

Clinical Protocol for Administration of Topical Pentoxifylline Gel on Behçet's Disease Oral Ulcers

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, and documented approval from the Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the EC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the EC before the changes are implemented to the study. All changes to the consent form will be EC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SUMMARY

Although Behçet's Disease (BD) has no FDA-approved therapies, numerous clinical reports suggest that oral ulcers of BD may resolve when treated with systemic ingested PTX. We here propose to investigate the therapeutic potential of PTX dissolved in muco-adherent formulation and directly applied to the oral lesions. This 60 patient, open label, proof of concept trial is designed to meet regulatory requirements for safety concerns while at the same time exploring the potential efficacy and clinical utility of this product. While topical PTX can never cure BD, the results of this trial may support its use in ameliorating the morbidity of these ulcers.

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
BD	Behçet's Disease
CFR	Code of Federal Regulations
CRF	Case Report Form
CYP1A2	Cytochrome P450 1A2
EC	Ethics Committee

Abbreviation or Specialist Term	Explanation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HLA	Human Leukocyte Antigen
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug
PI	Principal Investigator
POC	Proof of Concept
PTX	Pentoxifylline
SAE	Serious Adverse Event
SOA	Schedule of Activities
TNF	Tumor Necrosis Factor
US	United States

INTRODUCTION

Silk Road Therapeutics (İpekyolu İlaç Ltd. Şti.) is developing topical intraoral application of Pentoxifylline (PTX), for treatment of oral ulcers in Behçet's Disease patients.

Disease Background

Behçet's Disease (BD) is a complex, chronic, relapsing, multi-system inflammatory disorder that is characterized by oral ulcers, genital ulcers, ocular lesions and skin lesions. BD is usually a diagnosis of exclusion for which international diagnostic criteria have been developed (ISG, 1990, Hatemi et al., 2018). A genetic/immunologic basis for the disorder is suggested by its association with human leukocyte antigen HLA-B51, which occurs in around 60% of BD patients (Yazici, 1980, Gul, 2007, Kose, 2012, Alpsoy, 2016, Yazici et al., 2018). There is a concentrated prevalence of BD along the Silk Road, an ancient trading route extending from Japan to Turkey, with Turkey having the highest prevalence of BD (Azizlerli et al., 2003). There are reports of clinical responsiveness to immune modulatory agents (Sakane et al., 1999, Saenz et al., 2000, Hatemi et al., 2015, Alpsoy, 2016,).

Investigational Product Background Information

Since 1999, ingested (*p.o.*) PTX has been FDA-licensed for the treatment of intermittent claudication. The presumed mechanism of action is a rheological effect (i.e. an alteration in blood viscosity) of the drug, which enhances circulation. However, PTX also has well-documented anti-TNF and other anti-inflammatory actions (Aviado et al., 1984, Zabel, et al., 1993, Entzian et al., 1997, González-Espinoza et al., 2012, Green et al., 2012, Jull et al., 2012). Case series have suggested that ingested, systemic PTX may be beneficial for BD (Brenner, 1987, Yasui et al., 1996, Hisamatsu et al., 2001, Oliveira-Soares et al., 2002, Thornhill et al., 2007, Appenzeller et al., 2011, Jull et al., 2012, Ahmadi et al., 2016). For direct application on oral ulcers, a compounded formulation of PTX, applied topically, direct application of PTX on oral ulcers offers an opportunity for higher localized therapeutic concentrations, however, this has never been formally investigated in human clinical trials.

Non-Clinical Studies

A rich literature of PTX in wound healing exists. For detailed discussion of animal studies, see the investigator's brochure.

Clinical Studies

PTX has a well-defined adverse event profile derived from 50 years of experience in the marketplace and thousands of participants in clinical trials for various indications (Aviado, 1984, Jull et al., 2012, Salhiyyah, et al, 2015). In a 2015 Cochrane review of clinical trials utilizing PTX treatment for intermittent claudication, analyzed 24 trials conducted to test the safety and efficacy of PTX among 3,777 participants. The authors concluded that PTX was shown to be generally well tolerated. The most commonly reported side effects were of gastrointestinal symptoms such as nausea (Salhiyyah et al, 2015). Additionally, a 2012 Cochrane review of clinical trials utilizing PTX for treatment venous leg ulcers analyzed 12 trials conducted to test the safety and efficacy of PTX with

864 participants. Again, most reported adverse effects were gastrointestinal (Jull et al., 2012). We anticipate our topical application of PTX will have fewer adverse effects while at the same time increasing local therapeutic concentrations.

Risks/Benefit Assessment

The risks of PTX are well characterized and previously reported adverse events were primarily gastrointestinal. We expect fewer GI symptoms to result from our topical application. Benefits of PTX to BD patients were previously reported as noted above. We anticipate these benefits can be optimized by a topical application, but require a controlled trial to test that hypothesis.

RATIONALE AND TARGET POPULATION

The most common symptom of BD is recurrent oral ulcers, which profoundly affects patients' quality of life. The oral ulceration in BD is indistinguishable from recurrent aphthous stomatitis, they arise in crops as discrete, multiple aphthous ulcers, they are usually painful, persist for an average of two weeks, and subside without scarring (Saenz et al., 2000, Alpsoy, 2007, Taylor et al., 2014,). There is no cure or FDA-approved therapies for BD and the treatment of recurrent oral ulcers that are associated with BD is palliative (Taylor et al., 2014). We hypothesize that application of topical PTX will accelerate the healing of these lesions in a clinically meaningful way, and further hypothesize that topical PTX can become a valuable adjunct to any other systemic therapy for BD.

PURPOSE

Behçet's Clinic at Cerrahpaşa Medical Faculty at the University of Istanbul has a long history of supportive care for BD patients and is recognized as the world leader in this regard. By comparing patients receiving colchicine as part of supportive care to those who also receive topical PTX in addition to colchicine as part of supportive care, we seek to prove the concept that topical PTX may have clinical value. Additionally, we seek to demonstrate the safety and practicality of using topical PTX in BD patients.

Objectives

The overall objective is to measure the effects of PTX on speed of oral ulcer healing over time.

Primary Objectives

The primary objective is to measure the efficacy of daily dosing of topical PTX gel on speed of oral ulcer healing of BD patients.

Secondary Objectives

The secondary objective is to assess the safety and tolerability of daily dosing of topical PTX gel on BD patients.

Endpoints

This proof of concept trial will explore a number of efficacy endpoints including:

- Measurement of the index ulcer at enrollment
- Total number of ulcers
- Patient reported outcome pain scores (see Appendix)
- BD Quality of Life assessment (See Appendix)
- BD Activity Index (See Appendix)

In addition, pharmacovigilance for adverse events (AEs) will focus on already known and published PTX AEs as well as any experiences of local irritation that would be unique to this route of administration.

STUDY DESIGN

Overview of Study Design

We plan to enroll 60 patients with active oral ulcers of BD into an open label trial to determine the effects of topical PTX on healing duration of BD oral ulcers. This initial proof-of-concept trial will be conducted under US IND and with Turkish government and institutional permissions obtained for a single study site in Istanbul. We choose Turkey because in that country both the clinical expertise and the prevalent patients are sufficient to permit enrollment at a single center. We believe that a single enrollment center will provide us the greatest control over adherence to study protocols and eliminate inter-rater variability in endpoint assessments. However, we envision that a subsequent, registrational/pivotal trial will be conducted at multiple sites in both Turkey and the US.

Patients who are eligible for study entry (see inclusion/exclusion criteria below) will be randomized into two groups:

- Colchicine therapy as part of supportive care routinely offered in Behçet's Clinic-Istanbul

OR

- Colchicine therapy as part of supportive care as above with the addition of topical PTX

According to the EULAR 2018 recommended guidelines of Behçet's Disease (Hatemi et al., 2018), the first line of therapy to be used as standard therapy against recurring oral ulcers is colchicine. However, a significant portion of the patients undergoing colchicine therapy does not have sufficient response and require subsequent immune modulatory therapy. The goal of this study is to determine the effectiveness of PTX gel on oral ulcers. If the PTX gel therapy provides a sufficient response in patients, these patients might not need to undergo immune modulatory therapies.

For all patients in either group, we will collect an oral photograph, the size and location of the largest oral ulcer, number of ulcers, quality of life and BD activity assessments,

pain scores, and concomitant medications. This data will be collected either in person or by telephone for the following two weeks. Additionally, adverse event experiences will be solicited. Data analyses will be exploratory comparisons of differences in safety and efficacy endpoints between BD patients who did and did not receive topical PTX.

Stopping Criteria

Any adverse events, which occur among study subjects, will be reported to the study's PI, who will have authority to terminate enrollment for any patient. Additionally, in the event that any serious unexpected adverse event should occur among patients treated with topical PTX, the study's PI will have the authority to suspend enrollment of any future patients and cease treatment of any patients currently enrolled. Additionally, 30 days after the final dose, patients will be contacted to assure otherwise unrecorded adverse events have occurred.

Rationale for Study Design

While we acknowledge that an open label trial is not most methodologically robust because it may embrace placebo effect biases, evaluator biases, and patient reporting biases (among others), this design was favored by US regulatory authorities for several practical and safety-driven reasons. Remembering that this is a new drug product applied via a new route of administration to a new study population, open label design allows the clinician to know if study subjects are so exposed. Furthermore, an initial validation that this therapy is non-inferior to current practice is a reasonable precautionary first step.

Rationale for Dose Selection

Patients on topical PTX will be given 1 tube containing 1,000mg of PTX in a single day 20 ml dosage to be applied no fewer than four times per day with complete consumption of the entire tube each day. All digitally-accessible ulcers are to be treated. The rationale for this dose is based on the experience with *p.o.* PTX treatment.

Our dosing strategy is designed to maximize lesional concentrations of PTX through a minimum of four times daily applications of our drug. As, systemic gastrointestinal absorption is possible due to accidental swallowing, we will limit our total daily dosing for this topical preparation to no greater than the recommended dose for the licensed, intentionally ingested product. For our proposed formulation of 5% PTX, we calculate that dose to be no more than 20 grams of individually packaged drug applied four times or more daily with the goal of applying 1 package per day. Consequently, this yields a total maximal dose of 1,000 mg of active pharmacologic agent. This is slightly less than the total recommended dose of 1,200mg *p.o.* PTX.

The rationale for a topical formulation of PTX directly applied to BD oral ulcers is due to the potential therapeutic value of PTX in BD as suggested by some studies in combination with a potential improvement in PTX delivery via a topical oral formulation, which should maximize local concentrations of PTX to affected mucosal sites while minimizing adverse events that would otherwise occur from systemic PTX exposure.

End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Schedule of Activities (SoA). If topical PTX therapy was shown to be effective during the study, Silk Road Therapeutics will make every effort to get these participants access to topical PTX therapy.

STUDY TREATMENT

Study Treatment Administration

Study Treatment Description

PTX is a topical gel for intraoral application on the area of the oral ulcers.

Dosing and Administration

Our drug product requires digital application directly to accessible oral lesions. Hence, the drug administrator should wash their hands thoroughly before application, and put topical PTX gel liberally on the oral ulcer areas

Preparation/Handling/Storage/Accountability

Topical PTX gel will be supplied in tubes containing the daily dose of 20 ml of drug product.

Acquisition and accountability

Each patient in the treatment group will receive 14 days supply of topical PTX consisting of 14 tubes. Patients will be asked to present all used and unused tubes at every in person visit with study personnel. All used and unused tubes will be collected upon study completion.

Formulation, Appearance, Packaging, and Labeling

Study treatment will be a formulation of 5% hypromellose, 5% PTX, 1.3% of polyethylene oxide, 0.8% of methylparaben, 0.8% of propylparaben. 20 ml topical gel containing 1,000mg of PTX will be packaged in a light-opaque plastic tube. Please see the sample label in Appendix.

Product Storage and Stability

Product needs to be stored between 10°C and 30°C within the original packaging. Lots will be released subsequent to affirmation from stability testing that demonstrates acceptable stability and bioburden results. Our stability studies are currently ongoing, and in previous studies the stability of PTX in a topical cream formulation was confirmed for at least 62 days when stored in white opaque ointment jars at room temperature (Gupta, 2012).

Measure to Minimize Bias: Randomization

While neither placebo effect nor evaluator biases can be completely eliminated in the context of the open label trial, other potential biases will be mitigated by randomization. For example, because of our randomization strategy, we expect disease severity, co-morbidities, concomitant medications and other potential confounder, both known and unknown, to be equally represented in treatment and control groups.

Study Treatment Compliance

Treatment compliance will be monitored by daily phone calls and tube collections.

STUDY POPULATION

Number of Subjects

60

Inclusion Criteria

- Meets the International Study Group criteria for BD (ISG, 1990).
- Presents with at least one active lesions accessible to measurement, the largest of which is to be designated as the index ulcer
- Index oral ulcer to be assessed should be in the easily accessible areas of the oral mucosa, and the oral ulcer first began within 48 hrs prior to enrollment
- Adult (>18 years) male or a non-pregnant, non-lactating female.
- Has signed an Ethics Committee (EC) approved subject consent form.
- Has completed all screening procedures satisfactorily, is deemed to be an acceptable subject and is otherwise eligible for entry into the study.
- Is willing and able to comply with the protocol.
- Is being treated with colchicine.

Exclusion Criteria

- Has a severe, acute, or chronic systemic disease other than BD such as congestive heart failure, hepatic failure, renal failure, systemic lupus erythematosus, Stevens-Johnson syndrome, ulcerative colitis, cancer, leukemia, diabetes, AIDS, or any other condition for which they are immune-compromised.
- Has received PTX in any form over the previous 60 days prior to enrollment.
- Is under active treatment for dental conditions, such that multiple dental office visits would be required during the study period, or presents with oral conditions which are not thought to be related to BD and in the judgment of a qualified dentist, will require treatment during the study period.
- Is suffering from any medical condition other than Behçet's Disease known to cause oral ulcerations, such as erosive lichen planus, benign mucous membrane pemphigoid, Systemic Lupus Erythematosus, Crohn's disease, Reiter's syndrome, or AIDS. Has an eating disorder and/or psychiatric illness requiring treatment. Has a history of, or is currently exhibiting, any disease or condition, which, in the opinion of the principal investigator, would place the subject at increased risk during study therapy. Has any abnormality in hematological or biochemical variable, which, in the opinion of the principal investigator, would place the subject at increased risk during study therapy.
- Has experienced recent cerebral and/or retinal hemorrhage or in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.
- Is receiving immune suppressing or modulating therapy (e.g., apremilast) or topical corticosteroids within 2 weeks prior to enrollment.

- Has concomitant administration of strong CYP1A2 inhibitors (including e.g. ciprofloxacin or fluvoxamine) and other drugs that may increase the exposure to PTX.
- Is not being treated with colchicine.

Strategies for Recruitment and Retention

- The total duration of recruitment for the study will be approximately 4 months.
- We anticipate accruing a mean of 6 patients per week for 10 weeks.
- We anticipate to provide resources to a crew, from the rich history of the Behçet's Clinic at Cerrahpaşa Medical Faculty at the University of Istanbul
- The primary recruitment venue will be the Behçet's Clinic at Cerrahpaşa Medical Faculty at the University of Istanbul.
- All BD patients who attend the clinic weekly (100 per week) will be invited to enroll in a study upon their next outbreak of new oral ulcers.
- Additionally, patients known to the clinic to have regular intermittent-continuous oral ulcers will be directly contacted and invited to enter the study upon their next outbreak of new oral ulcers.
- Every effort will be made to accommodate the study subject's schedules and enhance subject retention. For example, at home visits, phone calls to collect data in lieu of direct visits and other accommodations will be made to assure the highest retention feasible.
- In order to enhance subject retention, subjects will be compensated for their travel/food and work loss costs during visit attendance.

Recruitment Definitions

- Screen Failure- Subjects whom the informed consent is obtained and do not proceed to study treatment (e.g. does not meet the entry criteria). Screening data will be documented on the study specific Screening Log. Reasons for screen failure will be documented in the subject's source documents and on the Screening Log.
- Enrolled- Subjects who pass all screening evaluations and are randomized to supportive care or supportive care in addition to study treatment.
- Treated- Subjects who are enrolled and receive at least one dose of randomized study treatment.
- Treatment Discontinuation- Subjects who receive randomized study treatment but fail to complete treatment through 2 weeks or hospital discharge.
- Study Discontinuation- Subjects who complete randomized study treatment, but not the follow-up visit.
- Completed Subject- Subjects who complete treatment and the follow-up visit.

PATIENT SAFETY

We have the following plan for mitigating risk to research subjects:

- direct examination of the oral mucosa to detect and control any local irritant effects
- intensive pharmacovigilance at each clinical contact that occurs no less than every 48hrs throughout the treatment period

Local Irritation

Because this will be one of the first carefully controlled trials of topically administered PTX, we will closely monitor the possible occurrence of any local oral mucosal irritation in study subjects.

By design, this study will require in-person examination of the oral mucosa no less than every 48 hrs through two weeks of study duration. At the time of in-person examinations, both ulcer-healing metrics and safety monitoring will be conducted. We posit that this very frequent, in-person pharmacovigilance is a superior means to ensure patient safety than any animal proxy might provide.

Intensive Pharmacovigilance

Additionally, targeted surveillance will be made for adverse events that were previously noted to occur in PTX treatments. Study subjects will be asked, no less frequently than every 48 hours, whether they have experienced any of these symptoms already documented for systemic PTX.

Adverse events will be categorized as serious or non-serious, expected or unexpected in accordance with ICH document. Rather than recapitulate the basis of this categorization, it is attached here as an appendix. All serious and all unexpected adverse events will be immediately reported to the study's PI.

Study Treatment Discontinuation and Subject Discontinuation and Withdrawal

As stipulated by the Informed Consent, study subjects are entitled to withdraw from the study at any time. Additionally, as previously noted in this document, the study's PI may withdraw the study subject or terminate the study entirely for bona fide medical reasons.

In the absence of a medical contraindication or significant protocol violation, Principal Investigator will make every effort to keep subject in the study. The reason for a premature subject withdrawal should be selected from the following standard categories:

- Adverse Event- clinical or laboratory events that in the judgment of the PI require discontinuation of study medication in the best interests of the subject.
- Death- death of the subject whether study related or not.
- Lost to follow-up- the subject did not return for follow-up visit(s) following the completion of study treatment and hospital discharge despite attempts to contact the subject to maintain scheduled appointments.

- Protocol Non-compliance- the subject's participation in the study failed to meet protocol requirements, which had a direct impact on subject safety and evaluation of the subject's data. The violation necessitated termination from the study.
- Subject meets withdrawal criteria- subject's condition meets the criteria for the withdrawal from the study.

Withdrawal Criteria

Subjects will be withdrawn from the study if the subject meets any of the following criteria after the initiation of study treatment.

- Allergic reaction to the topical PTX gel.

Withdrawal Procedures

All subjects who are withdrawn from the study will have a post dosing assessment completed.

Pre and Post Enrollment Restrictions

Two weeks prior to the start of the clinical trial do not use any drug that might interact with PTX. For example, avoid strong CYP1A2 inhibitors (including e.g. ciprofloxacin or fluvoxamine) and other drugs that may increase the exposure to PTX. Please see the exclusion criteria for more details about PTX risk factors.

Pre and Post Enrollment Recommendations

While not a formal restriction, the subjects should avoid eating/drinking within 1 hr after application of topical PTX gel.

Subjects should not use any other topical cream or gel other than topical PTX during the clinical trial. For example, topical corticosteroids should not be utilized during the clinical trial.

STUDY PROCEDURES

Recruitment

A description of the study's objectives-to assess the clinical utility of topical PTX for oral lesions- will be presented orally and with a written handout weekly to all patients in the Behçet's Clinic. Interested patient will contact the study nurse upon fresh outbreaks of oral lesions.

Additionally, phone screening will be conducted in order to determine potential study subjects that are most likely to participate in the study. The clinical site coordinator will prepare a list of potential subjects from the database of the Behçet's Clinic at Cerrahpaşa Medical Faculty at the University of Istanbul, and contact potential subjects and ask if they are interested in participating in this study.

Study Information Script

Study information script will be prepared that will contain the important details that need to be communicated to the potential study subject including the following:

- The purpose of this study is to determine the effect of topical PTX gel on BD oral ulcer healing.
- Previous studies suggest beneficial effects of oral PTX on ulcer healing and in treatment of BD, this study will use the same drug in a gel form to be applied inside your mouth onto the area of the BD oral ulcer.
- If the potential subject is interested in participating in this study, determine the study eligibility of the potential subject.

Study Eligibility Determination

- Potential study subject should be suffering from recent BD oral ulcers, and he/she has favorable opinion on trying to participate in a clinical trial for potential treatment.
- Please see the study population for more detailed information on inclusion/exclusion criteria.
- If the potential subject is not eligible for this study, ask him/her if he/she has any information on potential subjects who would be interested to participate in this study.

Study Expectations and Duration

- Subject is expected to participate in all the clinic/at home/phone visits, which is estimated to take 2 weeks of treatment with daily follow-up via clinic/at home or a phone visit.

Record of Eligibility and Reason of Eligibility

Clinical trial coordinator will record the reason of eligibility of the subject.

Patient Agreement to Visit within 48hrs of Ulcer Emergence

- Potential study subject should be communicated the importance of noting the time of oral ulcer emergence as soon as he/she realizes it, and visiting the clinic within 48hrs of oral ulcer emergence.
- Potential study subject should be informed to contact the clinical site coordinator in order to ensure timely scheduling of clinic visit.
- Potential study subject should be reminded that his/her transportation/food cost will be compensated upon visit attendance.
- Potential study subject should be asked if he/she has any information on potential subjects who would be interested to participate in this study.

Enrollment Visit Procedures

Subjects who meet the enrollment criteria will be randomized. Computer generated table of random numbers will be utilized in randomization to two groups:

- Colchicine therapy as part of supportive care routinely offered in Behçet's Clinic-Istanbul

OR

- Colchicine therapy as part of supportive care routinely offered in Behçet's Clinic-Istanbul as above with the addition of topical PTX

The investigational drug will be dispensed to the second group:

- 14 tubes of topical PTX gel will be given to the patient on the baseline visit.
- The instructions on how to administer the topical PTX gel will be explained to the patient and demonstrated by administering the first tube of topical PTX gel in the clinic.

Informed Consent Form

The subject will provide written informed consent using the current version of the Ethics Committee approved informed consent form.

The Principal Investigator (PI) and other site personnel as assigned by the PI will be responsible for obtaining informed consent after the study has been explained to the subjects, and all of the subject's questions are answered. The original signed consent form will be filed in the subject's records in accordance with institutional policy and a copy will be provided to the subject. The consent process will be documented in the subject's source documents and the Informed Consent Log supplied for the study.

Written informed consent must be obtained prior to performing any study related procedures.

If a protocol amendment requires revision to the informed consent form, the revised Ethics Committee approved form must be used to obtain and document re-consent from the subject.

History and Baseline Characteristics

The following history and demographic data will be collected:

Age, sex, race, ongoing medical conditions, concomitant medications.

Physical Examination

Because these patients are already enrolled in the Behçet's Clinic-Istanbul-Cerrahpasa, no additional physical examinations are required for the study. However, at each in-person clinical encounter, the study nurse will collect vital signs (temperature, pulse, respiration, blood pressure) and if significantly divergent from normal, inform the study's PI.

Patient Ulcer Documentation

The clinician will assess the current state of Behçet's Disease on the patient. The following will be documented on the CRF:

- The total number of visible oral ulcers
- The noted time of oral ulcer emergencies obtained from the patient
- The recently emerged oral ulcer will be determined and designated as the index ulcer by the clinician. The index ulcer will be measured with the pre-determined measuring device, and documented by imaging the index ulcer by photography

along with the measuring device that will serve as a constant measure for accurate size determination.

Quality of Life

Behçet's Disease Quality of Life Measure Form and Behçet's Disease Current Activity Form will be filled out with the help of the clinician.

Pain Assessment

Patient reported outcome pain scores will be assessed using the numerical rating system (see Appendix).

Phone Visit Procedures

Phone visits will be performed daily on days that the patient is not having a visit at home or in the clinic.

Adverse Events Assessment

At each clinical encounter, both in person and in telephone, patients will be queried about adverse events already known to occur with PTX treatment. Additionally, at each patient in-person encounter, patients will be examined for local irritation. Any unexpected medical events will also be collected and if serious as per ICH guidelines, will be reported immediately to study's PI.

List of Concomitant Medications

Patient's list of concomitant medications will be recorded.

Resolution of Existing Conditions or Prior Events

Patient will be asked about the state of the existing conditions and/or prior events since the last visit. The current state of these conditions/events will be recorded.

Pain Assessment

Patient reported outcome pain scores will be assessed using the numerical rating system (see Appendix).

Adherence

Patient's adherence to topical PTX gel will be assessed and recorded.

Home Visit Procedures

Vital Signs

Vital signs will be recorded.

Adverse Events Assessment

At each clinical encounter, both in person and in telephone, patients will be queried about adverse events already known to occur with PTX treatment. Additionally, at each patient in-person encounter, patients will be examined for local irritation. Any unexpected medical events will also be collected and if serious as per ICH guidelines, will be reported immediately to study's PI.

List of Concomitant Medications

Patient's list of concomitant medications will be recorded.

New or Emerging Events

New or emerging events since the last visit will be recorded.

Resolution or Change of Any Events

Patient will be asked about the state of the existing conditions and/or prior events since the last visit. The current state of these conditions/events will be recorded

Picture of Ulcer

The index ulcer will be documented by photography along with the measuring device that will serve as a constant measure for accurate size determination.

Measurement of Ulcer and Ulcer Count

The index ulcer will be measured with the pre-determined measuring device, and the area of the index ulcer will be recorded along with the total ulcer count.

Pain Assessment

Patient reported outcome pain scores will be assessed using the numerical rating system (see Appendix).

Adherence

Patient's adherence to topical PTX gel will be assessed and recorded.

Clinic Visit Procedures

Vital Signs

Vital signs will be recorded.

Adverse Events Assessment

At each clinical encounter, both in person and in telephone, patients will be queried about adverse events already known to occur with PTX treatment. Additionally, at each patient in-person encounter, patients will be examined for local irritation. Any unexpected medical events will also be collected and if serious as per ICH guidelines, will be reported immediately to study's PI.

List of Concomitant Medications

Patient's list of concomitant medications will be recorded.

New or Emerging Events

New or emerging events since the last visit will be recorded.

Resolution or Change of Any Events

Patient will be asked about the state of the existing conditions and/or prior events since the last visit. The current state of these conditions/events will be recorded

Picture of Ulcer

The index ulcer will be documented by photography along with the measuring device that will serve as a constant measure for accurate size determination.

Measurement of Ulcer and Ulcer Count

The index ulcer will be measured with the pre-determined measuring device, and the area of the index ulcer will be recorded along with the total ulcer count.

Pain Assessment

Patient reported outcome pain scores will be assessed using the numerical rating system (see Appendix).

Adherence

Patient's adherence to topical PTX gel will be assessed and recorded.

End of Study Visit Procedures

Vital Signs

Vital signs will be recorded.

Adverse Events Assessment

At each clinical encounter, both in person and in telephone, patients will be queried about adverse events already known to occur with PTX treatment. Additionally, at each patient in-person encounter, patients will be examined for local irritation. Any unexpected medical events will also be collected and if serious as per ICH guidelines, will be reported immediately to study's PI.

List of Concomitant Medications

Patient's list of concomitant medications will be recorded.

New or Emerging Events

New or emerging events since the last visit will be recorded.

Resolution or Change of Any Events

Patient will be asked about the state of the existing conditions and/or prior events since the last visit. The current state of these conditions/events will be recorded

Picture of Ulcer

The index ulcer will be documented by photography along with the measuring device that will serve as a constant measure for accurate size determination.

Measurements of Ulcer and Ulcer Count

The index ulcer will be measured with the pre-determined measuring device, and the area of the index ulcer will be recorded along with the total ulcer count.

Pain Assessment

Patient reported outcome pain scores will be assessed using the numerical rating system (see Appendix).

Quality of Life

Behçet's Disease Quality of Life Measure Form and Behçet's Disease Current Activity Form will be filled out with the help of the clinician.

Adherence

Patient's adherence to topical PTX gel will be assessed and recorded.

Collection of Used/Unused Tubes

The used and unused tubes of topical PTX gel will be collected from the patient. Patient's adherence to the daily drug dosage recommendation will be assessed from the tube content.

Post Dosing Procedures

As noted above, all patients on study drug will be contacted 30 days following the final dose to assess if there are any additional adverse events. This assessment can be performed using the aforementioned phone visit procedures. In the case of any adverse events, patients will be followed up until the resolution of the adverse event (or up to maximum of 30 days after the day of adverse event emergence), and in the case the adverse event does not resolve, PI will be informed of this issue.

Schedule of Activities (SoA)

The enrollment and the end of study visits will be performed in the clinic. If the visits in between the enrollment and the end of study visits (Visits #2,3,5,6) cannot be performed in the clinic, the patients can be visited at their home as part of a home visit. Face-to-face visits (clinic and home visits) should not be more than 48 hours apart. One exception to this schedule would be if the following 48hr visit is scheduled on a weekend, the time difference between the visits could be increased to 72hrs to accommodate a weekday schedule. Phone visits will be performed on the days that there are no face-to-face visits.

Procedure	Screening	Enrollment Visit	Tel. 1	Visit 2*	Tel. 2	Visit 3*	Tel. 3	Tel. 4	Visit 4	Tel. 5	Visit 5*	Tel. 6	Visit 6*	Tel. 7	Tel. 8	End of Study Visit 7	Follow Up Visit Day 45
Visit Number:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Determination of Study Eligibility	X																
Explanation of Study Expectations	X																
Agreement to Visit within 48hrs of Ulcer Emergence	X																
Informed Consent	X																
Medical History	X																
Concomitant Medication History	X																
Physical Examination	X	X							X				X			X	
Vital Signs	X	X		X		X			X		X		X			X	
Quality of Life Form		X		X		X			X		X		X			X	X
Current Activity Form		X		X		X			X		X		X			X	X
Identification of Index Ulcer		X		X		X			X		X		X			X	
Measurement of Index Ulcer		X		X		X			X		X		X			X	
Imaging of Index Ulcer		X		X		X			X		X		X			X	
Total Ulcer Count		X		X		X			X		X		X			X	
Pain Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X		X		X	X	X	X		X		X			X	
Adverse Event Assessment		X	X	X	X	X			X	X	X	X	X	X	X	X	X
Resolution of Any Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Check for Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug Adherence		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collection of Used/Unused Tubes				X		X	X	X	X		X		X				

*: Visits 2, 3, 5 and 6 can be a home visit if clinic visit is not possible or feasible for patients.

STATISTICAL CONSIDERATIONS

As noted above, this proof of concept trial aims to better define the primary endpoints for a future, pivotal, registrational trial. Given our early stage in drug development, we can, *a priori*, anticipate *post hoc* analyses of this trial that will enable refinement in the design and statistical analysis of that future trial. Our “registrational endpoint development” begins with three metrics: diameter of largest ulcer at enrollment, total number of ulcers and pain scores as measures followed over time.

We are preparing a survival analysis plan that compares the diminution in largest ulcer size over time. This endpoint is fundamental to our “proof of concept” because it directly measures, on one particular lesion, the healing effects of PTX compared to the standard of care.

Total ulcer number is a more problematic metric because our topical intervention is not expected to affect the development of new ulcers, only to accelerate the healing of existing ulcers. Regardless, total number of ulcers will be collected at each visit because it is a reasonable measure of the patient's overall BD control.

Lastly, pain scores suffer from all the subjectivity inherent to that individualized experience. As above, pain likewise may be altered by the “noise” of new ulcers, which this intervention is not expected to affect. Still, measuring pain offers an opportunity to correlate simple measurements of mucosal disruption with the patient's fundamental disease experience.

As this is a proof of concept study, and the methodology is likely to be modified, the details regarding the statistical considerations are not yet finalized.

In the event of the discovery of missing, repeated, unused or spurious data, these will be corrected as soon as possible.

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INVESTIGATOR AGREEMENT

I have reviewed the protocol entitled “ “ and agree that it contains all the information necessary to conduct the study as required. I will conduct the trial in accordance with the principles of ICH Good Clinical Practice and Declaration of Helsinki.

I will obtain written informed consent from each prospective trial subject prior to conducting any protocol-specified procedures. The consent form used will have the approval of the local EC.

I will maintain adequate source documents and record all observations, treatments, procedures pertinent to trial subjects in their medical records. I will complete the case report form supplied by Silk Road Therapeutics. I will ensure that my facilities and records will be available for inspection by representatives of Silk Road Therapeutics, the EC, or local regulatory authorities.

I will notify Silk Road Therapeutics, or its designated representative, within 24 hours of any serious adverse events. Following this notification, a written report describing the serious adverse event will be provided to Silk Road Therapeutics, or its designated representative, as soon as possible, but no later than three days following the initial notification.

My signature below indicates that my participation in this clinical study presents no conflict of interest for me or my sub-investigators participating in the study.

Investigator's Name (Print):

Investigator's Signature:

Date:

APPENDICES

BD Quality of Life Assessment

Behcet's Disease Quality of Life Measure

Please read each statement carefully and decide whether it applies to you at the moment

	True	Not True
1 My life revolves around hospital visits	<input type="checkbox"/>	<input type="checkbox"/>
2 Nothing interests me	<input type="checkbox"/>	<input type="checkbox"/>
3 It's too much effort to go out and see people	<input type="checkbox"/>	<input type="checkbox"/>
4 Walking is painful	<input type="checkbox"/>	<input type="checkbox"/>
5 It takes me longer to do things	<input type="checkbox"/>	<input type="checkbox"/>
6 I cannot stand for long	<input type="checkbox"/>	<input type="checkbox"/>
7 My condition interferes with my life	<input type="checkbox"/>	<input type="checkbox"/>

Please remember to read each statement thinking about your Behçet's Disease.
Please choose the response that applies best to you at the moment.

	True	Not True
8 It is difficult to get out of bed	<input type="checkbox"/>	<input type="checkbox"/>
9 I feel terrible about the way I look	<input type="checkbox"/>	<input type="checkbox"/>
10 Talking is stressful	<input type="checkbox"/>	<input type="checkbox"/>
11 I feel dependent on others	<input type="checkbox"/>	<input type="checkbox"/>
12 I feel older than my years	<input type="checkbox"/>	<input type="checkbox"/>
13 It limits the places I can go	<input type="checkbox"/>	<input type="checkbox"/>
14 I find it difficult to take care of the people I am close to	<input type="checkbox"/>	<input type="checkbox"/>
15 I cannot rely on how I will be tomorrow	<input type="checkbox"/>	<input type="checkbox"/>

Please read each statement carefully and decide whether it applies to you at the moment

	True	Not True
16 My condition is drastically affecting my life	<input type="checkbox"/>	<input type="checkbox"/>
17 I often get frustrated	<input type="checkbox"/>	<input type="checkbox"/>
18 I feel like a prisoner in my own home	<input type="checkbox"/>	<input type="checkbox"/>
19 My condition affects important decisions in my life	<input type="checkbox"/>	<input type="checkbox"/>
20 I do not like being touched	<input type="checkbox"/>	<input type="checkbox"/>
21 I cannot speak properly	<input type="checkbox"/>	<input type="checkbox"/>
22 It puts a strain on my personal relationships	<input type="checkbox"/>	<input type="checkbox"/>

Please remember to read each statement thinking about your Behçet's Disease.
Please choose the response that applies best to you at the moment.

	True	Not True
23 I feel useless	<input type="checkbox"/>	<input type="checkbox"/>
24 I worry that I hold others back	<input type="checkbox"/>	<input type="checkbox"/>
25 People close to me have lost out because of my condition	<input type="checkbox"/>	<input type="checkbox"/>
26 I feel unable to cope with my condition	<input type="checkbox"/>	<input type="checkbox"/>
27 I have lost contact with people	<input type="checkbox"/>	<input type="checkbox"/>
28 I worry about the effects on others	<input type="checkbox"/>	<input type="checkbox"/>
29 Everything is getting to me today	<input type="checkbox"/>	<input type="checkbox"/>
30 I feel lonely	<input type="checkbox"/>	<input type="checkbox"/>

BD Current Disease Activity Form

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	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Mouth Ulceration	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Genital Ulceration	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Erythema	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Skin Pustules	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Joints - Arthralgia	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Joints - Arthritis	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Nausea/vomiting/abdominal pain	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Diarrhoea+altered/frank blood per rectum	<input type="checkbox"/>	<input checked="" type="checkbox"/>

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"?

(circle the correct answer)

No ☒ Yes

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?

blackouts

please circle

No Yes

tick if new

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?"

had chest pain

please circle

No Yes

tick if new

had breathlessness

No Yes

coughed up blood

No Yes

had pain/swelling/dischouration of the face

No Yes

had pain/swelling/dischouration of the arm

No Yes

had pain/swelling/dischouration 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

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.

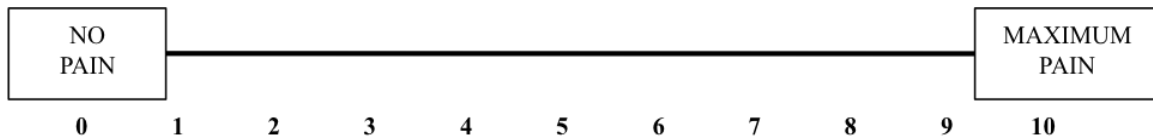
Patient Reported Outcome Pain Score

Patient Reported Outcome Pain Score Assessment

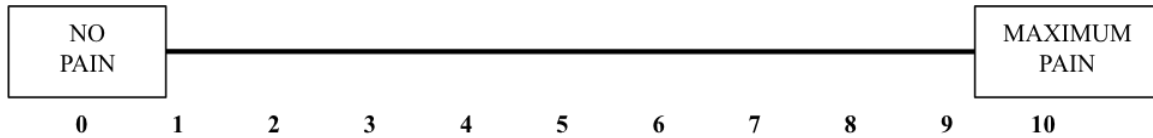
Patient Reported Outcome Pain Score Assessment

The subject can select the numerical value corresponding to her/his pain score. For more information, please consult the clinician.

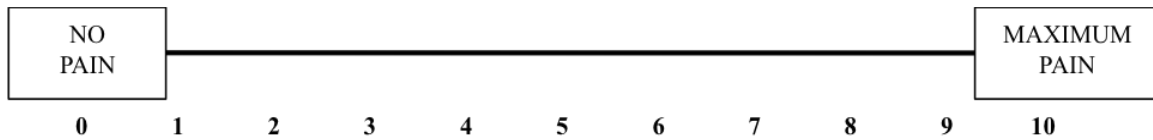
Pain score during eating:



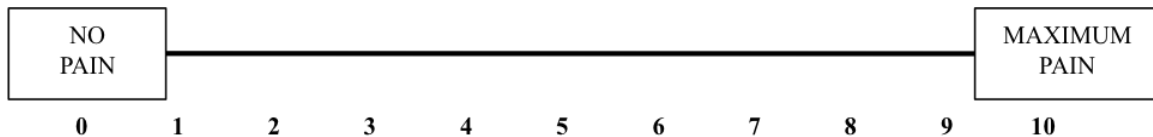
Pain score during drinking:



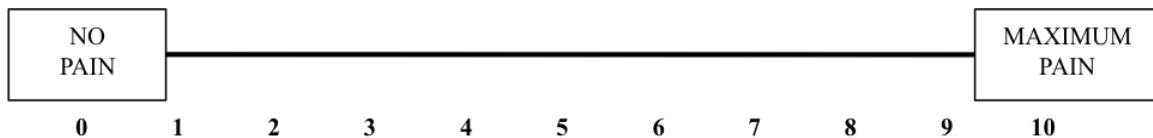
Pain score during speaking:



Pain score during dental care:



General pain score due to oral ulcers:



Sample Label

PENTOXIFYLLINE TOPICAL GEL

INTRAORAL MUCOSA GEL

Pentoxifylline, hypromellose, polyethylene oxide,
methylparaben, propylparaben.

1 Unit, Daily Dose (20g) gel tube

Caution: New Drug- Limited by Federal Law to Investigational Use

1000mg

Silk Road Therapeutics