be required to enroll in a long-term follow-up study of up to 15 years under a separate protocol for further safety evaluation beyond the EOS visit.

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 7.2.7.4.

7.2.1. Demographics

Data collected will include but is not limited to age (date of birth), sex, 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, , use of tobacco, alcohol and drugs of abuse. Use of alcohol and drugs of abuse will only be queried for the previous year from screening. Medical conditions that are a result of side effects from concomitant medications should be clearly defined and entered into the eCRF. For women of childbearing potential, the date of the first day of the last menstrual cycle should be documented.

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 (eg, 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 HS must be reported from the time of diagnosis through to the end of the study/early termination visit, where available. This includes biologics, corticosteroids, antiandrogenic medications, antibiotics, retinoids, and procedural therapies (eg, light, laser, surgical therapies).

A start date (year is sufficient if medication started >3 years prior to date of dosing) 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 focused dermatologic physical examination will be performed at specified timepoints (see SoA) or a symptom directed physical examination will be performed as indicated.

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal and complete dermatologic systems including the groin. A genitourinary or breast examination is not required unless clinically indicated, in the opinion of the Principal Investigator assessing the subject. Height and weight will also be measured and recorded at the timepoints indicated in the SoA.
- A symptom directed physical examination will include those organs, body sites required to assess the symptoms and associated findings.
- Neurologic assessment via Immune Effector Cell-Associated Encephalopathy (ICE) scoring (see Appendix G).

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 5 minutes, and while in a supine or sitting position.
- At a minimum, the following ECG parameters will be collected in the eCRF: HR, PR interval, RR interval, QTc, QTcF, QRS width.
- The 3 ECG recordings should be performed within a 20-minute period. If any abnormal findings are measured, then the ECGs will be repeated in triplicate (within 20 minutes).

7.2.4.3. Vital Signs

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

- Vital signs will include oral body temperature, systolic and diastolic blood pressure, pulse, respiratory rate, and oxygen saturation. 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 sitting position.
- Oxygen saturation will be measured with vital signs at screening, during apheresis, during infusion of study drug, and at unscheduled visits when applicable.
- Cardiorespiratory monitoring (eg, telemetry) is required during the 24 hours following administration of SBT777101.

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.

7.2.4.5. ICE Score

All subjects will be assessed for neurologic function according to the Immune Effector Cell-Associated Encephalopathy (ICE) score as specified in the SoA (see Appendix A and Appendix B), and as clinically indicated post-dose should neurotoxicity be suspected. For details on ICE Score evaluations and calculations, please refer to Appendix G.

7.2.5. Skin Biopsy

All subjects will undergo skin biopsy prior to dosing (after the pre-infusion eligibility confirmation) and post-dose at Weeks 4 and 12, to assess CAR-antigen reactivity and characterize the local inflammatory microenvironment, including the number and phenotype of T cell and other immune cell subtypes. There is an option to add a skin biopsy during the screening period. For each timepoint (ie, screening [if applicable], pretreatment, and Week 4 and Week 12 post-dose), up to two 6-mm punch biopsies will be taken as described in the Biopsy Manual.

The Week 4 and Week 12 skin biopsies can be performed at or up to 7 days after the scheduled assessment visit. The timing of the skin biopsy may be changed based on evaluation of data from the first dose escalation cohort. All skin biopsies should be preceded by a physical exam detailing the number of lesions. In addition, photographs should be taken of the location of the biopsies (refer to Section 7.2.7.4). For subjects who discontinue the study prior to Week 12, a skin biopsy at ET is optional.

Further 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 Principal 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 Principal 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).

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 to measure ADAs against the extracellular domain of the CAR and/or the EGFR tag
- PBMCs to measure cellular immunogenicity against CAR-derived and/or EGFR-derived peptides.

In addition, the Sponsor will evaluate the presence of SBT777101 in skin biopsies.

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 Mechanism of Action Biomarker Assessments

PBMC, serum, and plasma samples as well as skin will be collected to evaluate the PD of SBT777101 and for exploratory biomarker analysis.

PD effects of SBT777101 will be evaluated by measurement of relevant inflammatory cytokines [which may include 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 erythrocyte sedimentation rate (ESR).

Exploratory biomarkers will include but are not limited to enumeration and phenotyping of CAR Treg 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.

The Sponsor may store any biologic 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 HS or other diseases, the development of related or new treatments, or research methods.

7.2.7. Clinical Assessments

7.2.7.1. Assessment of Inflammatory Skin Lesions

- In addition to the dermatologic component of a complete physical examination, focused dermatologic physical examinations will be performed to obtain total counts of inflammatory nodules (N), abscesses (A), and draining tunnels (dT). Total N, A, and dT counts will be conducted at timepoints specified in the SoA. Lesion counts are optional at

the other times when physical examinations are performed. Lesion counts should be performed by the same assessor throughout the study where possible.

7.2.7.2. Clinical Stage Assessments:

Clinical stage, as determined by Hurley Stage, will be confirmed by physical examination, according to the following:

- Stage 1: ≥1 abscess(es); and no sinus tract or scar formation
- Stage 2: ≥1 widely separated recurrent abscesses with associated sinus tract/scar formation
- Stage 3: multiple interconnected sinus tracts and abscesses throughout the entire affected region

7.2.7.3. Exploratory Preliminary Efficacy Assessments

The following assessments will be analyzed at Week 4 and 12 following SBT777101 administration as compared to baseline and will be used to evaluate efficacy responses.

HS Clinical Response (HiSCR) and HiSCR modifications (HiSCR75 and HiSCR90). In order to calculate the HiSCR, the number of inflammatory nodules, abscesses, and draining tunnels will need to be measured at the appropriate timepoints:

- HiSCR: ≥50% reduction in abscess and inflammatory nodule (AN) count relative to baseline; AND no increase in abscesses relative to baseline; AND no increase in draining tunnel (dT) relative to baseline
- HiSCR75: ≥75% reduction from baseline in AN count, with no increase from baseline in abscess or dT count.
- HiSCR90: ≥90% reduction from baseline in AN count, with no increase from baseline in abscess or dT count.

The IHS4 score: number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). A total score of 3 or less signifies mild, 4 to 10 signifies moderate and 11 or higher signifies severe disease. The IHS4-55 score, defined as a 55% improvement from baseline in the IHS4 score, will be evaluated.

The Hidradenitis Suppurativa Quality of Life (HiSQOL) score, a validated patient-reported outcome (Kirby et al., 2020), will be assessed at various timepoints, including but not limited to Week 12 following SBT777101 administration. The HiSQOL is a 17-question scale that produces a numeric score that can range from 0 to 68. A higher score indicates greater health-related quality of life impairment.

Numerical Rating Scale (NRS30) in Patient's Global Assessment of Skin Pain (PGA Skin Pain) - proportion of participants achieving at least a 30% reduction and at least a 2-unit reduction from baseline in Numerical Rating Scale (NRS30) in Patient's Global Assessment of Skin Pain (PGA Skin Pain) among subjects with baseline NRS ≥3. The NRS is a numeric scale in which the respondent selects a whole number (0-10 integers) that best reflects the intensity of their pain ranging from 0 (no skin pain) to 10 (skin pain as bad as you can imagine).

These scores may be affected by the menstrual cycles of women who are pre-menopausal. As such, at each time these scales are completed, eligible women will be asked to provide the date of the first day of their last menstrual period.

7.2.7.4. Photography

Serial high-resolution photographs of all affected anatomic regions should be taken to document and follow appearance and location of inflammatory skin at the timepoints specified in the respective SoA. Photographs should also be taken of the location of the biopsies (refer to Section 7.2.5).

Photographs and lesion count at other timepoints should be taken at the discretion of the investigator. Please refer to the Study Operations Manual for guidance on uploading photos .

For subjects who discontinue the study prior to Week 12, a skin biopsy at Early Termination (ET), along with the photographs, is optional.

7.3. Order of Study Assessments

PROs must be performed prior to any discussions with care providers and interventional assessments including lab draws.

The preferred order of the remaining assessments during study visits is as follows:

- Demographics, medical history and concomitant medication review
- Physical exam including number of abscesses, nodules and tunnels
- Safety assessments: ECG must be performed first, followed by vital signs, where required
- Clinical laboratory tests
- Labs for RCL
- Labs for PK and immunogenicity
- Labs for PD/mechanism of action biomarkers
- Study drug administration or skin biopsy, as applicable

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 prior to receiving SBT77101 at the discretion of the Principal Investigator for behavioral or compliance reasons

- 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 who are dosed with SBT777101 and withdraw from the study will be encouraged to enroll in the long-term follow-up study of up to 15 years at the time of withdrawal.

The date and reason for study withdrawal, if available, must be recorded in the subject's eCRF. An 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 Principal 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 Principal 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 will be replaced for any of the following reasons:

- Received less than 85% of the planned study drug administration
- Discontinued, withdrew from, or lost to follow-up before completing the DLT evaluation period (up to study Day 28)

If a subject experiences a DLT they will not be replaced. Replacement of subjects for any reason is contingent on the approval by the independent SMC.

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, eg, 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 Principal Investigators, regulatory authorities and ethics committees, and will specify the reason(s) for termination.

8. ASSESSMENT OF SAFETY

8.1. Safety Plan

This is planned to be the second study in which SBT777101 will be administered to humans, with safety data from the first-in-human study not yet available at the initiation of this study. 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 eligibility criteria (see Section 4), and rigorous monitoring assessments as detailed in Section 8.1.1. As described in Section 3.1.1, treatment of the first 3 subjects in each dose escalation cohort will be staggered by at least 28 days in order to fully assess the safety of the product in the acute setting. Thereafter treatment of subject can be staggered by 14 days between subjects. All subjects receiving SBT777101will be monitored for onset of DLTs for at least 28 days prior to dose escalation. Dose escalation recommendations will be made by a SMC in collaboration with the study Principal 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 and for one hour thereafter.
- Subjects will undergo constant cardiopulmonary monitoring post receipt of study drug. Vital signs will then be assessed on a frequent basis (including telemetry and oxygen saturation) for 24 hours following administration of SBT777101.
- 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 in the presence 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 clinically assessed for adverse events (AEs) and serious adverse events (SAEs) using the CTCAE Grading Scale (see Appendix E). All AEs and SAEs will be recorded and reported as described in Section 8.2 and Appendix F.

CRS and neurotoxicity adverse events will be assessed using the American Society for Transplantation and Cellular Therapy (ASTCT) grading scales (Appendix F and Appendix G). Events will be reported as described in Section 8.2.

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. Pretreatment with an antipyretic (eg, acetaminophen 650 mg PO) and/or an antihistamine (eg, diphenhydramine 25-50 mg PO or IV) should be administered. Any infusion related AEs will be reported in the eCRF and treatment given according to standard of care.

A blood sample for potential analyses of infusion reaction mediators (eg, 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 (eg, 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 subjects that experience anaphylaxis, discontinue infusion and do not re-instate
- 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 the 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., poorly controlled diabetes). SBT777101 should not be administered to a subject with an active infection. If the subject requires rescue medication, the physician should evaluate the subject for infection and consider undertaking an infectious disease workup.

Close monitoring of subjects for signs of infection is recommended because 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.

8.1.1.3. Viral Reactivation

While reactivation of viral (eg, EBV) or other serious infections (eg, tuberculosis) has been observed with biologic therapies for HS (Humira, 2021), 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 studies in other autoimmune diseases using polyclonal Treg 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 Treg 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 IFNγ, and the sequelae may be severe or life-threatening. Administration of CAR Teff therapy is associated with CRS, with symptoms typically appearing within 14 days of CAR Teff administration (Chou and Turtle, 2020) and the overwhelming majority of cases developing within 1-2 days.

The risk of CRS with CAR Treg therapies such as SBT777101 is unknown. Notably, CRS was not observed in studies of either allogenic or autologous polyclonal Tregs in patients with multiple clinical indications (see SBT777101 Investigator Brochure). Given the difference in mechanism of action from CAR Teff therapies used in the oncology setting compared to the immunosuppressive mechanism of a CAR Treg, CRS is not anticipated. However, it is important to closely monitor subjects for signs and symptoms of CRS.

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

- High fever (≥38°C)
- Fatigue
- Nausea
- Headache
- Dyspnea
- Tachycardia
- Peripheral and/or pulmonary edema
- Coagulopathy
- Electrolyte abnormalities (eg, hypophosphatemia, hypokalemia, hyponatremia)
- Rigors
- Fluid-refractory hypotension
- Respiratory failure/hypoxia
- Myalgia/arthralgia
- Anorexia
- Neurological abnormalities (see Section 8.1.2.2)

CRS is a clinical diagnosis based on the presence of a fever, with or without variable degrees of hypotension, hypoxia, and other end-organ dysfunction. It is important to exclude other etiologies in any subject presenting with fever, and diagnostic workup will ensue at the discretion of the PI in consultation with the medical monitor.

CRS initially presents with a fever (temperature of ≥38°C or 100.4°F), a diagnostic requirement for all grades of severity (see Appendix F for guidance on grading CRS adverse events according to the ASTCT scale). CRS Grade 1 may also be associated with nonspecific clinical findings as outlined above. With worsening severity, subjects with CRS may also develop fluid-refractory hypotension, hypoxia, vascular leakage and peripheral/pulmonary edema, and multi-organ

failure, which may overlap with the clinical manifestations of other medical complications including, but not limited to, sepsis, uncontrolled systemic inflammatory response syndrome (SIRS) with circulatory collapse, macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), and pulmonary thromboembolism.

Because the diagnosis of CRS requires a fever, 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). Subjects should be instructed to monitor their temperature daily for the duration of the study and to contact their physician immediately if experiencing symptoms that suggest CRS in order to ensure rapid evaluation and appropriate treatment.

Laboratory studies for the evaluation of possible CRS are nonspecific and reflect a systemic inflammatory response. Markers of inflammation, especially IL-6, IFNγ, C-reactive protein (CRP), and ferritin, are elevated in CRS, but may also be acutely elevated with other systemic inflammatory conditions. Therefore, a diagnosis of CRS should not rely solely on abnormal inflammatory markers.

8.1.2.1.1. Management of Suspected CRS

For subjects for whom there is a high index of suspicion for CRS, a goal of management is to prevent worsening and deterioration to severe CRS. The ability to delineate mild CRS vs. other inflammatory etiologies is expected to be challenging and will require the collective knowledge and experience of Principal Investigators, the Sponsor Medical Monitor, and other members of the study medical and scientific team. ***It is critical that the Principal Investigator contact the Sponsor Medical Monitor for any subject presenting with a fever who develops any of the additional signs and symptoms listed previously.***

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

Subjects with severe CRS may require management in an intensive care unit or other setting where they can simultaneously receive aggressive management of hypotension (eg, fluids, vasopressors), oxygenation (eg, supplemental oxygen, mechanical ventilation), cardiac telemetry, infection (eg, routine empiric antibiotics), and other conditions.

Table 5 provides guidelines for the evaluation and management of suspected CRS, as well as study-specific instructions for sample collection of any subject who develops signs and symptoms consistent with CRS.

Table 5: Guidelines for the Evaluation, Management and Sample Collection for Suspected CRS

CRS Grade	CRS Management Recommendations*	Evaluation and Sample Collection (Including But Not Limited to):
Grade 1	• Close and continuous monitoring • Contact Sponsor Medical Monitor • Symptomatic treatment with antihistamines, antipyretics, IV fluids, etc. as needed • Antibiotics if the index of suspicion for infection is high • Consider tocilizumab ± high dose glucocorticoids (hydrocortisone/ dexamethasone/methylprednisolone).	• CBC with differential, coagulation tests (PT and PTT, fibrinogen, fibrin D-dimer), serum electrolytes, kidney and liver function tests, and uric acid • Continuous pulse oximetry. Consider arterial blood gas. • Microbiologic testing (blood culture, urinalysis/urine culture, etc.) • Blood sample for markers of inflammation: ferritin, IL-6, IL-10, IFNγ, CRP, ESR • Chest radiograph • Sponsor central lab samples (Unscheduled Visit) o Blood sample for PK o Blood sample for exploratory inflammatory markers o Blood sample for exploratory biomarkers
Grade 2	• Close and continuous monitoring • Contact Sponsor Medical Monitor • Symptomatic treatment with antihistamines, antipyretics, IV fluids, supplemental oxygen, etc. as needed. • Consider tocilizumab ± high dose glucocorticoids (hydrocortisone/ dexamethasone/methylprednisolone).	
Grade 3/4	• Close and continuous monitoring • Contact Sponsor Medical Monitor • Tocilizumab ± high dose glucocorticoids (hydrocortisone/dexamethasone/ methylprednisolone). • Symptomatic treatment with antihistamines, antipyretics, IV fluids, supplemental oxygen, etc. as needed. • Treatment with one or more vasopressors	

*CRS Management Recommendations are not intended to supersede or replace institutional protocols or the clinical judgement of the treating medical team.

8.1.2.2. Neurotoxicity

CAR Teff cell therapy has been associated with neurological toxicities, also known as CAR T-Cell Related Encephalopathy (CRES) or Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS). The pathophysiology of CRES/ICANS is not well understood but like CRS, it is thought to be a complication of enhanced immune activation, systemic inflammation and high inflammatory cytokine levels leading to endothelial cell activation, disruption of the blood brain barrier and a proinflammatory immune cascade within the CNS. CRES/ICANS is frequently associated with severe CRS but has also been reported to occur independent of CRS (Seigler and Kenderian, 2020).

The risk of neurotoxicity with SBT777101 treatment is unknown. However, CRES was not observed in studies of similar cell therapies (eg, HLA-matched, non-autologous Treg cells; alloantigen enriched Treg cells; autologous polyclonal Tregs) in subjects with multiple clinical indications (see SBT777101 Investigator Brochure). Given the difference in mechanism of action from CAR Teff therapies used in the oncology setting compared to the immunosuppressive mechanism of a CAR Treg, neurotoxicity/CRES is not anticipated.

Neurotoxicity can be characterized by the following signs and symptoms (Seigler 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 5 to 7 days after CAR Teff therapy administration. In subjects with CRS, neurologic symptoms may develop 2 to 4 days following onset of CRS. For the majority of subjects who develop neurotoxicity following CAR Teff therapy administration, signs and symptoms are transient. However, some deaths have been reported.

Laboratory abnormalities associated with neurotoxicity overlap with CRS and are nonspecific indicators of systemic immune activation. Serum levels of proinflammatory cytokines, CRP, ESR and ferritin are elevated. Cerebrospinal fluid (CSF) findings are also nonspecific. CSF may show mildly increased protein and/or pleocytosis; however, CSF may also be normal.

Neurotoxicity may be associated with an abnormal electroencephalogram (EEG), although specific findings may vary. Neuroimaging may show evidence of cerebral edema, infarctions, and/or focal or diffuse white matter injury. However, neuroimaging studies are normal in most cases.

Subjects receiving SBT777101 should be monitored closely for signs and symptoms of neurotoxicity. This protocol requires that all subjects be evaluated using the Immune Effector Cell-Associated Encephalopathy (ICE) score every 4 hours while awake during the post-infusion overnight safety evaluation period on Day 1, as well as at each subsequent scheduled study visit (see Schedule of Assessments, Appendix B). For details on ICE scoring see Appendix G.

8.1.2.2.1. Management of Neurotoxicity

Management of neurologic toxicity should occur according to site protocols or standard clinical practice. ***It is critical that the Principal Investigator contact the Sponsor Medical Monitor for any subject presenting with signs and symptoms consistent with neurotoxicity.***

Based on the potential for rapid decline, any subject exhibiting signs and symptoms consistent with neurotoxicity should be monitored closely in the inpatient setting by a multidisciplinary medical team that includes neurology and cell therapy-experienced specialists. ICU care may be required for any subject with progressive changes in mental status, impaired responsiveness, demonstrated seizure activity, or when the index of suspicion for cerebral edema is high. Work-up should exclude other potential causes of neurologic decline and the following clinical evaluations are recommended, including but not limited to:

- CBC with differential
- Examination of cerebrospinal fluid (CSF)
- CNS imaging
- EEG

In addition, the following samples should be obtained and sent to the Sponsor central laboratory (Unscheduled Visit) whenever possible:

- Blood sample for PK
- Blood sample for exploratory inflammatory markers
- Blood sample for exploratory biomarker evaluations
- CSF for PK and cytokines

In general, management of cell therapy-associated neurotoxicity is supportive. High-dose glucocorticoids (ie, dexamethasone 5-10 mg) and antiseizure prophylaxis should be considered for any subject with abnormal neurologic findings and moderate to severe CRS (≥ Grade 2 ICANS; See Appendix F for CRS grading).

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 lentiviral vector-mediated gene transfer into mature T cells (Milone and O'Doherty, 2018). An insertion site analysis conducted for SBT777101 showed a polyclonal integration site profile with no dominant integration site. Subjects will be monitored for 1 year in this study and longer term (up to 15 years) 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. Treatment emergent adverse events (TEAEs) are defined as AEs that start on or after the date of study drug administration.

AEs will be reported by the subject.

The Principal 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.

8.2.1.1. Adverse Events of Special Interest

AESIs are AEs (serious or nonserious) that are of special scientific and/or medical interest due to their relevance to the mechanism of action of the study drug. As such, ongoing and rapid communication by the Investigator to the Sponsor is paramount. The following events need to be reported to the Sponsor within 24 hours of site awareness, irrespective of seriousness, or causality:

- Any CRS Grade 3 or higher
- Any ICANS
- Any MAS/HLH

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.

All medical occurrences that are not SAEs or AEs as a result of protocol specified procedures 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 Principal Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Principal Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Principal 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 Principal 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 Principal 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 Principal 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 (eg, 21 CFR 312.32), institutional review boards (IRBs)/independent ethics committees (IECs), and Principal Investigators.
- A Principal Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, 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 Principal Investigators as necessary.
- The Sponsor is responsible for the final determination of causality for regulatory reporting.

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 Principal Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female subject's 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 (eg, 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 Principal Investigator will collect follow-up information on the subject 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 Principal Investigator will be reported to the Sponsor as described in Appendix E. While the Principal Investigator is not obligated to actively seek this information in former study subjects, 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 HS.

This study will enroll up to approximately 28 eligible adult subjects with HS.

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. The safety population will be used for both the safety and efficacy analyses.
- DLT evaluable population: All subjects who received study drug and did not meet the criteria for subject replacement criteria (in Section 7.4.3) during the DLT period.
- PK/PD population: All subjects in the safety analysis set with at least one pre- and post-dose measurement to provide interpretable results. Subjects will be excluded from the PK/PD analysis if they have a protocol deviation or any important event that would affect the interpretation and integrity of the concentration data.

9.4. Endpoints

Endpoints are listed in Section 2.

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 1 significant digit, respectively (eg, 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 study data. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (eg, 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), and disease duration. 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. Full details for safety analysis will be provided in the statistical analysis plan (SAP).

9.7.1. Adverse Events

Clinical and laboratory AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®). The severity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. AEs of CRS or neurotoxicity will be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) criteria. The number of subjects experiencing TEAEs and number of TEAEs will be summarized by dosing level using frequency counts. Infusion-related reactions, AESIs 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 statistics will be generated to summarize data for physical examination findings, concomitant medications, and medical history. Concomitant medications will be coded using the most recent World Health Organization (WHO) drug dictionary . The number and percentage of subjects 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 noncompartmental methods.

Immunogenicity data will be listed by subject. The proportion of subjects with a positive anti-drug antibody or cellular immunogenicity result will be summarized over time and by dosing level. The 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 Treg 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 to 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 Principal 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 Principal 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 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 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 Principal 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 Principal 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 Principal Investigators via data queries.

A Safety Monitoring Committee will periodically review safety data (eg, AEs and SAEs, laboratory data) as the clinical study 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 study 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 Principal 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 PRETREATMENT PERIODS

	Screening [a]	Pretreatment [b]		
		Apheresis [c]	Pre-infusion	Biopsy
Study Day (visit window)			**-10 to -4**	**-7 to 1**
Procedure				
Informed consent	●			
Eligibility criteria	●	●	●	
Demographics	●			
Medical history [d]	●		●	
Prior/Concomitant medications	●	●	●	
Vital signs	●		●	
Full physical exam [e]	●			
Directed dermatologic physical exam [e]			●	
ICE			●	
Height	●			
Weight	●		●	
12-lead triplicate ECG	●		●	
Chest X-ray			●	
Skin biopsy and corresponding lesion photograph [f]	●			●
Skin photography of affected lesions [g]	●		●	
Vein assessment [h]	●	●		
Apheresis [c]		●		
Infectious disease serology [i]	●			
TB screening [i]	●			
Serum pregnancy test	●		●	
Lipid tests [i]			●	
Coagulation [i]	●		●	
Hematology [i]	●		●	
Clinical chemistry [i]	●		●	
Urinalysis [i]	●		●	
Markers of acute inflammation [j]			●	
CRP and ESR [j]			●	
Lesion count [k]	●		●	
Subject HiSQOL score [l]	●		●	
NRS-30 [l]	●		●	
Collect date of the first day of the last menstrual period	●		●	
Blood samples for PK (ddPCR)			●	
PBMC sample for cellular immunogenicity			●	
Serum sample for ADA			●	
Plasma for exploratory markers	●		●	
Serum for exploratory markers	●		●	
PBMC for exploratory biomarkers	●		●	
PBMC samples for RCL			●	
Concomitant medications	●	●	●	●
Adverse events [l]	●	●	●	●

A = abscess; ADA = anti-drug antibody; APH = apheresis; CRP = C-reactive protein; ddPCR = droplet digital polymerase chain reaction; dT = draining tunnel (fistula/sinus); ECG = electrocardiogram; ESR = erythrocyte

sedimentation rate; HiSCR = hidradenitis suppurativa clinical response; HiSQOL = Hidradenitis Suppurativa Quality of Life; ICE score = Immune Effector Cell-Associated Encephalopathy Score; N = inflammatory nodule; PK = pharmacokinetic; RCL = replication competent lentivirus; TB = tuberculosis; UV = unscheduled visit

a. The Screening period is expected to last approximately 4 weeks (but up to 2 months is permitted).
b. The Pretreatment period is expected to last approximately 6 weeks (but up to date of drug product expiration is permitted).
c. Apheresis should be scheduled and performed as soon as possible but no later than 4 weeks after enrollment and the subject enters the Pretreatment period.
d. Medical history to include history of HS flares and treatments for flares in the 6 months prior to screening.
e. For all physical examinations, whether full or directed, the dermatologic examination should include total N, A, and dT counts.
f. Pretreatment skin biopsy (6-mm punch biopsy) is to be performed after the pre-infusion confirmation of eligibility, up to 7 days before study drug administration. There is an option to add a skin biopsy during the screening period. Please photograph the lesion that is to be biopsied. Please refer to the Biopsy Manual for further information.
g. Photographic documentation of all affected anatomic regions should be obtained. Photographs at other timepoints should be taken at the discretion of the investigator.
h. Assessment of vascular access and if central line is indicated [vs peripheral intravenous catheter or peripherally-inserted central catheter (PICC)] for apheresis and/or administration of SBT777101 should be determined by the Principal Investigator with subject input.
i. Tests included in laboratory assessments are described in protocol Appendix C. Fasting glucose should be collected at the pretreatment visit and as clinically indicated.
j. Markers of acute inflammation for safety assessment include ferritin, IL-6, IFNγ, CRP, and ESR.
k. Lesion counts will be used to calculate HiSCR 50, 75 and 90 as well IHS4.
l. 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.

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

	Treatment and Safety Follow-Up																UV[a]	ET
Study Week	**1**				**2**		**3**	**4**	**6**	**8**	**10**	**12**	**18**	**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**	**126 ±7**	**168 ±7**	**252 ±7**	**336 ±7**		
Procedure																		
Vital signs [b]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Adverse events [c]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Prior/Concomitant medications	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Full physical exam [d]				●				●		●						●		●
Directed physical exam [d]	●	●	●		●	●	●		●		●	●	●	●	●		●	
ICE score [e]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●
Weight								●		●						●		●
12-lead triplicate ECG				●				●								●	●	●
Skin biopsy and corresponding lesion photograph [f]								●				●						●
Skin photography of affected lesions [g]								●		●		●	●	●	●	●		
Urine pregnancy test	●							●				●	●	●		●		●
Lipid tests [h]								●								●		
Coagulation [h]								●						●		●		
Hematology [h]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Clinical chemistry [h]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Urinalysis [h]										●					●	●		●
Markers of acute inflammation [i]																	●	
CRP and ESR		●		●		●	●	●	●	●	●	●	●	●	●	●	●	●
Lesion count[j]						●		●	●	●	●	●	●	●	●	●	●	●
Subject HiSQOL score								●		●		●	●	●		●		●
NRS30								●		●		●	●	●	●	●	●	●
Collect date of the first day of the last menstrual period								●		●		●	●	●	●	●	●	●
Blood samples for PK (ddPCR) [k]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
PBMC sample for cellular immunogenicity								●		●		●				●	●	●
Serum sample for ADA								●		●		●	●			●	●	●
Plasma for exploratory markers		●		●		●	●	●	●	●	●	●	●	●	●	●	●	●
Serum for exploratory markers		●		●		●	●	●	●	●	●	●	●	●	●	●	●	●
PBMC for exploratory biomarkers		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

	Treatment and Safety Follow-Up																UV[a]	ET
Study Week	**1**				**2**		**3**	**4**	**6**	**8**	**10**	**12**	**18**	**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**	**126 ±7**	**168 ±7**	**252 ±7**	**336 ±7**		
Procedure																		
PBMC samples for RCL												●		●		●	●	
SBT777101 administration [l]	●																	
Overnight stay/acute safety monitoring (post-dose)	●																	
Subject self-temperature monitoring [m]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Subject check-in (phone call, text etc) [n]		●	●	●														

A = abscess; ADA = anti-drug antibody; CRP = C-reactive protein; ddPCR = droplet digital polymerase chain reaction; dT = draining tunnel (fistula/sinus); ECG = electrocardiogram; ES = End of Study; ET = early termination; HiSCR = hidradenitis suppurativa clinical response; HiSQOL = Hidradenitis Suppurativa Quality of Life; ICE score = Immune Effector Cell-Associated Encephalopathy Score; PK = pharmacokinetic; RCL = replication competent lentivirus; UV = unscheduled visit

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

a. Assessments (which may include safety labs, ECG, ICE assessment, PK, ADA, and biomarker sample collection and skin biopsy) should be performed as clinically indicated.
b. Vital signs must be measured approximately 15 minutes prior to infusion, then approximately every 15 minutes during the infusion and for one hour thereafter. Vitals should include cardiorespiratory monitoring (CRM, eg, telemetry) and be recorded approximately every 4 hours during the first 24 hours from initiation of infusion.
c. After informed consent has been obtained but prior to initiation of study drug, all SAEs plus any AE that is the result of a protocol-specified procedure or intervention will be collected. After initiation of study drug administration, all AEs will be reported until the end of the study. After this period, the Sponsor should be notified if the Principal Investigator becomes aware of any SAE that is believed to be related to prior study drug treatment.
d. Lesion counts are optional at the physical examinations at which photographs are not taken.
e. Approximately every 4 hours while awake during the first 24 hours after initiation of infusion, with vital signs.
f. The skin biopsy can be performed at or up to 7 days after the scheduled assessment visit. The timing of the skin biopsy may be changed based on evaluation of data from the first dose escalation cohort. For subjects who discontinue the study prior to Week 12, a skin biopsy at ET is optional. Please include a photograph of the lesion which is to biopsied. Please refer to the Biopsy Manual for further information.
g. Photographic documentation of all affected anatomic regions should be obtained. Photographs at other timepoints should be taken at the discretion of the investigator.
h. Tests included in laboratory assessments are described in protocol Appendix C.
i. A sample to test for markers of inflammation, including but not limited to ferritin, IL-6, IFNγ, CRP and ESR, should be collected as soon as possible after the onset of a suspected adverse event per institutional standards of care.
j. Lesion counts at Weeks 2, 6 and 10 will be optional. Lesion counts will be used to calculate HiSCR 50, 75 and 90 as well as IHS4.
k. The PK sample collected on study Day 2 should be collected at approximately 24 hours (±1 hour) post infusion of study drug on study Day 1. An unscheduled PK sample should be collected as soon as possible after a suspected infusion related reaction adverse event.
l. 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 visit.

m. Subjects are required to measure and record their temperatures in the subject diary at least once daily. Sites are required to review subject diaries at each visit.
n. Subjects should be contacted daily by the site (eg, by phone or text) following discharge through Day 7.

APPENDIX C. CLINICAL LABORATORY TESTS

The tests detailed in Table 6 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 Principal Investigator or required by local regulations.

Table 6: 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)	Creatinine	Sodium
	Potassium	Chloride	Calcium
	Phosphate	Bicarbonate	Albumin
	Total protein	Total and direct bilirubin	Alkaline phosphatase
	Aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT)	Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT)	Gamma-glutamyl transferase (GGT)
	Lactate dehydrogenase (LDH)	Glucose (fasting at the pretreatment visit and as clinically indicated)	HbA1c (only for subjects with a history of glucose intolerance, pre-diabetes or diabetes)
Markers of acute inflammation	Ferritin	Interleukin-6 (IL-6)	Interferon gamma (IFNγ)
	C-reactive protein (CRP)	Erythrocyte sedimentation rate (ESR)	
Lipid tests	Low density lipoprotein (LDL)	Total cholesterol	Triglycerides

Table 6: Protocol-Required Safety Laboratory Tests (Continued)

Laboratory Tests	Parameters	
Serology	Hepatitis B surface antigen (HbsAg)	Hepatitis C virus antibody
	HIV screening: Fourth generation antigen/antibody combination HIV-1/2 immunoassay, or similar	
Tuberculosis screening	Quantiferon Gold	
Coagulation	Prothrombin time (PT)	International normalized ratio (INR)
	Activated partial thromboplastin time (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)	

Principal 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 (eg, 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 2 methods of contraception for at least 1 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*
• Injectable progestogen-only hormone contraception 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.*
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), Principal 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 (eg, condom) for 1 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 preexisting 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 Principal 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 <u>NOT</u> 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:
Results in death
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.
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.

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.

Is a congenital anomaly/birth defect

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 subject
- 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 Principal Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- For AESIs, the Principal Investigator will fill out a targeted questionnaire provided by the Sponsor to collect additional clinical information about the event.
- The Principal 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 Principal 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 Principal 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.

AEs of CRS or neurotoxicity should be assessed according to the American Society for Transplantation and Cellular Therapy (ASTCT) grading criteria (see Appendix F and Appendix G).

For AEs not adequately addressed in the NCI-CTCAE Version 5.0, (or the ASTCT) the criteria in Table 7 should be used.

Table 7: 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 Principal Investigator will assess the relationship between study intervention and the occurrence of each AE/SAE. The Principal 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 Principal 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 Principal 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 Principal Investigator has minimal information to include in the initial report to the Sponsor. However, the Principal Investigator should always assess causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Principal 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 Principal 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 Principal 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 Principal 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 subjects 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 subject 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 AND ICE SCORING FOR ADULTS

Immune Effector Cell-Associated Encephalopathy (ICE) scores are calculated using the following algorithm (Lee et al., 2019):

Orientation: orientation to year, month, city, hospital: 4 points

Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points

Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point

Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point

Attention: ability to count backwards from 100 by 10: 1 point

The scoring system is as follows:

Scoring: 10, no impairment;

7-9, Grade 1 ICANS;

3-6, Grade 2 ICANS;

0-2, Grade 3 ICANS;

0 due to subject unarousable and unable to perform ICE assessment, Grade 4 ICANS

The following ICANS grading should be used for recording neurotoxicity adverse events. In the grading system, the final ICANS grade is determined by the most severe event among the different domains.

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (subject is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject 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

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
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 subject with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a subject 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 subject with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

APPENDIX H. 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
AN	abscess or inflammatory nodule
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and cellular Therapy
AUC	area under the curve
BID	twice per day
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CAR	chimeric antigen receptor
Cit-Prot	citrullinated protein
C_{max}	maximum concentration
CRA	clinical research associate
CRO	contract research organization
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CTCAE	common terminology criteria for adverse events
CV	citrullinated vimentin
CV%	coefficient of variation
DAMP	damage-associated molecular patterns
DLT	dose-limiting toxicity
dT	draining tunnel
ECG	electrocardiogram
ECM	extracellular matrix
EEG	electroencephalogram
EGFR	epidermal growth factor receptor
ESR	erythrocyte sedimentation rate
ET	early termination
eCRF	electronic case report form

Abbreviation	Definition
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
HiSCR	hidradenitis suppurativa clinical response
HiSQOL	Hidradenitis Suppurativa Quality of Life
HIV Ab	human immunodeficiency virus antibody
HLH	hemophagocytic lymphohistiocytosis
HS	hidradenitis suppurativa
IC_{50}	half-maximal inhibitory concentration
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell- associated encephalopathy
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IgG1	immunoglobulin G1
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	interleukin
IM	intramuscular
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JAK	Janus kinase
LFA-3	leukocyte function-associated antigen 3
MAS	macrophage activating syndrome
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil

Abbreviation	Definition
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
MTX	methotrexate
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
NRS30	pain numerical rating score
NSAID	nonsteroidal anti-inflammatory drug
PAD	peptidylarginine deiminase
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PI	Principal Investigator
PK	pharmacokinetic(s)
PO	by mouth
QD	daily
QOL	quality of life
QTcF	QTc calculated using Fridericia's formula
QW	once per week
RBC	red blood cell
RCL	replication-competent lentivirus
SAD	single ascending dose(s)
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
scFv	single-chain variable fragment
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SMC	Safety Monitoring Committee
SoA	schedule of assessments
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
T1D	type 1 diabetes mellitus

Abbreviation	Definition
TBD	to be determined
T_{CM}	central memory T cell
TEAE	treatment-emergent adverse event
Teff	effector T cell
T_{EM}	effector memory T cell
THC	tetrahydrocannabinol
T_{max}	time to maximum concentration
$T_{naïve}$	naïve T cell
TNF	tumor necrosis factor
Treg	regulatory T cell
ULN	upper limit of normal
UV	unscheduled visit
WBC	white blood cell
WHO	World Health Organization

APPENDIX I. DOCUMENT HISTORY

Version Number	Version Date	Summary of Changes
3.0	May 01, 2025	Table 8
2.0	December 11, 2023	Inclusion Criteria: Increase lesion size from >1 cm to >1.5 cm Administrative adjustments for Reference citations.
1.0	November 23, 2023	NA

Table 8: Summary of Changes from Version 2.0 to Version 3.0

Section	Change	Rationale
Protocol Synopsis 3.1.1 Overall Study Design (Figure 1) 3.1.3 Starting Dose and Dose Levels 3.6 End of Study Definition 9.1 Determination of Sample size	• Increase sample size to 28 (increased from up to 6 to up to 10 beyond the planned 18 in the dose escalation safety cohorts) • Clarify that if a dose limiting toxicity is observed in the first 3 subjects of a given cohort, that cohort can be expanded to 6 subjects	• Additional subjects to allow for adequate characterization of preliminary efficacy, PK and PD parameters and dose determination for Phase 2. • For clarity
4.2 Exclusion Criteria Appendix C Clinical Laboratory Tests (Table 6)	• Clarify exclusion criterion 8 about use of oral antimicrobials • Exclude HIV positivity at screening (exclusion criterion 34) and add HIV screening to Table 6	• For clarity • For consistency
5.2 Therapeutic Modalities for HS	• Delete Appendix H and Appendix I • Clarify use of corticosteroids before (Table 3) and during study • Clarify allowed rescue therapy during the study (text and Table 4)	• Information was redundant with section 5.2 • For clarity
6.8 SBT777101 Administration	• Clarify in-patient stay is required for at least 24 hours post infusion	• For clarity
7.1 Study Visits Appendix A SoA Screening / Pretreatment (footnote a)	• Clarify definition of eligibility and enrolled • Clarify pretreatment duration (up to date of study drug product expiry)	• For clarity
7.2.2 Medical History	• Clarify information collected as part of medical history, includes date of last menstrual cycle	• For clarity
7.2.4.1 Physical Examinations (old)	• Move lesion photography to be a separate section from physical examination, under clinical assessments	• For clarity

Section	Change	Rationale
7.2.7.1 Assessment of Inflammatory Skin Lesions 7.2.7.7 Photography (new) Appendix A and Appendix B Schedule of Assessments	• Clarify that lesion counts to be done by the same assessor (if possible) and are optional at Week 2, 6 and 10 • Clarify that all affected lesions should be photographed	
7.2.7.3 Exploratory Preliminary Efficacy Assessment Appendix A and Appendix B Schedule of Assessments	• Clarify impact of menstrual cycle and add collection of date of first day of last cycle at visit where HiSCR is assessed	• For clarity
8.2.1 AEs, SAEs and Other Safety Reporting	• Add definitions of TEAEs and AESIs	• For clarity
9.3 Analysis Datasets	• Add definition of DLT evaluation population	• For clarity
Appendix A and Appendix B (Schedule of Assessments)	• Align with above changes	• For accuracy and consistency
General	• Update Sponsor Signatory and Sponsor's Medical Director • Minor clarifications and editing (e.g., systemic estrogen, update names of approved medications, methods of collecting ECG and vital signs, safety plan) as well as minor updates to introduction section • Remove redundancy • Formatting, fix hyperlinks, delete unnecessary hyperlinks • Use consistent terminology (e.g., subject) • Update Abbreviations • Update footer with current amendment version/date	• For accuracy and consistency