CLINICAL RESEARCH PROTOCOL

DRUG:	SGX945 (Dusquetide)
STUDY NUMBER(S):	DUS-AUBD-01
PROTOCOL(S) TITLE:	Pilot Study of SGX945 (Dusquetide) in the Treatment of Aphthous Ulcers in Behçet's Disease
IND NUMBER:	[redacted]
SPONSOR:	Soligenix, Inc.
ORIGINAL PROTOCOL DATE:	18 October 2023
VERSION NUMBER:	Amendment 2
VERSION DATE:	22 July 2024

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CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: Pilot Study of SGX945 (Dusquetide) in the Treatment of Aphthous Ulcers in Behçet's Disease

Study No: DUS-AUBD-01

Original Protocol Date: 18 October 2023

Protocol Version No: Amendment 2

Protocol Version Date: 22 July 2024

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the sponsor. The information contained in this protocol is consistent with:

The current risk-benefit evaluation of the investigational product.

The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Approval	Signature	Date
Author: [redacted]	☒ Yes ☐ No (select one)	[redacted]	
Clinical Operations: [redacted]	☒ Yes ☐ No (select one)	[redacted]	
Regulatory Affairs: [redacted]	☒ Yes ☐ No (select one)	[redacted]	
Quality Assurance: [redacted]	☒ Yes ☐ No (select one)	[redacted]	
Other: [redacted]	☒ Yes ☐ No (select one)	[redacted]	

DUS-AUBD-01

PILOT STUDY OF SGX945 (DUSQUETIDE) IN THE TREATMENT OF APHTHOUS ULCERS IN BEHÇET'S DISEASE

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to dusquetide are the confidential and proprietary information of Soligenix, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Soligenix.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Soligenix, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about dusquetide and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____

Site Name

_____ _____

Date Site Number

STUDY SYNOPSIS

Name of Sponsor/Company: Soligenix, Inc.		(For National Authority Use only)
Name of Finished Product: SGX945		
Name of Active Ingredient: Dusquetide		

Title of Study: Pilot Study of SGX945 (Dusquetide) in the Treatment of Aphthous Ulcers in Behçet's Disease

Investigators: Gülen Hatemi

Study Centre(s): Istanbul University - Cerrahpasa, Cerrahpasa School of Medicine

Publication (reference): N/A

Study Period (years): 0.5 year **Date of First Enrollment:** August 2024 **Date of Last Visit Completed:** February 2025	**Phase of Development:** Phase 2

Objectives: The objectives of this study are to:

1. Obtain preliminary evidence of the impact of dusquetide on oral and genital ulcer resolution in Behçet's Disease (BD)
2. Obtain preliminary assessment of safety of dusquetide in patients with BD

Methodology: This will be an open-label trial enrolling patients with BD and a history of oral and/or genital ulcers with at least two active oral ulcers and/or one active genital ulcer and with well documented details of prior treatments and responses to that treatment. Patients will receive dusquetide (1.5 mg/kg based on the patient's Baseline body weight) administered every 3 days (-1/+2) as a 4-minute infusion.

Patients will be treated for a total of 4 weeks (8 treatments), with weekly follow-up visits for an additional 4 weeks. At Baseline and at each visit, the number of genital ulcers, the number of oral ulcers, the pain due to oral ulcers, the pain due to genital ulcers, and vital signs will be recorded. Female patients will undergo a pelvic exam at the Baseline visit in order to note any genital ulcers that may be present internally. The pelvic exam will be repeated at Week 4 Treatment 2 and the Week 8 follow-up visit if the patient states that they have vaginal ulcers. At each infusion visit, vital signs will be collected once prior to the infusion, as well as four times post-infusion (every 5 minutes for 20 minutes). The degree of oral and genital ulcer scarring and quality of life and disease severity assessments (Leeds Behçet's Disease Quality of Life Assessment [BD-QoL], Behçet's Disease Current Activity Form [BDCAF], Behçet's Syndrome Activity Score [BSAS], peripheral joint count and evaluation for tenderness and swelling, and both Physician and Patient Global Assessment [PGA and PtGA] of skin lesions) will additionally be assessed at Baseline, at the last treatment visit (Week 4 Treatment 2) and at the last follow-up visit (Week 8). Physical examinations and safety labs (hematology and chemistry) will be analyzed at Baseline, at the last treatment visit (Week 4 Treatment 2) and at the last follow-up visit (Week 8). The Behçet's Disease History Patient Questionnaire (BDHPQ) will be assessed at the Baseline Visit and at the last treatment visit (Week 4 Treatment 2). AE's will be recorded throughout the study.

Rationale: BD has been increasingly associated with genetic abnormalities causing or concurrent with innate immune amplification (Shimizu 2023). Skin histopathology indicates neutrophilic dermatitis or panniculitis while pathergy tests in BD patients result in persistent lymphocyte and monocyte infiltrations compared to healthy individuals (Shimizu 2023). In both oral and genital lesions, lymphocyte infiltration is frequently observed in the lamina propia. In addition to neutrophil infiltration, macrophages have also been shown to have altered response profiles in response to BD sera, suggesting a prevalence of M1 type macrophages in BD patients (Shimizu 2023). Similarly, impairment of M2 mediated anti-inflammatory function has been proposed as an underlying etiology of BD (Hirahara 2022). IL-1β, IL-6 and TNFα are all known to be elevated in serum from patients with BD (Li 2023, Shimizu 2023).

Dusquetide has been shown to alter the inflammatory response profile in response to lipopolysaccharide and other inflammatory stimulation, resulting in an increased anti-inflammatory response – specifically increasing IL-1ra relative to IL-1β and TNF RII relative to TNFα (Yu 2009, North 2016). Biological responses on oral aphthous ulcers formed in the context of chemotherapy and radiation treatment for cancer (oral mucositis) have been observed after systemic administration of dusquetide (Kudrimoti 2016). Dusquetide is known to bind (but not inhibit) sequestome-1 (Yu 2009, Zhang 2022) which has been implicated in a number of innate immune pathways and macrophage M2 function. Based on these findings, it is postulated that dusquetide will be beneficial as a systemic treatment for the mitigation and enhanced resolution of aphthous ulcers in BD.

Number of patients (planned): At least 25 subjects

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

In order to be enrolled into the trial, subjects must meet ***all*** of the criteria below:

1. ≥18 years of age.
2. Patients must have a clinical diagnosis of BD meeting the International Study Group criteria.
3. Patients must have at least two oral ulcers and/or one genital ulcer on the day of randomization.
4. Patients willing to follow the clinical protocol and voluntarily give their written informed consent.
5. Female patients not pregnant or nursing and willing to undergo a pregnancy test prior to treatment initiation and at the end of the treatment period.

Exclusion Criteria:

In order to be enrolled into the trial, subjects ***cannot*** have any of the following criteria:

1. Pregnancy or mothers who are breast-feeding.
2. All women of childbearing potential (WOCBP) and males with female partners who are WOCBP ***NOT WILLING*** to agree to the use of effective contraception during the trial (refer to Section 5.3, Exclusion Criteria, Exclusion Criterion #2 for more detail).
3. Evidence of significant renal, hepatic, hematologic or immunologic disease (refer to Section 5.3, Exclusion Criteria, Exclusion Criterion #3 for more detail).
4. Subject has any condition that, in the judgment of the PI, is likely to interfere with participation in the study.
5. Use of any investigational medication within 4 weeks prior to enrollment or 5 pharmacokinetic/pharmacodynamic half-lives (whichever is longer).
6. Having received concomitant immune modulating therapy (except colchicine) within:
    a. Ten days prior to enrollment for azathioprine and mycophenolate mofetil
    b. Four weeks (28 days) prior to enrollment for cyclosporine, methotrexate, cyclophosphamide, thalidomide and dapsone
    c. Oral and topical corticosteroids must have been tapered as appropriate and discontinued 3 days prior to day of enrollment
    d. At least 5 terminal half-lives for all biologics including, but not limited to, those listed below; within:
        i. Four weeks prior to enrollment for etanercept
        ii. Eight weeks prior to enrollment for infliximab
        iii. Ten weeks prior to enrollment for adalimumab, golimumab, certolizumab, abatacept, and tocilizumab
        iv. Six months prior to enrollment for secukinumab
7. Having received oral or parenteral corticosteroids within 6 weeks (42 days) prior to enrollment.
8. Having received apremilast (Otezla®) within 4 weeks prior to enrollment.
9. Presence of non-BD related genital ulcers, including both infectious and non-infectious etiologies.
10. Active organ involvement requiring immunosuppressive treatment.

Test product, dose and mode of administration: SGX945 is administered as a 4-minute, 25 mL infusion yielding a dose of 1.5 mg/kg based on the patient's Baseline body weight. SGX945 is administered every 3 days (-1/+2).

Duration of treatment: Patients will receive SGX945 every 3 days (-1/+2) for a total of 4 weeks (8 treatments). Following completion of treatment, patients will return to the clinic for weekly follow-up visits for an additional 4 weeks.

Reference therapy, dose and mode of administration: Not applicable

Criteria for evaluation:

Efficacy:

This is a pilot study to determine the efficacy and safety of SGX945 (dusquetide) in BD patients with oral and/or genital ulcers. No formal efficacy statistics will be performed. Results will be presented as tables and listings.

Endpoints for investigation will include:

- Proportion of patients with complete resolution of oral ulcers
- Proportion of patients with complete resolution of genital ulcers
- Number of genital ulcers over time throughout the 4-week treatment window (area under the curve)
- Number of oral ulcers over time throughout the 4-week treatment window (area under the curve)
- Time to complete resolution of genital ulcers (if present)
- Time to complete resolution of oral ulcers (if present)
- Time to complete resolution of any ulcers
- Time to recurrence or new occurrence of genital ulcers
- Time to recurrence or new occurrence of oral ulcers
- Change from Baseline score of pain due to genital ulcers
- Change from Baseline score of pain due to oral ulcers
- Change from Baseline score in the BD-QoL
- Change from Baseline score in the BDCAF
- Change from Baseline score in the BSAS
- Change from Baseline score in number of peripheral joints with arthralgia and severity of pain
- Change from Baseline score in number of peripheral joints with arthritis and the severity of swelling and tenderness
- Change from Baseline score in the PGA and PtGA of skin lesions
- Number of ulcers with a clinical diagnosis of infection
- Presence and severity of any scarring within 4 weeks post-treatment

Data will be compared to historical outcomes for each patient with respect to resolution of genital and oral ulcers (descriptive analysis) and historical resolution rates for both genital and oral ulcers in the literature.

Safety:

The safety variables evaluated are: clinical hematology assessments, clinical chemistry assessments, physical examinations, vital signs, and the collection of adverse/serious adverse events. Any infection adverse events will be characterized as distal or proximal to site of ulceration.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BAL	Bronchoalveolar Lavage
BD	Behçet's Disease
BDCAF	Behçet's Disease Current Activity Form
BDHPQ	Behçet's Disease History Patient Questionnaire
BD-QoL	Leeds Behçet's Disease Quality of Life
BSAS	Behçet's Syndrome Activity Score
BUN	Blood Urea Nitrogen
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CO_2	Serum Bicarbonate
CRF	Case Report Form
CRT	Chemoradiation Therapy
CV	Cardiovascular
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice

GLP	Good Laboratory Practice
h	Hour
HED	Human Equivalent Dose
HNC	Head and Neck Cancer
HPV	Human Papillomavirus
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IP	Intraperitoneal
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IV	Intravenous
kg	Kilogram
LPS	Lipopolysaccharide
mg	Milligram
min	Minute
mITT	Modified Intent-To-Treat
mL	Milliliter
mm	Millimeter
MRSA	Methicillin-Resistant Staphylococcus aureus
MTD	Maximum Tolerated Dose
NDA	New Drug Application

NHP	Non-human Primate
NOAEL	No Observed Adverse Event Level
OM	Oral Mucositis
PD	Pharmacodynamic
PGA	Physician Global Assessment
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PtGA	Patient Global Assessment
QoL	Quality of Life
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation Therapy
SAE	Serious Adverse Event
SC	Subcutaneous
SOM	Severe Oral Mucositis
SOP	Standard Operating Procedure
T_{max}	Time of Maximum Concentration
US	United States
VAS_{pain}	Visual Assessment Score of Pain
W	Week
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Background

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

race, and prior tumor surgery). The additional findings of an increase in the number of

[redacted]

patients, organs, and joints (Turkcu 2015, Gholijani 2017, El Boghdady 2019, van der Houwen 2023). Thus, a treatment that lowers, but does not ablate, inflammation while stimulating wound healing and exerting an anti-bacterial effect would appear to be a reasonable approach to the disease.

1.2 Study Rationale

BD has been increasingly associated with genetic abnormalities causing or concurrent with innate immune amplification (Shimizu 2023). Skin histopathology indicates neutrophilic dermatitis or panniculitis while pathergy tests in BD patients result in persistent lymphocyte and monocyte infiltrations compared to healthy individuals (Shimizu 2023). In both oral and genital lesions, lymphocyte infiltration is frequently observed in the lamina propia. In addition to neutrophil infiltration, macrophages have also been shown to have altered response profiles in response to BD sera, suggesting a prevalence of M1 type macrophages in BD patients (Shimizu 2023). Similarly, impairment of M2 mediated anti-inflammatory function has been proposed as an underlying etiology of BD (Hirahara 2022). IL-1β, IL-6 and TNFα are all known to be elevated in serum from patients with BD (Li 2023, Shimizu 2023).

1.2.1 Pharmacokinetics

As noted above in the Phase I trial, following IV administration in human subjects, dusquetide is cleared within minutes from the circulation. In the single-dose phase of the Phase 1 trial, dusquetide was rapidly eliminated, with plasma levels decreasing to less than 10% of the maximum concentration (C_{max}) within 9 minutes after the start of the 4-minute IV infusion. Following the rapid decline, a slower elimination phase was observed. The mean time of maximum concentration (T_{max}) ranged between approximately 4 to 4.8 minutes after the start of infusion for the dose range of 0.15 - 8 mg/kg. Maximum plasma concentrations and total exposure levels were dose-proportional and clearance of dusquetide from the circulation was rapid, consistent with the mouse and NHP experience. Considering the high clearance and short elimination half-life, accumulation following daily injection was not expected to occur. In the multiple-dose Phase 1 study, dusquetide was administered daily for 7 days and the pre-dose concentrations measured on Days 5, 6, 7, as well as on Day 8 (24 hours after the start of infusion on Day 7) were below the lower limit of quantitation for all of the subjects.

1.2.2 Clinical Adverse Event Profile

As noted above in the Phase 2 and 3 trials, comparison of the AEs and SAEs across the dose groups (ie, 1.5, 3.0, and 6.0 mg/kg) did not reveal any substantive differences in the incidence, severity, or PI judgments as to relatedness or severity of the AEs, or specific AEs. The infusion procedures themselves were well tolerated.

1.2.3 Dosing Regimen

[redacted]

[redacted]









2 STUDY OBJECTIVES

This is a Phase 2 study using dusquetide for the first time in Behçet's Disease (BD) patients. The objectives of the trial are to:

- Obtain preliminary evidence of the impact of dusquetide on oral and genital ulcer resolution in BD

- Obtain preliminary assessment of safety of dusquetide in patients with BD

3 STUDY ENDPOINTS

This is a pilot study to determine the efficacy and safety of SGX945 (dusquetide) in BD patients with oral and/or genital ulcers. No formal efficacy statistics will be performed. Results will be presented as tables and listings.

3.1 Efficacy Endpoints

- Proportion of patients with complete resolution of oral ulcers
- Proportion of patients with complete resolution of genital ulcers
- Number of genital ulcers over time throughout the 4-week treatment window (area under the curve)
- Number of oral ulcers over time throughout the 4-week treatment window (area under the curve)
- Time to complete resolution of genital ulcers (if present)
- Time to complete resolution of oral ulcers (if present)
- Time to complete resolution of any ulcers
- Time to recurrence or new occurrence of genital ulcers
- Time to recurrence or new occurrence of oral ulcers
- Change from Baseline score of pain due to genital ulcers
- Change from Baseline score of pain due to oral ulcers
- Change from Baseline score in the BD-QoL
- Change from Baseline score in the BDCAF
- Change from Baseline score in the BSAS
- Change from Baseline score in number of peripheral joints with arthralgia and severity of pain
- Change from Baseline score in number of peripheral joints with arthritis and the severity of swelling and tenderness
- Change from Baseline score in the PGA and PtGA of skin lesions

- Number of ulcers with a clinical diagnosis of infection
- Presence and severity of any scarring within 4 weeks post-treatment

Data will be compared to historical outcomes for each patient with respect to resolution of oral and genital ulcers (descriptive analysis) and historical resolution rates for both genital and oral ulcers in the literature.

3.2 Safety Endpoints

The safety variables evaluated will include:

- Clinical hematology assessments
- Clinical chemistry assessments
- Physical examinations
- Vital signs
- The number, time course, severity, relatedness, and types of Adverse Events (AEs) reported
- The number, time course, severity, relatedness, and types of Serious Adverse Events (SAEs) reported
- The number of infection adverse events categorized as distal or proximal to the site of ulceration

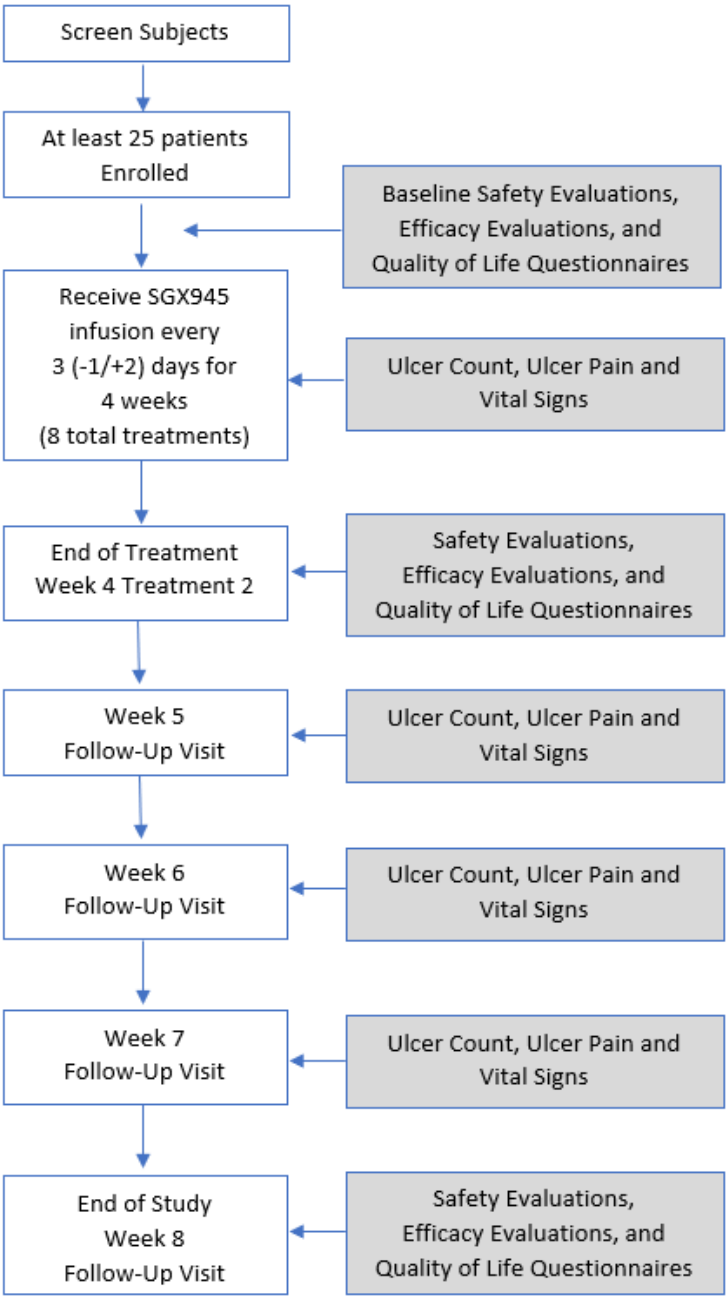
4 STUDY PLAN

4.1 Study Design

This will be an open-label trial enrolling patients with BD and a history of oral and/or genital ulcers with at least two oral ulcers and/or one genital ulcer at enrollment and with well documented details of prior treatments and responses to that treatment. Patients will receive dusquetide (1.5 mg/kg based on the patient's Baseline body weight) administered every 3 days (-1/+2) as a 4-minute infusion.

Patients will be treated for a total of 4 weeks (8 treatments), with weekly follow-up visits for an additional 4 weeks. At Baseline and at each visit, the number of genital ulcers, the number of oral ulcers, the pain due to oral ulcers, the pain due to genital ulcers, and vital signs will be recorded. Female patients will undergo a pelvic exam at the Baseline visit in order to note any genital ulcers that may be present internally. The pelvic exam will be repeated at Week 4 Treatment 2 and the Week 8 follow-up visit if the patient states that they have vaginal ulcers. At each infusion visit, vital signs will be collected once prior to the infusion, as well as four times post-infusion (every 5 minutes for 20 minutes). The degree of oral and genital ulcer scarring and quality of life and disease severity assessments (BD-QoL, BDCAF, BSAS, peripheral joint count and evaluation for tenderness and swelling, and both PGA and PtGA of skin lesions) will additionally be assessed at Baseline, at the last treatment visit (Week 4 Treatment 2) and at the last follow-up visit (Week 8). Physical examinations and safety labs (hematology and chemistry) will be analyzed at Baseline, at the last treatment visit (Week 4 Treatment 2) and at the last follow-up visit (Week 8). The BDHPQ will be assessed at the Baseline Visit and at the last treatment visit (Week 4 Treatment 2). AE's will be recorded throughout the study.

4.2 Study Schematic



4.3 Schedule of Assessments

The schedule of assessments for the trial are shown in Table 4, below.

Table 4: Schedule of Events

Assessment	Screen	W1[a] Baseline	W1 T1	W1 T2	W2 T1	W2 T2	W3 T1	W3 T2	W4 T1	W4 T2	*W5 FU[b]*	*W6 FU[b]*	*W7 FU[b]*	*W8 FU[b]*
Medical history[c]	X													
Informed Consent	X													
Entry Criteria	X	X												
Serum pregnancy[d]		X[e]								X				
Intravaginal assessment		X[f]								X[g]				X[g]
Infusion			X	X	X	X	X	X	X	X				
Genital ulcer count		X	X	X	X	X	X	X	X	X	X	X	X	X
Oral ulcer count		X	X	X	X	X	X	X	X	X	X	X	X	X
Genital VAS_{pain}		X	X	X	X	X	X	X	X	X	X	X	X	X
Oral VAS_{pain}		X	X	X	X	X	X	X	X	X	X	X	X	X
Genital scarring		X								X				X
Oral scarring		X								X				X
Vital signs		X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X	X	X
Interim Medical History/ AEs		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant drugs		X	X	X	X	X	X	X	X	X	X	X	X	X
BD-QoL		X								X				X
BDCAF		X								X				X

Assessment	**Screen**	**W1[a] Baseline**	**W1 T1**	**W1 T2**	**W2 T1**	**W2 T2**	**W3 T1**	**W3 T2**	**W4 T1**	**W4 T2**	***W5 FU[b]***	***W6 FU[b]***	***W7 FU[b]***	***W8 FU[b]***
BSAS		X								X				X
BDHPQ		X								X				
Joint assessments[i]		X								X				X
PGA and PtGA		X								X				X
Physical exam		X								X				X
Safety Labs[j]		X								X				X

[a] Baseline can be on the same day as the first infusion but ***MUST*** be prior to the first infusion
[b] FU = Follow-up Visit
[c] Medical history should include details of previous outbreaks
[d] Women of child bearing potential only
[e] This test must be completed and results reviewed within 30 days of starting treatment
[f] To be conducted on female patients only
[g] To be conducted on female patients only, if vaginal ulcers are present
[h] Vital signs will be collected once prior to the infusion, and four times post-infusion (every 5 minutes for 20 minutes)
[i] Joint assessment includes count and severity of swollen and tender peripheral joints
[j] Safety laboratory evaluations includes standard hematology and clinical chemistry panel

5 POPULATION

5.1 Number of Subjects

At least 25 patients will be enrolled in this Phase 2 study. Patients dropped from the study will not be replaced.

5.2 Inclusion Criteria

In order to be enrolled into the trial, subjects must meet ***all*** of the criteria below:

1. ≥18 years of age.

2. Patients must have a clinical diagnosis of BD meeting the International Study Group criteria.

3. Patients must have at least two oral ulcers and/or one genital ulcer on the day of randomization.

4. Patients willing to follow the clinical protocol and voluntarily give their written informed consent.

5. Female patients not pregnant or nursing and willing to undergo a pregnancy test prior to treatment initiation and at the end of the treatment period.

5.3 Exclusion Criteria

In order to be enrolled into the trial, subjects ***cannot*** have any of the following criteria:

1. Pregnancy or mothers who are breast-feeding.

2. All women of childbearing potential (WOCBP) and males with female partners who are WOCBP ***NOT WILLING*** to agree to the use of effective contraception during the trial.

    a. Women are considered to be WOCBP following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    Effective contraception methods for WOCBP should be started prior to enrollment and continued for a minimum of 35 days following completion of study drug administration.

    b. Acceptable contraceptive methods for WOCBP are those that achieve a failure rate of less than 1% per year and include:

i. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

(1) Oral

(2) Intravaginal

(3) Transdermal

ii. Progestogen-only hormonal contraception associated with inhibition of ovulation:

(1) Oral

(2) Injectable

(3) Implantable

iii. Intrauterine device (IUD)

iv. Intrauterine hormone-releasing system (IUS)

v. Bilateral tubal occlusion

vi. Vasectomized partner

vii. Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments

c. Male subjects should use condoms during treatment and for 98 days following the last study drug administration period.

3. Evidence of significant renal, hepatic, hematologic or immunologic disease determined by any one of the following (the below are examples of evidence of significant disease, not required tests):

a. Estimated creatinine clearance <30 mL/min

b. ALT or AST or total bilirubin greater than 3-fold the upper limit of normal

c. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy

d. Thrombocytopenia (<60,000 cells/mm^3)

e. CD4+ T-cell count <200 cells/μL (verification only required if there is a clinical diagnosis of HIV infection)

4. Subject has any condition that, in the judgment of the PI, is likely to interfere with participation in the study.

5. Use of any investigational medication within 4 weeks prior to enrollment or 5 pharmacokinetic/pharmacodynamic half-lives (whichever is longer).

6. Having received concomitant immune modulating therapy (except colchicine) within:

    a. Ten days prior to enrollment for azathioprine and mycophenolate mofetil

    b. Four weeks (28 days) prior to enrollment for cyclosporine, methotrexate, cyclophosphamide, thalidomide and dapsone

    c. Oral and topical corticosteroids must have been tapered as appropriate and discontinued 3 days prior to day of enrollment

    d. At least 5 terminal half-lives for all biologics including, but not limited to, those listed below; within:

        i. Four weeks prior to enrollment for etanercept

        ii. Eight weeks prior to enrollment for infliximab

        iii. Ten weeks prior to enrollment for adalimumab, golimumab, certolizumab, abatacept, and tocilizumab

        iv. Six months prior to enrollment for secukinumab

7. Having received oral or parenteral corticosteroids within 6 weeks (42 days) prior to enrollment.

8. Having received apremilast (Otezla®) within 4 weeks prior to enrollment.

9. Presence of non-BD related genital ulcers, including both infectious and non-infectious etiologies.

10. Active organ involvement requiring immunosuppressive treatment.

5.4 Deviation from Inclusion/Exclusion Criteria

Patients not meeting the entry criteria should not be enrolled. Any deviations from the entry criteria require written permission from both the PI and the Soligenix Medical Monitor.

6 STUDY CONDUCT

6.1 General Instructions

Patients will be treated every 3 days (-1/+2). Patients will receive a 25 mL infusion of 1.5 mg/kg of dusquetide diluted in 0.9% normal saline. The solution must be delivered using either a syringe pump or infusion pump over exactly 4 minutes with a constant infusion rate over that period. Patients should be observed for 20 minutes after each infusion with vital signs taken every 5 minutes.

6.2 Study Procedures by Time Point

6.2.1 Screening

During the screening visit, patients will be presented with the study details and the Informed Consent signed. A complete medical history will be completed, determining eligibility for enrollment. Details of the patient's previous outbreaks should be reviewed and as much detail as possible including the duration, severity, extent of involvement and treatment for the outbreaks collected. Patients will be informed that consistent oral hygiene is important to the management of their oral ulcers and recommended to brush their teeth at least 2 times per day in addition to daily flossing.

6.2.2 Week 1

6.2.2.1 Baseline

If the Baseline visit takes place on the same day as the first infusion treatment (which is acceptable), all Baseline measurements ***must be obtained PRIOR*** to the first dusquetide infusion. This includes the following procedures:

- History of any medical changes
- Collection of all concomitant medications
- Confirmation that the patient meets all inclusion and exclusion criteria
- Obtaining and reviewing the results of a serum pregnancy test for women of child-bearing potential (blood taken within the last 30 days)
- Genital ulcer count (including assessment of intravaginal region for female patients if genital ulcers are reported)
- Oral ulcer count
- Patient's completion of the Genital VAS_{pain} form

- Patient's completion of the Oral VAS_{pain} form
- Collection of the degree of genital scarring
- Collection of the degree of oral scarring
- Completion of the BD-QoL
- Completion of the BDCAF
- Completion of the BSAS
- Collection of the BDHPQ
- Collection of the count and severity of swollen and tender peripheral joints (arthritis)
- Collection of the count and severity of painful peripheral joints (arthralgia)
- Collection of the PGA and PtGA form
- Collection of blood for safety labs
- Physical examination
- Vital signs, including weight to determine study drug infusion dosing
- Collection of AEs

6.2.2.2 Treatment 1

Patients will come in to the clinic for their study drug infusion and the following will be performed:

- Genital ulcer count
- Oral ulcer count
- Patient's completion of the Genital VAS_{pain} form
- Patient's completion of the Oral VAS_{pain} form
- Pre-infusion vital signs (if Week 1 Treatment 1 occurs on the same day as Baseline, the vital signs taken for Baseline can serve as the pre-infusion vital signs)

- Infusion of dusquetide 1.5 mg/kg diluted in 0.9% normal saline in a total volume of 25 mL infused using either a syringe pump of infusion pump given at a consistent rate over exactly 4 minutes
- Vital signs taken every 5 minutes for 20 minutes after completion of the infusion
- Collection of AEs
- Collection of all concomitant medications

6.2.2.3 Treatment 2

Patients will come in to the clinic for their study drug infusion and the following will be performed:

- Genital ulcer count
- Oral ulcer count
- Patient's completion of the Genital VAS_{pain} form
- Patient's completion of the Oral VAS_{pain} form
- Pre-infusion vital signs
- Infusion of dusquetide 1.5 mg/kg diluted in 0.9% normal saline in a total volume of 25 mL infused using either a syringe pump of infusion pump given at a consistent rate over exactly 4 minutes
- Vital signs taken every 5 minutes for 20 minutes after completion of the infusion
- Collection of AEs
- Collection of all concomitant medications

6.2.3 Week 2 and Week 3

6.2.3.1 Treatment 1

Patients will come in to the clinic for their study drug infusion and the following will be performed:

- Genital ulcer count
- Oral ulcer count

- Patient's completion of the Genital VAS_{pain} form
- Patient's completion of the Oral VAS_{pain} form
- Pre-infusion vital signs
- Infusion of dusquetide 1.5 mg/kg diluted in 0.9% normal saline in a total volume of 25 mL infused using either a syringe pump of infusion pump given at a consistent rate over exactly 4 minutes
- Vital signs taken every 5 minutes for 20 minutes after completion of the infusion
- Collection of AEs
- Collection of all concomitant medications

6.2.3.2 Treatment 2

Patients will come in to the clinic for their study drug infusion and the following will be performed:

- Genital ulcer count
- Oral ulcer count
- Patient's completion of the Genital VAS_{pain} form
- Patient's completion of the Oral VAS_{pain} form
- Pre-infusion vital signs
- Infusion of dusquetide 1.5 mg/kg diluted in 0.9% normal saline in a total volume of 25 mL infused using either a syringe pump of infusion pump given at a consistent rate over exactly 4 minutes
- Vital signs taken every 5 minutes for 20 minutes after completion of the infusion
- Collection of AEs
- Collection of all concomitant medications

6.2.4 Week 4

6.2.4.1 Treatment 1

Patients will come in to the clinic for their study drug infusion and the following will be performed:

- Genital ulcer count
- Oral ulcer count
- Patient's completion of the Genital VAS_{pain} form
- Patient's completion of the Oral VAS_{pain} form
- Pre-infusion vital signs
- Infusion of dusquetide 1.5 mg/kg diluted in 0.9% normal saline in a total volume of 25 mL infused using either a syringe pump of infusion pump given at a consistent rate over exactly 4 minutes
- Vital signs taken every 5 minutes for 20 minutes after completion of the infusion
- Collection of AEs
- Collection of all concomitant medications

6.2.4.2 Treatment 2

Patients will come in to the clinic for their study drug infusion and the following will be performed:

- Genital ulcer count (including assessment of intravaginal region for female patients if genital ulcers are reported)
- Oral ulcer count
- Serum pregnancy test for women of child-bearing potential
- Patient's completion of the Genital VAS_{pain} form
- Patient's completion of the Oral VAS_{pain} form
- Pre-infusion vital signs

- Infusion of dusquetide 1.5 mg/kg diluted in 0.9% normal saline in a total volume of 25 mL infused using either a syringe pump of infusion pump given at a consistent rate over exactly 4 minutes
- Vital signs taken every 5 minutes for 20 minutes after completion of the infusion
- Collection of the degree of genital scarring
- Collection of the degree of oral scarring
- Completion of the BD-QoL
- Completion of the BDCAF
- Completion of the BSAS
- Collection of the BDHPQ
- Collection of the count and severity of swollen and tender peripheral joints (arthritis)
- Collection of the count and severity of painful peripheral joints (arthralgia)
- Collection of the PGA and PtGA form
- Collection of blood for safety labs
- Physical examination
- Collection of AEs
- Collection of all concomitant medications

6.2.5 Week 5 (Follow-up Visit 1), Week 6 (Follow-up Visit 2), and Week 7 (Follow-up Visit 3)

Patients will come in to the clinic for their follow-up visit and the following will be performed:

- Genital ulcer count
- Oral ulcer count
- Patient's completion of the Genital VAS_{pain} form
- Patient's completion of the Oral VAS_{pain} form

- Vital signs
- Collection of AEs
- Collection of all concomitant medications

6.2.6 Week 8, Follow-up Visit 4

Patients will come in to the clinic for their follow-up visit and the following will be performed:

- Genital ulcer count (including assessment of intravaginal region for female patients if genital ulcers are reported)
- Oral ulcer count
- Patient's completion of the Genital VAS_{pain} form
- Patient's completion of the Oral VAS_{pain} form
- Vital signs
- Collection of the degree of genital scarring
- Collection of the degree of oral scarring
- Completion of the BD-QoL
- Completion of the BDCAF
- Completion of the BSAS
- Collection of the count and severity of swollen and tender peripheral joints (arthritis)
- Collection of the count and severity of painful peripheral joints (arthralgia)
- Collection of the PGA and PtGA form
- Collection of blood for safety labs
- Physical examination
- Collection of AEs
- Collection of all concomitant medications

6.3 Premature Discontinuation

Patients have the right to withdraw from this trial at any time (as described in the informed consent document) without prejudice to further care. An investigator may terminate a patient's treatment during the study at any time for any of the following reasons:

- The patient develops an adverse event whose severity starts with or develops into a Grade 2 (Moderate) or Grade 3 (Severe) event. The decision to terminate treatment will be made by the investigator in conjunction with the patient.
- The patient is lost to follow-up and will not attend further study visits.
- The investigator determines that further participation would be detrimental to the patient's health or well-being.
- The patient fails to comply with the study requirements to cause harm to self or seriously interfere with the validity of the study results.
- The female patient becomes pregnant during the treatment period. In this case, treatment should be halted and the patient followed until the end of the pregnancy. If a child is born, the infant should be followed through at least 6 months of age.
- At the discretion of the site investigator if he/she feels that it is in the best medical interest of the patient.

Patients withdrawn from the study or whose treatment is terminated will have as many of the trial assessments completed as the patient permits. Patients withdrawn from the trial will not be replaced.

The study may be terminated early for any of the following reasons:

- A health authority requests termination of the study.
- It has been determined that the risk level associated with the experimental drug is significant and warrants termination of the study.
- Soligenix, for reasons other than safety, may terminate the study at any time by written notice of intended termination provided at least thirty (30) days prior to termination.
- The investigator or IRB/IEC, for reasons other than safety, may terminate participation of this site in the study by written notice of intended termination provided at least thirty (30) days prior to termination.
- Any other clause described in the individual site Study Agreement (eg, if GCPs or other regulatory procedures are not followed; if enrollment rate is not sufficient to meet study goals).

7 DESCRIPTION OF STUDY PROCEDURES

7.1 Behçet's Disease Current Activity Form (BDCAF)

The Behçet's Disease Current Activity Form (BDCAF) is the most widely utilized instrument to assess BD activity in patients with BD. The instrument assesses all aspects of BD including ulcers, GI, neurologic and eye disease. A copy of the form is presented in Appendix III – Behçet's Disease Current Activity Form (BDCAF) on page 80. This will be completed at Baseline, the end of treatment (Week 4 Treatment 2), and at the end of follow-up (Week 8).

7.2 Leeds Behçet's Disease Quality of Life (BD-QoL) Assessment

The BD-QoL is a BD specific quality of life instrument that has been validated and translated into several languages (Gilworth 2004). This is a patient self-administered questionnaire consisting of 30 questions. A copy of the BD-QoL form will be provided to the site. This will be completed at Baseline, the end of treatment (Week 4 Treatment 2), and at the end of follow-up (Week 8). A copy of this form is presented in Appendix IV – Leeds Behçet's Disease Quality of Life (BD-QoL) Assessment on page 83.

7.3 Behçet's Syndrome Activity Score (BSAS)

The BSAS is a validated activity score (Forbess 2008) which consists of a patient self-administered questionnaire with 10 questions scored out of a total of 100. Questions 1, 3, 5 and 10 are scored 0 to 10, Questions 2, 4 and 6 are scored 0, 5 or 10 depending on which of the 3 choices are selected and Questions 7, 8 and 9 are scored 0 or 10. A copy of the form is presented in Appendix VII – Behçet's Syndrome Activity Score on page 87. This will be completed at Baseline, the end of treatment (Week 4 Treatment 2) and at the end of follow-up (Week 8).

7.4 Behçet's Disease History Patient Questionnaire (BDHPQ)

The BDHPQ questionnaire is designed to establish an understanding of the historical clinical course of previous oral and/or genital flares at Baseline and a patient's perception of the current flare at end of treatment. The BDHPQ is comprised of 21 questions that will be asked at Baseline (Appendix VIII – Behçet's Disease History Patient Questionnaire - Baseline on page 89) and 9 questions that will be asked at the end of treatment (Appendix IX – Behçet's Disease History Patient Questionnaire - End of Treatment on page 93).

7.5 Ulcer Count

The number of oral and genital ulcers should be counted at each visit from Baseline onward and the number of new lesions in each location should be noted at each visit. It will also be noted if any of the ulcers have a clinical diagnosis of infection.

7.6 Visual Assessment Score of Pain (VAS_{pain})

Patients will be asked to grade the amount of pain associated with genital and oral ulcers using a Visual Analog Score (VAS). Patients will be asked to mark on a line exactly 10 cm long where the level pain for each ulcer location that they have experienced over the last 24 hours with the ends of the scale labelled as "No pain" to the "Worst pain imaginable". A copy of the form is presented in Appendix V – VASpain Form on page 85. This will be noted at each visit from Baseline onward.

7.7 Ulcer Scarring Assessment

The percent of ulcers leading to scarring should be noted. The degree of scarring should be graded as:

Table 5: Grading of Ulcer Scarring

Scarring Score	Description
0	No scarring
1	Mild scarring
2	Moderate scarring
3	Severe scarring

This will be completed at Baseline, the end of treatment (Week 4 Treatment 2), and at the end of follow-up (Week 8).

7.8 Joint Assessment

The number of joints with patient reports of pain (arthralgias) will be noted and the number of joints with evidence of swelling (arthritis) will be collected. The number of affected joints will be counted using the 28 Joint Count of the Disease Activity Score (Pisaniello 2022). This is the most common method for joint counts in Rheumatology and the simplest. Assessed joints are:

- Shoulders
- Elbows
- Wrists
- Metacarpophalangeal joints
- Proximal interphalangeal joints
- Knees

Each of the joints in the above areas should be assessed for swelling (arthritis) and pain (arthralgia). The severity of each swelling and tenderness should be captured as the worse score and the percentage of joints with findings using the following:

Table 6: Joint Grading

Score	Description
0	No findings
1	Mild
2	Moderate
3	Severe

7.9 Global Assessment

Both a Physician Global Assessment (PGA) and Patient Global Assessment (PtGA) will be assessed through a single question ("How active was your/the patient's BD during the last week?") on an anchored 10-cm visual analogic (0.5-cm graded), where 0 corresponded to "no disease activity" and 10 to "the highest disease activity." (Floris 2020). A copy of the form is presented in Appendix VI – Global Assessment Form on page 86. This will be completed at Baseline, the end of treatment (Week 4 Treatment 2), and at the end of follow-up (Week 8).

7.10 Vital Signs

Vital signs will be obtained by site personnel at every visit from Baseline onward. On all infusion visits (Week 1 Treatment 1 through Week 4 Treatment 2), vital signs will be collected once prior to the infusion, and four times post-infusion (every 5 minutes for 20 minutes). Vital signs obtained will consist of:

- Resting Blood Pressure while sitting
- Heart Rate
- Respiratory Rate

7.11 Clinical Laboratory Tests

7.11.1 Hematology Tests

The hematology panel will be performed at the local Laboratory on samples collected at Baseline, the end of treatment during the second infusion visit in Week 4, and the last follow-up visit in Week 8. The panel will consist of the following tests:

- Red blood cell count (RBC)
- Hematocrit

- Hemoglobin
- RBC indices
- Platelet count
- White blood cell count (WBC)
- WBC differential count

7.11.2 Clinical Chemistry Laboratory Tests

The clinical chemistry panel will be performed at the local Laboratory on samples collected at Baseline, the end of treatment during the second infusion visit in Week 4, and the last follow-up visit in Week 8. The panel will consist of the following tests:

- Serum sodium
- Serum potassium
- Serum chloride
- Serum bicarbonate (CO_2)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Alkaline phosphatase
- Total protein
- Serum creatinine
- Blood urea nitrogen (BUN)

7.12 Serum Pregnancy Test

A serum pregnancy test will be collected for all women of child bearing potential only (WOCBP) at Baseline and at the end of treatment (Week 4 Treatment 2).

7.13 Physical Exam

A complete Physical Exam will be conducted at Baseline, the end of treatment (Week 4 Treatment 2), and at the end of follow-up (Week 8).

8 STUDY DRUG MANAGEMENT

8.1 Description

8.1.1 Formulation

[redacted]

8.1.2 Storage

Study drug is to be stored at room temperature 15-30°C (59-86°F).

8.2 Packaging and Shipment

A description of the SGX945 study drug is given in Table 7 below.

[redacted]

8.3 Dose and Administration

[redacted]



8.4 Accountability

The PI and responsible site Pharmacist must ensure that all investigational product is kept under lock and key with access limited to those authorized by the investigator. The PI must maintain accurate records of the receipt of all study medication received, including date received, vial number, amount received, and disposition of all study medication. Dispensing records will be maintained and include date and amount of medication dispensed, identification code of the patient receiving the medication, and any amount of medication not used or returned (or lost) and the vial number for each vial dispensed. Empty and unused vials should be stored and will be monitored by Soligenix for Drug Accountability purposes. All remaining medication not required to be held by the clinical facility, must be destroyed following all appropriate regulatory guidelines, or returned to Soligenix immediately after the study is completed. Any lost, spilled or missing drug must be documented.

8.5 Prohibited Concomitant Therapy

Current maintenance therapy for BD (eg, colchicine) should be maintained, except for those medications noted in the Exclusion Criteria. No new BD specific medications, other than planned study drug, should be initiated or discontinued without discussion with the Sponsor.

8.6 Compliance

The IV infusion will be documented in the source documentation and Case Report Form.

9 ADVERSE EVENTS

Timely, accurate and complete reporting and analysis of safety information from trials is crucial for the protection of subjects, investigators and the Sponsor, and is mandated by regulatory agencies worldwide. Soligenix has established standard operating procedures (SOPs) in conformity with regulatory requirements to ensure appropriate reporting of safety information. All trials that are the responsibility of Soligenix must be conducted in accordance with the procedures as provided below.

9.1 Definitions

9.1.1 Adverse Experience (AE)

Any noxious or unintended event that occurs in association with the use of an investigational agent in humans***, whether considered related to the investigational agent or not.*** This definition encompasses symptoms or signs reported by the subject or detected by the Investigator or other competent observer, as well as medically important deviations from normality in the results of ancillary investigations. If present at time of first dose of study drug, such AEs must be recorded as part of the medical history.

9.1.2 Treatment-Emergent AE

An AE that is new in onset or aggravated in severity or frequency following entry into the study. In addition, any pathological finding on physical examination or diagnostic procedure that is new in occurrence or exacerbated in comparison with the subject's status at study entry is considered a treatment-emergent AE if it requires any medical or surgical intervention whatsoever (including, but not limited to, additional diagnostic procedures or alteration of prescribed therapy).

9.1.3 Potentially Serious Adverse Experience

Any AE that is sufficiently severe or alarming as to require any form of significant medical intervention. Note: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed in the SAE definition.

9.2 Relationship to Study Drug

The relationship of an AE to the assigned study drug is assessed using the following definitions:

Not Related: The drug experience is clearly related to other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs.

Possibly Related: The drug experience follows a reasonable sequence from the time of drug administration and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the

patient's/subject's clinical state, therapeutic interventions or concomitant drugs.

Related: The drug experience follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs.

9.3 Severity of Adverse Event

A clinical determination of the intensity of an AE should be done for all reported AEs. The severity assessment for AEs should be completed using the following definitions as guidelines:

Mild: Awareness of sign or symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

Severe: Incapacitating with inability to work or do usual activity.

Not applicable: In some cases, an AE may be an "all or nothing" finding, which cannot be graded.

9.4 Recording Adverse Events

All AEs, whether judged to be related or not to the study drug, should be recorded in both the medical record and the CRF. The start and resolution dates, the judgment of the severity of the AE, the judgment of the relationship of the AE to the study drug, the action taken for subsequent dose of study drug, and the outcome should be noted. Any presence of new BD organ involvement during the study (including the follow-up visits) will be recorded as an AE.

10 SERIOUS ADVERSE EVENT

10.1 Definition of Serious Adverse Event

A SAE is any event that meets any of the following criteria:

1. Death
2. Life-threatening
3. Inpatient hospitalization or prolongation of existing hospitalization
4. Persistent or significant disability/incapacity
5. Congenital anomaly/birth defect in the offspring of a subject who received SGX945
6. Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
    a. Intensive treatment in an emergency room or at home for allergic bronchospasm
    b. Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    c. Development of drug dependency or drug abuse

10.2 Definition of Terms

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred; ie, it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalization signifies that the subject has been detained (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. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

10.3 Reporting Serious Adverse Events

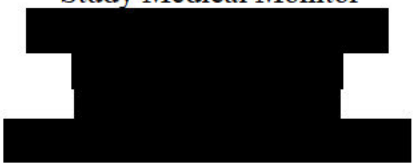
When the Investigator, or trained designee, becomes aware that a serious or potentially serious AE (as defined above) has occurred, the site monitor or Medical Monitor must be notified ***immediately*** (and no later than 24 hours after notification) by telephone, regardless of the relationship (or lack thereof) of the AE to study therapy.

All reports of serious or potentially serious AEs must be followed within 24 hours (or sooner at the request of the Soligenix Medical Monitor) by the completion of a serious AE form signed by the investigator. This should be emailed to the site monitor and/or Medical Monitor.

In accordance with Soligenix SOPs and Health Authority regulations, investigators may be notified from time to time of the occurrence of serious, unexpected AEs. If such AEs are associated with the use of the study drug (ie, there is a reasonable possibility that the AE may have been caused by the drug) and are thus deemed significant new AEs or risks with respect to the drug, the investigator must promptly inform the relevant Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), in accordance with the ICH Guidance on Good Clinical Practices (E6, April 1996).

FOR SAE REPORTING OR MEDICAL QUESTIONS
THE MEDICAL MONITOR SHOULD BE CONTACTED:

Richard Straube, MD
Senior Vice President & Chief Medical Officer,
Study Medical Monitor



If above contact is not accessible, please call:
Soligenix, Inc., 29 Emmons Drive, Suite B-10, Princeton, NJ 08540
Phone: (609) 538-8200

FOR ADDITIONAL ASSISTANCE:
For additional assistance, please contact your clinical research monitor(s) OR
Christopher Pullion, DO
Medical Director



11 STATISTICS

11.1 General Procedures

This is an open-label, pilot trial and no formal statistics are planned.

11.2 Sample Size

A sample size of at least 25 was chosen as enough patients to assess the observed rates in the trial while being of a feasible size in this orphan disease.

11.3 Statistical Methods

All results will be presented as the mean, standard deviation, and 95% confidence interval for continuous variables and the median, maximum and minimum values and the 95% confidence interval for dichotomous variables.

11.4 Interim Analysis

No interim analysis will be done.

12 ETHICS AND RESPONSIBILITIES

12.1 Good Clinical Practice

The study will be performed in accordance with the ethical principles in the Declaration of Helsinki (Appendix II – Declaration of Helsinki), Good Clinical Practices (GCPs) and applicable regulatory requirements.

12.2 Institutional Review Board/Independent Ethics Committee

The final study protocol, including the final version of the Subject Information and Consent Forms, must be approved in writing by an IRB/IEC that meets the minimum FDA standards before enrollment of any subject into the study. The PI or their designee is responsible for informing the IRB/IEC of any SAE and amendment(s) to the protocol as per regulatory requirements.

12.3 Informed Consent

The Investigator will ensure that the subject or a legally authorized representative of the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. ***The subject's signed and dated informed consent must be obtained before conducting any study specific procedure***. The consent form that is used must meet the requirements as outlined in the ICH Guidance on GCPs (E6) and must be approved by both the reviewing IRB/IEC and by Soligenix.

12.4 Subject data protection

The Subject Information and Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality. Subjects in this database will be identified by initials or enrollment code/subject number only. Authorized representatives of a regulatory authority (eg, FDA) may require direct access to parts of the trial site records relevant to the study, including subjects' medical history for data verification purposes.

12.5 Financial Disclosure

The FDA has issued regulations (21 CFR Part 54) that require Sponsors (in this case Soligenix) to submit complete and accurate certification or disclosure statements to certify the absence of certain financial interests of clinical investigators and/or disclose those financial interests, as required, when clinical studies are submitted to the FDA in support of marketing approval of a new drug application (NDA). These regulations are intended to ensure that financial interests and arrangements of clinical investigators, that

could affect reliability of data submitted to the FDA in support of marketing approval, are identified and disclosed by the Sponsor.

Clinical investigators shall be asked to disclose proprietary (eg, patent, licensing agreement) and financial (eg, stock options, royalty) interests as they pertain to Soligenix, prior to participating in the study. In addition, clinical investigators will be required to consult with Soligenix before acquiring any financial interest in the company and must disclose any change in their proprietary or financial interests if it occurs during the course of the study and for one year following study completion. Clinical Investigator is defined under Title 21 CFR Part 54 as an investigator or sub-investigator listed on the FDA Form 1572 that is directly involved in the treatment or evaluation of research subjects. The requirement for proprietary and financial disclosure also includes any ownership by the spouse or any dependent child of the investigator.

If the FDA determines that the financial interests of any clinical investigator raise serious questions about the integrity of the data, the FDA will take any action it deems necessary to ensure the reliability of the data, including:

1. Initiating agency audits of the data derived from the clinical investigator in question;

2. Requesting that the Sponsor submit further analyses of data, eg, to evaluate the effect of the clinical investigator's data on overall study outcome;

3. Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and/or

4. Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

If the Sponsor does not include certification or disclosure, or both, if required, or does not certify that it was not possible to obtain the information, the FDA may refuse to file the NDA.

13 RECORDS MANAGEMENT

13.1 Source Documentation

Original source documents include all informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses and dates of therapy prior to and during this study, drug dispensing/disposition records which are used to support the data recorded CRFs of each subject. When possible, all data should be documented in an original source document and copied into the CRF.

13.2 Study Files and Record Retention

Copies of CRFs should be retained by sites along with all original source documents (eg, informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses and dates of therapy prior to and during this study, drug dispensing/disposition records) that support CRFs of each subject must be retained in the files of the responsible investigator or in hospital records for a minimum of two (2) years following notification by Soligenix that all investigations have been discontinued or that the last approval of a marketing application has been obtained.

If the responsible investigator retires, relocates, or for other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Soligenix must be notified in writing of the name and address of the new custodian.

14 AUDITING AND MONITORING

14.1 Study Monitoring

It is the responsibility of the PI and site personnel to assure that the data recorded in the CRF is accurate, complete and can be verified from the medical records.

In accordance with the Guidelines for the Monitoring of Clinical Investigations presented in the ICH Guidance on GCPs (E6), Soligenix will select, either directly or through subcontract, qualified individuals to monitor the progress of the study and adherence to protocol by the individual clinical sites.

It is the responsibility of the PI to assure that, at mutually agreed upon times, the clinical monitor has appropriate access to all medical records, study materials, study and regulatory binders, laboratory and radiographic results, study personnel, their time to allow adequate assessment as to the quality, completeness and adherence to all aspects of the protocol.

14.1.1 Pre-study Evaluation

This initial encounter with the site will establish that the site has all of the necessary elements to successfully participate in the proposed protocol including adequately trained staff, adequate free time of the staff, adequate facilities for safe and proper trial conduct, evidence for potential enrollment of suitable patients, adequate research pharmacy support, the presence of an IRB/IEC meeting the local and FDA requirements, and a commitment for training of all involved staff on the protocol.

14.1.2 Site Initiation Visit

Once all required trials documents have been processed, the Medical Monitor (or trained designee) will initiate the study after on-site training of the participating staff at the institution. Topics covered will include training on:

- The investigational status of the study drug and the requirements for its accountability.
- Background on the study drug.
- Details of the protocol including patient selection, study drug administration, procedures to be performed, and visit schedules.
- Critical nature of obtaining informed consent in accordance with the Declaration of Helsinki and ICH Guidance on GCPs (E6) before enrolling each subject in the study.
- The obligation to ensure IRB/IEC review and approval for the study, including the protocol, amendments, ICF and any advertisements, is obtained prior to its initiation at his/her clinical site, to ensure continuing review of the study by the IRB/IEC, and to keep Soligenix informed of such approval and subsequent actions concerning the study.

14.1.3 Monitoring Visits

Soligenix or their trained designee will perform at least three (3) monitoring visits. At these visits, the site monitor will compare the data entered into the CRFs with the source documents and check for protocol compliance including a record of informed consent, enrollment criteria, all subject assessments, all AEs and all concomitant medications. In addition, study drug and supporting records will be reviewed. Additionally, they assure that all serious, life-threatening or fatal AEs are being reported immediately [and in no case later than twenty-four (24) hours after the event] to the Medical Monitor or designee at Soligenix.

Findings from these reviews will be discussed with the investigator and staff. Completed pages of the CRFs will be evaluated at each visit. The dates of the monitoring visits will be recorded in a sign-in log that will be kept at the site. The study coordinator and investigator are expected to be available for questions, the source documentation readily available, and a suitable environment provided for review of study-related documents.

14.1.4 Close-out Visit

The clinical research monitor(s) will perform an end of trial visit to ensure that:

- All drug reconciliation forms are accurate and complete.
- All unused study drug is returned to the appropriate location.
- All data issues are resolved and CRFs are completed and verified.
- The IRB/IEC has been notified that the study has been completed.
- The investigator at each site is aware that the study has been completed and no further subjects are enrolled.

14.2 Audits and Inspections

Health Authorities (eg, FDA), in the person of a trained and properly authorized employee, may request access to all study records, including source documents, for inspection and copying. The investigator will immediately notify Soligenix of any upcoming inspections.

Periodic auditing inspections may also be conducted by a representative of the Quality Assurance Department of Soligenix or its designee(s).

15 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Soligenix. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Soligenix will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Soligenix, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

16 STUDY REPORT AND PUBLICATIONS

Soligenix is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

Soligenix's publication policy is discussed in the investigator's Clinical Research Agreement. It is expected that the results of the trial will be published in a peer-reviewed medical journal with the PI of the study listed as the primary author,

17 STUDY DISCONTINUATION

Both Soligenix and the Principal Investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Soligenix or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, Soligenix and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

18 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Soligenix. However, authorized regulatory officials, IRB/IEC personnel, Soligenix and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by initials, screening and treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

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20 APPENDICES

20.1 Appendix I – Names of Study Personnel

Sponsor:	Soligenix, Inc. 29 Emmons Drive Princeton, NJ 08540
Medical Monitors:	Richard Straube, MD 29 Emmons Drive Princeton, NJ 08540 [redacted]
	Christopher Pullion, DO 29 Emmons Drive Princeton, NJ 08540 [redacted]

20.2 Appendix II – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles

for

Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for

them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

20.3 Appendix III – Behçet's Disease Current Activity Form (BDCAF)

ISBD
International Society for Behcet's Disease

BEHÇET'S DISEASE CURRENT ACTIVITY FORM 2006

Date: Name: Sex: M/F
Centre: Telephone Date of birth:
Country:
Clinician: Address:

All scoring depends on the symptoms present over the **4 weeks** prior to assessment.
Only clinical features that the **clinician feels are due to Behçet's Disease** should be scored.

PATIENT'S PERCEPTION OF DISEASE ACTIVITY
(Ask the patient the following question:)

"Thinking about your Behçet's disease only, which of these faces expresses how you have been feeling over the last four weeks? "(Tick one face)



HEADACHE, MOUTH ULCERS, GENITAL ULCERS, SKIN LESIONS, JOINT INVOLVEMENT AND GASTROINTESTINAL SYMPTOMS

Ask the patient the following questions and fill in the related boxes **"Over the past 4 weeks have you had?"**

(please tick one box per line)

	not at all	Present for up to 4 weeks
Headache		
Mouth Ulceration		
Genital Ulceration		
Erythema		
Skin Pustules		
Joints - Arthralgia		
Joints - Arthritis		
Nausea/vomiting/abdominal pain		
Diarrhoea+altered/frank blood per rectum		

EYE INVOLVEMENT
(Ask questions below)

		(please circle) Right Eye		Left Eye	
"Over the last 4 weeks have you had?"	a red eye	No	Yes	No	Yes
	a painful eye	No	Yes	No	Yes
	blurred or reduced vision	No	Yes	No	Yes

If any of the above is present: "Is this new"? No Yes
(circle the correct answer)

NERVOUS SYSTEM INVOLVEMENT (include intracranial vascular disease)

New Symptoms in nervous system and major vessel involvement are defined as those not previously documented or reported by the patient
(Ask questions below)

Over the last 4 weeks have you had any of the following?	*please circle*		tick if new
blackouts	No	Yes	
difficulty with speech	No	Yes	
difficulty with hearing	No	Yes	
blurring of/double vision	No	Yes	
weakness/loss of feeling of face	No	Yes	
weakness/loss of feeling of arm	No	Yes	
weakness/loss of feeling of leg	No	Yes	
memory loss	No	Yes	
loss of balance	No	Yes	

Is there any evidence of new active nervous system involvement? No Yes

MAJOR VESSEL INVOLVEMENT(exclude intracranial vascular disease)
(Ask question below)

"Over the last 4 weeks have you had any of the following?"	*please circle*		tick if new
had chest pain	No	Yes	
had breathlessness	No	Yes	
coughed up blood	No	Yes	
had pain/swelling/discolouration of the face	No	Yes	
had pain/swelling/discolouration of the arm	No	Yes	
had pain/swelling/discolouration of the leg	No	Yes	

Is there evidence of new active major vessel inflammation? No Yes

CLINICIAN'S OVERALL PERCEPTION OF DISEASE ACTIVITY

Tick one face that expresses how you feel the patient's disease has been over the last 4 weeks.



BEHÇET'S DISEASE ACTIVITY INDEX

Add up all the scores which are highlighted in blue (front page items, one tick = score of 1 on index, all other items score 'yes' = 1. You should now have a score out of 12 which is the patient's Behçet's Disease Activity Index Score.

SCORE

Patients index score	0	1	2	3	4	5	6	7	8	9	10	11	12
Transformed index score on interval scale	0	3	5	7	8	9	10	11	12	13	15	17	20

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Explanation to doctor completing the form;

1. Use your clinical judgment recording only those features you believe are due to Behcet's disease.

2. Please explain to the patient the meaning of the words used, if necessary.

3. If there is pain in a joint (whether or not there is swelling etc) score 'arthralgia'.

4. If there is swelling or inflammation of a joint score 'arthritis'. Thus you can score 'arthralgia' and 'arthritis'.

5. The form concerns the impairments relating to Disease Activity. It is produced by Rasch analysis and is psychometrically robust. It is not measuring the impact of the disease activity.

20.4 Appendix IV – Leeds Behçet's Disease Quality of Life (BD-QoL) Assessment

BD-QoL

Date:

Name:_____ Age:_____Sex: _____

On the following pages you will find some statements which have been made by people who have Behçet'sDisease

Instructions: This questionnaire consists of 30 statements. Please read each statement carefully, and then choose **True** if the statement applies to you and choose **Not True** if it does not apply to you **at the moment**. Circle the appropriate number.

1. **My life revolves around hospital visits**
   1 True
   0 Not True

2. **Nothing interests me**
   1 True
   0 Not True

3. **It's too much effort to go out and see people**
   1 True
   0 Not True

4. **Walking is painful**
   1 True
   0 Not True

5. **It takes me longer to do things**
   1 True
   0 Not True

6. **I cannot stand for long**
   1 True
   0 Not True

7. **My condition interferes with my life**
   1 True
   0 Not True

8. **It is difficult to get out of bed**
   1 True
   0 Not True

9. **I feel terrible about the way I look**
   1 True
   0 Not True

10. **Talking is stressful**
    1 True
    0 Not True

11. **I feel dependent on others**
    1 True
    0 Not True

12. **I feel older than my years**
    1 True
    0 Not True

13. **It limits the places I can go**
    1 True
    0 Not True

14. **I find it difficult to take care of the people I am close to**
    1 True 0 Not True

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Continue on Back

15. I cannot rely on how I will be tomorrow
    1 True
    0 Not True

16. My condition is drastically affecting my life
    1 True
    0 Not True

17. I often get frustrated
    1 True
    0 Not True

18. I feel like a prisoner in my own home
    1 True
    0 Not True

19. My condition affects important decisions in my life
    1 True
    0 Not True

20. I don't like being touched
    1 True
    0 Not True

21. I cannot speak properly
    1 True
    0 Not True

22. It puts a strain on my personal relationships
    1 True
    0 Not True

23. I feel useless
    1 True
    0 Not True

24. I worry that I hold others back
    1 True
    0 Not True

25. People close to me have lost out because of my condition
    1 True
    0 Not True

26. I feel unable to cope with my condition
    1 True
    0 Not True

27. I have lost contact with people
    1 True
    0 Not True

28. I worry about the effects on others
    1 True
    0 Not True

29. Everything is getting to me today
    1 True
    0 Not True

30. I feel lonely
    1 True
    0 Not True

20.5 Appendix V – VAS_{pain} Form

Pain Score

Please indicate if you have had any ulcers over the last 24 hours and, if you have had ulcers, draw a vertical mark on the scale below indicating the degree of pain you had from your ulcers.

Genital Ulcers

☐ I have no genital ulcers ☐ I have genital ulcers (please fill in the scale below)

No pain |_____| The worst imaginable pain

Mouth Ulcers

☐ I have no mouth ulcers ☐ I have mouth ulcers (please fill in the scale below)

No pain |_____| The worst imaginable pain

20.6 Appendix VI – Global Assessment Form

Physician Global Assessment (PGA)

How active was the patient's Behçet's Disease during the last week?

No disease activity |_____| The highest disease activity

Patient Global Assessment (PtGA)

How active was your Behçet's Disease during the last week?

No disease activity |_____| The highest disease activity

20.7 Appendix VII – Behçet's Syndrome Activity Score (BSAS)

Behçet's Syndrome Activity Scale (BSAS)

Your name:_____ **Date of Birth:** _____ **Today's Date:**_____

Your: SEX: ☐ Female ☐ Male **ETHNIC** ☐ Asian ☐ Hispanic ☐ Other _____ **GROUP:** ☐ Black ☐ White

1. How much have **ulcers in your mouth** bothered you over the last 4 weeks? Please indicate below

NO ULCERS ○○○○○○○○○○○○○○○○○○○○ **ULCERS WERE A MAJOR PROBLEM**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

2. How many **ulcers (new or old)** did you have in your **mouth** over the last 4 weeks?
0 ☐
1-3 ☐
More than 3 ☐

3. How much has **ulcers in genital area** bothered you over the last 4 weeks? Please indicate below

NO ULCERS ○○○○○○○○○○○○○○○○○○○○ **ULCERS WERE A MAJOR PROBLEM**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

4. How many **ulcers (new or old)** did you have in your **genital area** over the last 4 weeks?
0 ☐
1-3 ☐
More than 3 ☐

5. How much has **acne or acne like skin lesions (new or old)** bothered you over the last 4 weeks? Please indicate below

NO SKIN LESIONS ○○○○○○○○○○○○○○○○○○○○ **SKIN LESIONS WERE A MAJOR PROBLEM**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

6. How many **acne or acne like skin lesions (new or old)** did you have over the last 4 weeks?
0 ☐
1-5 ☐
More than 5 ☐

7. Have you had **abdominal pain and diarrhea** lasting most of the day for most days of the week over the last 4 weeks?
☐**No** ☐ **Yes**

8. Did you have **painful or red eyes and/or blurred or reduced vision** over the last 4 weeks?
☐**No** ☐ **Yes**

9. Did you have any **swelling/discoloration of your lower extremities, or a blood clot** over the last 4 weeks?
☐**No** ☐ **Yes**

10. In terms of your **Behcet's activity, (oral ulcers, genital ulcers, skin problems, joint pains, eye, neurologic problems),** how active would you say your condition has been over the last 4 weeks?

NOT ACTIVE AT ALL ○○○○○○○○○○○○○○○○○○○○ **EXTREMELY ACTIVE**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

Scoring:

Questions 1, 3, 5, and 10 are scored 0-10

Questions 2, 4, 6, are scored 0, 5 or 10 depending on which of the 3 are checked

Questions 7, 8, 9 are scored 0 or 10

For a total score of 100

20.8 Appendix VIII – Behçet's Disease History Patient Questionnaire - Baseline

Behçet's Disease History Patient Questionnaire
Protocol DUS-AUBD-01
Baseline

Patient ID: _____ Today's Date ___ ___/ ___ ___/ 202___

Please check the box to indicate your answer to each of the questions:

1. How many episodes of BD oral (mouth) ulcers have you had?
   - ☐ None
   - ☐ First episode
   - ☐ 1-3 episodes
   - ☐ 4-10 episodes
   - ☐ More than 10 episodes
   - ☐ Not applicable

2. How often do you get BD oral (mouth) ulcers?
   - ☐ Never
   - ☐ Less than 1 time every 3 years
   - ☐ Every 2-3 years
   - ☐ 1 time per year
   - ☐ 2 to 4 times per year
   - ☐ Every month
   - ☐ Not applicable

3. How long do your BD oral (mouth) ulcers last?
   - ☐ 1 to 6 days
   - ☐ 7 to 10 days
   - ☐ 2 to 3 weeks
   - ☐ 4 to 6 weeks
   - ☐ >6 weeks
   - ☐ Not applicable

4. On a scale of 0 (no pain) to 10 (the worst imaginable pain), how painful are your typical episodes of BD oral (mouth) ulcers?
   - ☐ 0 to 3
   - ☐ 4 to 6
   - ☐ 7 or 8
   - ☐ 9 or 10
   - ☐ Not applicable

5. When was the last episode of BD oral (mouth) ulcers that you have had?
   - ☐ Less than 2 weeks ago
   - ☐ 1 to 2 months ago
   - ☐ 3 to 6 months ago
   - ☐ 7 to 12 months ago
   - ☐ 1 to 2 years ago
   - ☐ More than 2 years ago
   - ☐ Not applicable

6. How long did your last episode of BD oral (mouth) ulcers last?
   - ☐ 1 to 6 days
   - ☐ 7 to 10 days
   - ☐ 2 to 3 weeks
   - ☐ 4 to 6 weeks
   - ☐ >6 weeks
   - ☐ Not applicable

7. On a scale of 0 (no pain) to 10 (the worst imaginable pain), how painful was your last episode of BD oral (mouth) ulcers?
   - ☐ 0 to 3
   - ☐ 4 to 6
   - ☐ 7 or 8
   - ☐ 9 or 10
   - ☐ Not applicable

8. Did you take anything for your last episode of BD oral (mouth) ulcers?
   - ☐ Not applicable
   - ☐ No
   - ☐ Yes. If yes, what did you take: _____

9. Do you usually have both oral and genital ulcers at the same time?
   - ☐ Yes
   - ☐ No
   - ☐ Not applicable

10. How many episodes of BD genital ulcers have you had?
    - ☐ None
    - ☐ First episode
    - ☐ 1-3 episodes
    - ☐ 4-10 episodes
    - ☐ More than 10 episodes
    - ☐ Not applicable

11. How often do you get BD genital ulcers?
    - ☐ Never
    - ☐ Less than 1 time every 3 years
    - ☐ Every 2-3 years
    - ☐ 1 time per year
    - ☐ 2 to 4 times per year
    - ☐ Every month
    - ☐ Not applicable

12. How long do your BD genital ulcers last?
    - ☐ 1 to 6 days
    - ☐ 7 to 10 days
    - ☐ 2 to 3 weeks
    - ☐ 4 to 6 weeks
    - ☐ >6 weeks
    - ☐ Not applicable

13. On a scale of 0 (no pain) to 10 (the worst imaginable pain), how painful are your typical episodes of BD genital ulcers?
    - ☐ 0 to 3
    - ☐ 4 to 6
    - ☐ 7 or 8
    - ☐ 9 or 10
    - ☐ Not applicable

14. When was the last episode of BD genital ulcers that you have had?
    - ☐ Less than 2 weeks ago
    - ☐ 1 to 2 months ago
    - ☐ 3 to 6 months ago
    - ☐ 7 to 12 months ago
    - ☐ 1 to 2 years ago
    - ☐ More than 2 years ago
    - ☐ Not applicable

15. How long did your last episode of BD genital ulcers last?
    - ☐ 1 to 6 days
    - ☐ 7 to 10 days
    - ☐ 2 to 3 weeks
    - ☐ 4 to 6 weeks
    - ☐ >6 weeks
    - ☐ Not applicable

16. On a scale of 0 (no pain) to 10 (the worst imaginable pain), how painful was your last episode of BD genital ulcers?
    - ☐ 0 to 3
    - ☐ 4 to 6
    - ☐ 7 or 8
    - ☐ 9 or 10
    - ☐ Not applicable

17. Did you take anything for your last episode of BD genital ulcers?
    - ☐ No
    - ☐ Yes. If yes, what did you take: _____

18. Did you have both oral and genital ulcers during that episode?
    - ☐ Yes
    - ☐ No
    - ☐ Not applicable

19. How often do you brush your teeth?
    - ☐ Occasionally
    - ☐ 1 time per month
    - ☐ 1 to 4 time per month
    - ☐ Every 3 to 6 days
    - ☐ Every other day
    - ☐ Daily
    - ☐ More than once a day

20. What toothpaste do you use? _____

21. Do you use any other mouth products?
    - ☐ No
    - ☐ Yes. If yes, what do you use: _____

22. Do you smoke cigarettes?
    - ☐ No
    - ☐ Yes. If yes:
        - o 20 or more cigarettes per day
        - o 10 to 19 cigarettes per day
        - o 5 to 9 cigarettes per day
        - o 1 to 4 cigarettes per day
        - o Occasionally but not daily

20.9 Appendix IX – Behçet's Disease History Patient Questionnaire - End of Treatment

Behçet's Disease History Patient Questionnaire
Protocol DUS-AUBD-01
End of Treatment

Patient ID: _____ Today's Date ___ ___/ ___ ___/ 202___

Please check the box to indicate your answer to each of the questions:

1. On a scale of 0 (no pain) to 10 (the worst imaginable pain), how painful was this episode of BD oral (mouth) ulcers? You stated that your usual pain is ____.
   - ☐ 0 to 3
   - ☐ 4 to 6
   - ☐ 7 or 8
   - ☐ 9 or 10
   - ☐ Not applicable

2. How long did this episode of BD oral (mouth) ulcers last? You stated that your usual duration is ____ days.
   - ☐ 1 to 6 days
   - ☐ 7 to 10 days
   - ☐ 2 to 3 weeks
   - ☐ 4 to 6 weeks
   - ☐ >6 weeks
   - ☐ Not applicable

3. Except for the study drug infusion, did you take anything for this episode of BD oral (mouth) ulcers?
   - ☐ Not applicable
   - ☐ No
   - ☐ Yes. If yes, what did you take: _____

4. Did you have both oral and genital ulcers during this episode?
   - ☐ Yes
   - ☐ No

5. On a scale of 0 (no pain) to 10 (the worst imaginable pain), how painful was this episode of BD genital ulcers? You stated that your usual pain is ____.
   - ☐ 0 to 3
   - ☐ 4 to 6
   - ☐ 7 or 8
   - ☐ 9 or 10
   - ☐ Not applicable

6. How long did this episode of BD genital ulcers last? You stated that your usual duration is ____ days.
   - ☐ 1 to 6 days
   - ☐ 7 to 10 days
   - ☐ 2 to 3 weeks
   - ☐ 4 to 6 weeks
   - ☐ >6 weeks
   - ☐ Not applicable

7. Except for the study drug infusion, did you take anything for this episode of BD genital ulcers?
   - ☐ No
   - ☐ Yes. If yes, what did you take: _____

8. Do you think the infusions were useful in treating your BD ulcers?
   - ☐ Yes
   - ☐ No

9. What aspects of study drug treatment were most beneficial to you?

   _____

   _____

   _____