A Neurokinin-1 Receptor Antagonist for the Treatment of Pruritus in Patients With Epidermolysis Bullosa

Study Protocol and Statistical Analysis Plan

NCT03836001

March 25, 2021

1. Title: A Phase 2 trial of Neurokinin-1 Receptor Antagonist for the Treatment of Itch in Epidermolysis Bullosa Patients

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3. Funding sources for this project:
Epidermolysis Bullosa Research Partnership (EBRP) – providing funding (SPO # [redacted])
Menlo Therapeutics, Inc. – providing study medication

4. Abstract:
This is a follow-up study to a prior pilot phase 2 trial conducted here at Stanford and will assess the effect of serlopitant (5 mg daily) on EB-related itch in adolescents (≥13 y.o.) and adults with EB. We will evaluate the degree of itch relief in participants taking serlopitant as compared to placebo. This will be determined by comparing the proportion of participants with 3 point or greater reduction in average daily itch severity as measured by numeric rating scale (NRS) score following two months of treatment. Secondary aims include continuous change in average daily NRS and worst itch NRS over time, proportion of participants achieving 2-point and 4-point reductions in average itch severity following two months of treatment and change in median NRS as compared to baseline. Finally, we will assess the safety profile of serlopitant in study participants. It is our hope that serlopitant will reduce itch in adolescents and adults with EB.

5. General background:
Management of chronic pruritus is notoriously challenging for patients with epidermolysis bullosa (EB). In a comprehensive survey of 146 EB patients, itch was reported as the most bothersome EB symptom, ranking higher than acute or chronic pain or problems eating.[1] Furthermore, pruritus can induce an itch-scratch-blister cycle, which can exacerbate existing wounds or induce new wounds.[2] There have been no new drugs for chronic pruritus, and the current management of pruritus in EB with antihistamines and topical steroids only minimally relieve itch.[3]

Recent insights into the underlying pathogenesis of pruritus have revealed that substance P and its receptor, neurokinin-1 (NK1), are key transmitters of the itch signal. By inhibiting the NK1 receptor, serlopitant blocks the transmission of itch from the skin to the central nervous system. NK1 receptor antagonists (aprepitant and serlopitant) were originally tested in clinical trials as antiemetics and medications to treat overactive bladder.[1] Since 2005, NK1 receptor antagonists have been evaluated in more than a dozen completed Phase 1 studies and two Phase 2b studies (N=300 participants).

Serlopitant was evaluated in a multi-center, double blind, 6-week randomized trial of 257 adults with chronic pruritus for the treatment of severe, chronic pruritus.[2] There was a statistically significant and dose-dependent reduction in pruritus at the end of six weeks at the 1 mg and 5 mg doses. Participants in this study had chronic pruritus due to a variety of dermatologic, neuropathic, and psychogenic causes that was unresponsive to topical steroids and antihistamines. Serlopitant was well tolerated and safe in doses up to 5 mg daily, and there were no treatment related serious adverse events. When assessed with a visual analog scale (VAS), pruritus was significantly reduced in both the 1 mg ($p = 0.001$) and the 5 mg ($p = 0.002$) groups compared to placebo. After 6 weeks of treatment, nearly 70% of participants taking 5 mg of serlopitant reported a 2-point reduction in VAS while nearly 50% of participants reported a 4-point decrease in VAS.

We recently reported the results of a prior phase 2 randomized, double blind, placebo-controlled trial evaluating the effects of serlopitant over 8 weeks for treatment of EB-related itch.[3] Participants were age > 13 years old,

with any EB subtype. Although the 14 participant trial was only powered to detect large differences in numeric rating scale (NRS) itch scores, we observed a small magnitude reduction in NRS itch score over time in favor of serlopitant relative to placebo (0.08 point/week comparative reduction) although this difference did not meet statistical significance (p=0.11). This was equivalent to a 0.64-point reduction in the NRS itch score (rated 0-10) by the end of the active treatment period. In post-hoc analysis, we found a significant majority of participants in the serlopitant arm (86%) experienced at least a 1-point reduction in NRS score by end of treatment. More participants in the active group (43% vs. 14%) achieved at least a 3-point reduction in NRS itch score by the end of treatment as compared to placebo, although this was not statistically significant (p=0.35). Serlopitant was well tolerated, with no new safety signals observed.

6. Study design:
This is an investigator-initiated, single-center, randomized, double-blind, placebo controlled, parallel arm trial evaluating the effects of serlopitant at 5 mg by mouth daily on EB-related itch. Eligible participants must have a clinical diagnosis of EB and average daily pruritus rated at least 5 based on a 0-10 Numeric Rating Scale (NRS) persistent for at least 6 weeks.

We aim to recruit at least 40 participants, age 13 and older, of all EB subtypes. Participants will be assigned to placebo or serlopitant in a 1:1 ratio. Participants randomized to serlopitant will receive a loading dose of serlopitant 15 mg PO once, followed by serlopitant 5 mg PO daily for 2 months. This dosing regimen is identical to that investigated during our pilot phase 2 trial.

After completing the double-blind phase of the trial, all participants will undergo one month of wash-out before being offered the option of participating in an open label extension phase with serlopitant 5 mg PO daily for continued monitoring of toxicity and efficacy. This extension phase will be 12 months for participants enrolled prior to May 2020, and 3 months for participants enrolled after May 2020, due to drug availability.

Due to the potential pain and skin injury that can be incurred with travel for participants with more severe EB subtypes, this trial is intentionally designed to minimize the number of in-person clinic visits through use of home itch diaries and phone follow-up, as recommended by the FDA in their EB-specific guidance document.[4]

7. Efficacy Endpoints:
Based on the data from our pilot study, the primary statistical endpoint will be the proportion of participants who achieve at least a 3-point reduction in average daily NRS itch severity from baseline at the end of the two-month double-blind phase.

Secondary endpoints will include:
1. Comparative weekly change in daily worst-itch NRS during the double-blind phase
2. Safety, as measured by adverse events during the course of the double-blind and open label phases of the trial. These will also include changes in ECG parameters and safety labs following drug exposure.
3. Comparative weekly change in average daily NRS itch severity during the double-blind phase
4. Proportion of participants who achieve at least 2 and 4-point reductions in average daily NRS itch severity from baseline at the end of the double-blind phase
5. Proportion of participants who achieve at least a 30% or 50% reduction in average daily NRS itch severity from baseline at the end of the double-blind phase
6. Change in participant-reported outcomes of global assessment of change in itch and overall improvement as measured by static participant assessment of itch, participant global assessment of change in itch severity, and caregiver global assessment of change in itch severity.

The Stanford EB Itch Survey also captures additional measures related to symptoms during dressing changes, sleep quality, and other quality of life measures which may be explored.

Additional exploratory endpoints will revolve around mean comparative change in wound surface areas, comparative change in NRS itch severity at target wounds, and the change in median NRS score by group from baseline at month 1, month 2, and month 3.

We will also assess participant and caregiver perceived change in wound size and number, and pain as measured with the Wong-Baker FACES[5] scale, and changes in quality of life assessed with ItchyQoL,[6] and the Dermatology Quality of Life Index (DLQI).[7]

Further exploratory analysis comparing multiple pruritus-related instruments will be explored to determine the most appropriate measures of pruritus for this participant population.

8. Inclusion / Exclusion Criteria:

Inclusion criteria:

1. Males or females who are at least 13 years of age.
2. Willing and able to understand and sign informed assent/consent. Adolescents will need a parent or guardian willing and able to give consent.
3. Clinical diagnosis of epidermolysis bullosa (Dystrophic EB, EB Simplex, Junctional EB, or Kindler syndrome).
4. History of chronic pruritus of at least 6 weeks in duration
5. NRS pruritus score of at least 5 on average itch score in the past 24 hours at Screening Visit or Pre-Screening Phone Call
6. Female participants of childbearing potential, must have a confirmed negative urine pregnancy test prior to study treatment and be willing to use effective contraception for the duration of the trial
7. Judged to be in good health based upon the results of a physical examination, medical history, and safety laboratory tests.

Exclusion criteria:

1. Have any medical condition or disability that would interfere with the assessment of safety or efficacy in this trial or would compromise the ability of the participant to travel to Stanford, to undergo study procedures, or to give informed consent.
2. History of sensitivity to any components of the study material.
3. Females of childbearing potential who are unwilling to use adequate contraception or who are breast feeding.
4. Have any chronic or acute medical condition that, in the opinion of the investigator, might interfere with the study results or place the participant at undue risk.
5. Have chronic renal disease, i.e., serum creatinine greater than 2 times the upper limit of normal.
6. Have chronic liver disease, i.e., AST or ALT greater than 2 times the upper limit of normal. Participants with hepatitis B and C who have normal liver function may be enrolled.
7. Have a current malignancy (e.g. Hodgkin's lymphoma, myeloma, B or T cell lymphoma) or blood cell dyscrasia (e.g., polycythemia or myelofibrosis) that could lead to systemic chronic pruritus.
8. History of thyroid cancer, thyroid nodules, inadequately treated thyroid disease, or abnormal TSH or free T4 at screening: TSH >10, TSH > 5 with low free T4, TSH <0.1, TSH < 0.4 with high free T4.
9. Known history of abnormalities in adrenal or pituitary function (pituitary adenoma, adrenal insufficiency, or adrenal nodule).
10. Screening cortisol < 3 mcg/dL
11. Unevaluated abnormalities in cortisol, ACTH, or prolactin.
12. Have pruritus of psychogenic etiology (delusions of parasitosis, obsessive compulsive disorder and major depression) or neuropathic etiology (due to shingles, spinal cord injury or with neurologic deficit).

13. Have pruritus due to urticaria, drug allergy, or infection (such as pityriasis rosacea or tinea or active human immunodeficiency virus [HIV]). Note: Participants with HIV who have undetectable viral load, CD 4 counts >200 cells/cc, and stable retroviral therapy may enroll.
14. Have taken investigational medications within 30 days prior to Screening.
15. Are unwilling to discontinue specific medications that, in the view of the investigator may have significant interactions with the trial drug, for at least 30 days prior to initiation of study and throughout the study period (all severe CYP34A inhibitors - this includes miconazole, delavirdine, conivaptan, clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir).
16. Are unable or unwilling to maintain their current anti-itch and opioid-based pain medications at a stable dosage through the course of the two months of active treatment (including but not limited to opioid pain medications, antihistamines, tri-cyclic antidepressants, and gabapentin)
17. Started or changed medications, creams, or emollients including over the counter preparations or bath oils specifically for treatment of pruritus within 30 days prior to Screening.
18. Have expressed suicidal ideation with some intent to act in the past 12 months
19. Have any social or medical condition (e.g. alcoholism, drug dependency, psychotic state) that, in the investigator's opinion, might interfere with the participant's ability to comply with the requirements of the protocol.

9. Study visits: (see Appendix, Schedule of Events)

9.A. Screening Visit:

Participants will be pre-screened over the phone prior to the screening visit to assess inclusion criteria. During the screening visit, following informed consent (and assent as applicable for adolescents), medical history, medication history, and relevant medical records will be collected. Vital signs (including weight) will be recorded and a physical examination will be performed.

When obtaining medical history in female participants we will specifically inquire about:

- Menstruation: Amenorrhea (in participants that had previously reached menarche), abnormal menses, significant abnormal vaginal bleeding
- Significant abnormal vaginal discharge.
- Known breast lumps, nipple discharge
- Participants > 40 years old: if they have had previous mammograms, when their last mammogram occurred, if any mammograms have been abnormal.

If any of the above abnormalities are present, they will evaluated prior to trial entry.

9.A.i. Wound Assessments:

Investigators will quantify and assess affected skin surface area with body map diagrams and photography. Photography may be obtained using the Tissue Analytics smartphone app. This is a HIPAA-compliant app that is able to photograph a wound, measure the wound, and track it over time. Wounds will be classified as chronic open (unhealed for > 12 weeks) or recurrent (heals in < 12 weeks and re-opens).

If applicable, we will identify up to 4 target wounds that meet the following criteria:

1) Measure at least 10 cm^2
2) Wound-specific NRS itch score of at least 5 during the past 24 hours

We will aim to capture the participant's most pruritic wounds as target wounds.[8] Target wounds will be photographed.

Participants will evaluate the following characteristics of each target wound: average itch in past 24 hours (NRS), worst itch in past 24 hours (NRS), average pain in past 24 hours (Wong Baker FACES Pain Scale). If

the participant's most pruritic wounds do not meet criteria for inclusion as target wounds, we will not photograph any wounds, but will ask participants to evaluate wound characteristics.

9.A.ii. Global Pruritus Assessments:
In addition to the NRS, pruritus will be evaluated with the following questionnaires:

1) Stanford EB Itch Survey
2) Itch Man[9]
3) Dermatology Quality of Life Index (DLQI)[7]
4) ItchyQoL[6]
5) Leuven Itch Scale[10]
6) Static Participant Global Assessment of Itch Severity
7) PROMIS Scales – Pediatric versions for participants <18y
8) Itch Controlled Days Questionnaire

9.A.iii. Electrocardiogram:
Baseline electrocardiogram (ECG) will be performed, using our established technique using non-stick pads to prevent injury due to electrodes. The overall ECG assessment (abnormal or normal) will be summarized. We will review whether the participant has had previous echocardiogram and the results will be included in the chart.

9.A.iv. Safety Laboratory Assessments:
We will assess the following labs:

1) Complete blood count (CBC)
2) Complete metabolic panel (CMP)
3) Urinalysis
4) Urine pregnancy test (if applicable)
5) Thyroid stimulating hormone (TSH)
6) Free T4
7) Cortisol
8) ACTH
9) Prolactin

Labs will ideally be drawn in the morning. Participants with low cortisol will be referred to their primary care physician or endocrinologist for further evaluation which may include AM cortisol level or dynamic testing with a standard cosyntropin stimulation test. If prolactin is abnormal, participants will be required to have this evaluated prior to study participation.

At the discretion of the investigator, labs drawn by non-study providers within 60 days of screening and baseline may be substituted for the trial screening labs so long as they include the same studies of interest. This is in order to reduce unnecessary skin trauma and a potentially psychologically traumatic blood draw.

9.A.v. Home Diaries and Preparation for Month 1:
Participants will be asked to complete a daily itch diary with their average itch score (NRS) over the past 24 hours and their itch score during dressing changes or bathing (NRS). This may either be an online diary (administered securely through REDCap[11]) or a paper diary, based on participant preference.

Female participants of childbearing potential (including participants that have not yet undergone menarche) who are not using hormonal contraception will be provided with a menstrual diary to complete.

Participants will be provided with a lab requisition form to have their Month 1 labs drawn at a Quest lab near their home.

Participants will also be specifically educated about the signs and symptoms of adrenal insufficiency (e.g. fatigue, abdominal pain, dizziness, etc.) and will be instructed to report these symptoms to study investigators.

9.B. Baseline Visit (Within 30 Days of Screening):
Participants will return to Stanford for a baseline visit within 30 days of screening. Per the discretion of the investigator(s), screening and baseline may be combined into the same visit. Outside of this window, participants will be considered a "screen fail" and would have to undergo another screening visit.

9.B.i Eligibility Confirmation and Randomization:
Vital signs, medical history, concomitant medications, ECG results, and safety lab results obtained at screening will be reviewed for eligibility. Once participant eligibility is confirmed, randomization will occur.

9.B.ii. Assessments:
Target wounds will again be characterized and photographed. The study diary will be reviewed to assess participants' mean daily pruritus rating and variation of itch scores at baseline.

If the baseline and screening visit are combined, participants will be instructed to complete a minimum of 7 days of their nightly itch diary prior to starting medication in order to establish baseline itch severity.

Study medication will be dispensed one week after eligibility is confirmed to reduce confusion about when to begin study medication.

The scheduling of the Month 1 phone call will account for this 1-week lag prior to starting medication.

9.C. Month 1 Phone Call:
Month 1 phone call will occur 30 days after starting the study medication, +/- 14 days.

9.C.i. Safety Laboratory Assessments:
Safety labs will be drawn as early as 10 days prior to scheduled phone follow-up at month 1 following initiation of active treatment. Labs will be drawn at a local laboratory convenient for the participant. They will have the option to have labs drawn at Stanford if they prefer.

At the discretion of the investigator, labs drawn by non-study providers within this time window (1 month after medication initiation, +/- 10 days) may be substituted for the study lab draw, as long as they include the same studies of interest. This is in order to reduce unnecessary skin trauma and a potentially psychologically traumatic blood draw.

Safety labs will include:
1) Complete blood count (CBC)
2) Complete metabolic panel (CMP)
3) Urinalysis
4) Urine pregnancy test (if applicable)

Medication will not be sent until safety labs have been reviewed by the investigator. Any abnormal labs will be reviewed by investigator and appropriate follow-up will be initiated as needed.

9.C.ii. Assessments by Phone:

Participants will be queried for any adverse events and changes to concomitant medications or wound dressing regimen. These will be assessed by investigators.

Participants will specifically be asked about any symptoms of adrenal insufficiency (e.g. fatigue, abdominal pain, dizziness, etc.). Participants who report symptoms concerning for adrenal insufficiency will be evaluated with instructions to follow-up urgently with their primary care provider for further evaluation, which should include an AM cortisol. If this is abnormal, we will coordinate with their primary care provider for urgent referral to endocrinology for further evaluation including cosyntropin stimulation testing.

Female participants will specifically be queried regarding abnormal vaginal bleeding (new and different from any related to any known EB wounds in the genital area), new breast findings (not related to EB wounds), expulsion of an intrauterine device or implant, or vaginal discharge. If any of these concerns are identified, the participant will be urgently referred to their primary care provider for further evaluation.

9.C.iii. Assessments via REDCap:
A link will be sent to the participant to complete the following assessments via REDCap:

1. Stanford EB Itch Survey
2. Itch Man
3. DLQI
4. ItchyQoL
5. Leuven Itch Scale
6. Static Participant Global Assessment of Itch Severity (sPGAIS)
7. Participant Global Impression of Change in Itch Severity (pGICIS)
8. Caregiver Global Impression of Change in Itch Severity (cGICIS)
9. PROMIS scales – Pediatric versions for participants <18y
10. Itch Controlled Days Questionnaire

If a participant is unable to access REDCap, these questionnaires will be administered over the phone. Instruments requiring visual analog scale (VAS), such as the Leuven Itch Scale, will be mailed, faxed, or emailed to enable the participant to physically complete the VAS.

9.C.iv. Reminders and Instructions:
Participants will be reminded to comply with completing their itch journals and medication.

Participants will be instructed to mail back their month 1 itch diaries once they receive their new itch diaries (not applicable if participant has chosen to utilize a REDCap based online diary). Additional medication will be dispensed pending acceptable safety labs and mailed to participants along with new Month 2 itch diaries (if participant has chosen physical diary). Participants will be asked to set aside any medication from their month 1 medication bottle and seal the bottle to be returned at their next visit and begin month 2 treatment from the new bottle.

9.D. Month 2 Study Visit:
At 60 days following initiation of study medication (+/- 14 days), participants will return to Stanford for a follow up clinic visit.

Participants will be queried for any adverse events and changes to concomitant medications or wound dressing regimen. These will be assessed by investigators. Menstrual diaries will be collected and reviewed. Participants will be asked to submit their nightly itch diary (NRS), along with any unused medications from the prior two months of treatment for assessment of medication adherence.

Participants will specifically be asked about any symptoms of adrenal insufficiency (e.g. fatigue, abdominal pain, dizziness, etc.). Participants who report symptoms concerning for adrenal insufficiency will be evaluated with instructions to follow-up urgently with their primary care provider for further evaluation, which should include an AM cortisol. If this is abnormal, the participant will be referred urgently to endocrinology for further evaluation including cosyntropin stimulation testing.

Female participants will again be queried regarding abnormal vaginal bleeding (new and different from any related to any known EB wounds in the genital area), new breast findings (not related to EB wounds) and vaginal discharge. If any of these concerns are identified, the woman will be referred to their primary care provider for evaluation.

Vital signs (including weight) will be recorded. Physical examination will be performed.

9.D.i. Wound Assessments:
Participants will be reminded of the location of their target wound(s). Target wounds will be photographed. Participants will evaluate the following characteristics of each target wound: average itch in past 24 hours (NRS), worst itch in past 24 hours (NRS), average pain in past 24 hours (Wong Baker FACES Pain Scale).

If the participant's most pruritic wounds did not meet initial criteria for inclusion as target wounds, we will ask participants to evaluate wound characteristics of these same wounds evaluated at Screening.

Participants and caregivers will be asked about their perceived change in wound size for each target wound and for perceived change in total wound number.

9.D.ii. Global Pruritus Assessments:
The following questionnaires will be completed:

1) Stanford EB Itch Survey
2) Itch Man
3) Dermatology Quality of Life Index (DLQI)
4) ItchyQoL
5) Leuven Itch Scale
6) Static Participant Global Assessment of Itch Severity
7) Participant Global Impression of Change in Itch Severity
8) Caregiver Global Impression of Change in Itch Severity
9) PROMIS scales – Pediatric versions for participants <18y
10) Itch Controlled Days Questionnaire

9.D.iii. Electrocardiogram:
Electrocardiogram (ECG) will be performed, using our established technique using non-stick pads to prevent injury due to electrodes. The overall ECG assessment (abnormal or normal) will be summarized and changes from baseline will be descriptively characterized.

9.D.iv. Safety Laboratory Assessments:
Safety labs will again be assessed:

1) Complete blood count (CBC)
2) Complete metabolic panel (CMP)
3) Urinalysis
4) Urine pregnancy test (if applicable)
5) Thyroid stimulating hormone (TSH)
6) Free T4

7) Cortisol
8) ACTH
9) Prolactin

Labs will ideally be drawn in the morning. At the discretion of the investigator, labs drawn by non-study providers within this time window (2 months after medication initiation, +/- 10 days) may be substituted for the study lab draw, as long as they include the same studies of interest. This is in order to reduce unnecessary skin trauma and a potentially psychologically traumatic blood draw.

Any abnormal labs will be reviewed by investigator and appropriate follow-up will be initiated as needed.

Any clinically significant abnormalities identified in prolactin or thyroid function will be followed until the level returns to baseline or appropriate follow-up can be established with a local provider.

9.D.v. Reminders and Home Diaries:
Participants will be given new daily itch diaries to complete during the wash-out period. They will be reminded to continue to complete their daily diary entries.

Female participants of childbearing potential (including participants that have not yet undergone menarche) who are not using hormonal contraception will be provided with a menstrual diary to complete.

Female participants of childbearing potential will be reminded to continue their acceptable form of contraception until 2 weeks after study drug discontinuation.

9.E. Month 3 Phone Call / End of Wash Out Phase:
One month (30 days, +/- 14 days) after completing the double-blind phase participants will be contacted by phone.

9.E.i. Assessments by Phone:
Participants will be queried for any adverse events and changes to concomitant medications or wound dressing regimen. These will be assessed by investigators. Participants will specifically be asked about any symptoms of adrenal insufficiency (e.g. fatigue, abdominal pain, dizziness, etc.).

Female participants will specifically be queried regarding abnormal vaginal bleeding (new and different from any related to any known EB wounds in the genital area), new breast findings (not related to EB wounds), expulsion of an intrauterine device or implant, or vaginal discharge. If any of these concerns are identified, the participant will be referred to their primary care provider for further evaluation.

9.E.ii. Global Pruritus Assessments by REDCap:
A link will be sent to the participant to complete the following assessments via REDCap:
1. Stanford EB Itch Survey
2. Itch Man
3. DLQI
4. ItchyQoL
5. Leuven Itch Scale
6. Static Patient Global Assessment of Itch Severity (sPGAIS)
7. Patient Global Impression of Change in Itch Severity (pGICIS)
8. Caregiver Global Impression of Change in Itch Severity (cGICIS)
9. PROMIS scales – Pediatric versions for participants <18y
10. Itch Controlled Days Questionnaire

If a participant is unable to access REDCap, these questionnaires will be administered over the phone. Instruments requiring visual analog scale (VAS), such as the Leuven Itch Scale, will be mailed, faxed, or emailed to enable the participant to physically complete the VAS.

9.E.iii. Safety Laboratory Assessments:
Safety labs will again be assessed:

1) Complete blood count (CBC)
2) Complete metabolic panel (CMP)
3) Urinalysis
4) Urine pregnancy test (if applicable)
5) Thyroid stimulating hormone (TSH)
6) Free T4
7) Cortisol
8) ACTH
9) Prolactin

Labs will ideally be drawn in the morning. At the discretion of the investigator, labs drawn by non-study providers within this time window (30 days, +/- 10 days) after completing the double-blind phase may be substituted for the study lab draw, as long as they include the same studies of interest. This is in order to reduce unnecessary skin trauma and a potentially psychologically traumatic blood draw.

Any abnormal labs will be reviewed by investigator and appropriate follow-up will be initiated as needed.

Any clinically significant abnormalities identified in prolactin or thyroid function will be followed until the level returns to baseline or appropriate follow-up can be established with a local provider.

9.F. Continuation of Optional Open Label Phase:
Participants who are eligible for the Open Label Phase in the opinion of the investigators (taking into consideration participant's prior documented adverse events, current medical status, and adherence to trial protocol) and who elect to participate in the Open Label Phase will then be mailed serlopitant 5mg tablets as well as a new study diary to be completed weekly.

This extension phase will be 12 months for participants enrolled prior to May 2020, and 3 months for participants enrolled after May 2020, due to drug availability.

Participants who elect to participate in the open label study (who enrolled prior to May 2020) will undergo open label study phone visits at Baseline, Open Label Month 1, Open Label Month 3, Open Label Month 6, and Open Label Month 12.

Participants who elect to participate in the open label study (who enrolled after May 2020) will undergo open label study phone visits at Baseline, Open Label Month 1, and Open Label Month 3.

9.F.i. Safety Laboratory Assessments:
The safety labs obtained for the Month 3 visit may be used as baseline labs for the Open Label Phase, as long as the labs are drawn within 4 months of the open label baseline visit. Safety labs will be drawn as early as 10 days prior to scheduled phone follow-ups. Labs will be drawn at a local laboratory convenient for the participant. They will have the option to have labs drawn at Stanford if they prefer.

Safety labs will include:

1) Complete blood count (CBC)
2) Complete metabolic panel (CMP)
3) Urinalysis
4) Urine pregnancy test (if applicable)
5) Thyroid stimulating hormone (TSH)
6) Free T4
7) Cortisol
8) ACTH
9) Prolactin

Serlopitant will not be sent until safety labs have been reviewed by the investigator. Any abnormal labs will be reviewed by investigator and appropriate follow-up will be initiated as needed.

9.F.ii. Assessments by phone:
Participants will be queried for any adverse events and changes to concomitant medications or wound dressing regimen. These will be assessed by investigators. Participants will specifically be asked about any symptoms of adrenal insufficiency (e.g. fatigue, abdominal pain, dizziness, etc.). Participants who report symptoms concerning for adrenal insufficiency will be instructed to follow-up urgently with their primary care provider including an AM cortisol assessment. If this is abnormal, we will coordinate with their primary care provider for urgent referral to endocrinology for further evaluation including cosyntropin stimulation testing.

Female participants will specifically be queried regarding abnormal vaginal bleeding (new and different from any related to any known EB wounds in the genital area), new breast findings (not related to EB wounds), expulsion of an intrauterine device or implant, or vaginal discharge. If any of these concerns are identified, the participant will be referred to their primary care provider for further evaluation.

9.F.iii. Assessments via REDCap:
A link will be sent to the participant to complete the following assessments via REDCap:

1. Stanford EB Itch Survey
2. Itch Man
3. DLQI
4. ItchyQoL
5. Leuven Itch Scale
6. Static Patient Global Assessment of Itch Severity (sPGAIS)
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8. Caregiver Global Impression of Change in Itch Severity (cGICIS)
9. PROMIS scales – Pediatric version for participants <18y
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If a participant is unable to access REDCap, these questionnaires will be administered over the phone. Instruments requiring visual analog scale (VAS), such as the Leuven Itch Scale, will be mailed, faxed, or emailed to enable the participant to physically complete the VAS.

Participant Instruments requiring visual analog scale (VAS), such as the Leuven Itch Scale, will be mailed, faxed, or emailed to enable the participant to physically complete the VAS.

9.C.iv. Reminders and Instructions:
Participants will be instructed to mail back their diaries, remaining serlopitant, and empty bottles.

9.C.v. Dispensing Serlopitant:
Additional serlopitant will be dispensed pending investigator review of safety labs.

9.G. Early Termination Protocol:

9.G.i. Early Termination in Double Blind Phase:
If a participant terminates study participation early, while in the double-blind phase, they will be asked to return to Stanford for an Early Termination visit.

Study staff will review the reason for early termination and investigators will facilitate medical follow-up as needed. Study staff will review adverse events, changes to concomitant medications, diaries, medication adherence, and will administer questionnaires.

We will request that the participant have safety labs drawn.

They will be instructed to return study diaries, remaining medication, and empty medication bottles.

If the participant is willing to come to Stanford, we will perform vital signs, physical examination, target wound assessment and photographs, and ECG.

9.G.ii. Early Termination in Open Label Phase:
If a participant terminates study participation early, while in the open label phase, study staff will call the participant for an Early Termination call.

Study staff will review the reason for early termination and investigators will facilitate medical follow-up as needed. Study staff will review adverse events, changes to concomitant medications, diaries, medication adherence, and will administer questionnaires.

We will request that the participant have safety labs drawn.

They will be instructed to return study diaries, remaining medication, and empty medication bottles.

9.H Modification to Study Procedures Due to COVID-19
Due to the pandemic caused by the COVID-19 virus, at the discretion of the Principal Investigator, it may be necessary for participants and staff welfare that study visits under this protocol are conducted remotely. This may apply to both initial enrollment visits, alongside follow up visits. All remote study visits will be conducted securely using HIPAA compliant telemedicine tools, including but not limited to the integrated EPIC telemedicine system, ensuring patient confidentiality and data security. As a consequence of conducting remote study visits, it may not be feasible to conduct all study related procedures as documented in the schedule of events.

As such, the following modifications to these procedures may be required:

9.H. i. Consent: Potential participants will be provided with advanced copies of the informed consent form either by mail or email. During the remote combined screening/baseline visit, participants will be consented remotely and will then return the signed consent form by mail or secure email. Participants may sign consent electronically via secure database.

9.H. ii. Physical Exam: Examination elements that are feasible will be conducted remotely using video streaming. All practical attempts will be made to obtain physical examination records from the last 12 months.

9.H. iii. Vital Signs, Height & Weight: These events will be omitted during remote study visits, as it is not feasible to conduct these measurements remotely. As these do not contribute to the eligibility assessment nor

adversely affect Serlopitant's safety profile, they are not necessary for study participation. If there are concerns about participant's medical stability, investigators may refer patients to their primary care physicians or other providers for their assessment prior to making determination of eligibility for the study.

9.H. iv. Electrocardiogram (ECG): This test will be omitted during remote study visits to avoid potential harm to the participant, as ECG leads will tear their fragile skin and result in painful wounds. At Stanford, we have developed a protocol to perform ECGs on EB patients safely by knowledgeable, specifically trained personnel. Therefore, we will only perform ECGs at in-person visits at Stanford. 31 patients previously completed Serlopitant in studies where ECGs were not performed.

9.H. v. We will schedule lab draws and urine tests at local labs convenient for the participant. Labs and urine test will ideally be drawn within 72 hours of remote visit.

9.H. vi. Photographs: A subset of participants with target wounds as defined in the protocol will be asked to securely send digital photos during or after combined screening/baseline visit (or follow up visits as applicable) using Tissue Analytics smart phone application or secure email. Participants will be instructed on how to take these photos, which will include a ruler for measurement. Measurements will be taken from these photos and used for analysis.

9.H. vii. Serlopitant Drug Dosing & Dispensing: Serlopitant dosing instructions will be provided during the combined screening/baseline visit as usual. Study drug will be dispensed only after consent has been obtained, eligibility verified, and participant randomized to receive placebo or active drug. Medication will be shipped to patients overnight at ambient temperature. Adult signature will be required for delivery.

10. Statistical Analysis Plan:

10.A. Randomization Plan

Participants who are determined to be eligible and proceed to randomization will be assigned a unique randomization code. The randomization key will be held by the trial statistician or a blinded member of the study team. Unblinding for each participant will occur for each participant once they complete the randomized phase AND their data is locked, or if a trial participant experiences an adverse event or any other significant safety concern where the investigator deems unblinding of that individual necessary for participant safety. This unblinding strategy was chosen to facilitate participants' decisions on whether to participate in the open label phase. Given that the critical endpoints in this trial are participant-reported, the investigators deemed that equipoise would be maintained under these circumstances.

In order to prevent operational bias (which could theoretically arise should interim aggregate analysis be performed), individual participants' itch scores will be data locked upon completion of the randomized phase and accessible thereafter only to their assigned coordinators and/or coordinators tasked with auditing a participant's data for data integrity. Investigators will not be provided REDCap access for aggregate analysis until the final participant has completed the randomized phase of the trial.

In order to balance allocation of more severe EB subtypes, participants with either dystrophic EB (including both dominant and recessive types) or junctional EB will receive a separate set of randomization codes for binary stratification of these more severe EB subtypes among the two treatment arms.

10.B. Sample Size Calculation:

This Phase 2 clinical trial involving at least 40 participants is powered to determine statistically significant differences in the placebo (N=20 participants) vs. 5 mg (N=20 participants) groups. The sample size is powered to detect moderate differences in the proportion of responders (3-point NRS decrease in itch) between the active and placebo groups.

Results from our Phase 2 trial showed that 43% of active participants were responders vs. only 14% in placebo were responders (1 out of 7). Using a one-sided Fisher's exact test, our power calculations show that we need to enroll a total of 40 participants (1:1) to have 80% power to detect a difference of 50% vs 10% responder rates in active and placebo groups, respectively.

	Responder	None	Total
Active	10	10	20
Placebo	2	18	20
Total	12	28	40

Fisher's exact test
The two-tailed P value equals 0.01

Because itch is subjective and varies daily, participants will be asked to keep an itch diary nightly before bedtime when itch has been reported to be the worst. According to recent psychometric studies, the important difference for clinical improvement of chronic pruritus ranks between a drop of 2 to 3 points on the NRS[7,8,12]. This trial is powered to be able to detect this level of clinically meaningful reduction in itch.

10.C. Statistical plan for efficacy endpoints:
The proportion of participants achieving 2, 3, and 4-point reductions in average daily NRS with serlopitant at the end of 8 weeks of active treatment will be compared to placebo using Fisher's Exact test. A similar approach will be utilized to compare the proportion of participants achieving at least a 30% or 50% reduction in itch as measured by NRS from baseline at 8 weeks.

We will also measure continuous change in average daily NRS and worst-itch NRS score by group over time. For each participant, we will plot their average itch scores over time before and after drug intervention. For each dosage group, we will use linear regression methods with mixed effects (GLM, SAS) to track the change in itch in each of the groups from baseline.

Furthermore, we will evaluate monthly change in median NRS itch scores by group as compared to baseline, which will enable evaluation of durability through assessment of NRS itch scores at month 3 of washout.

Primary and secondary endpoints will be performed on an intention to treat basis. This study will provide the effect size, standard deviation and range of itch scores in EB participants in order to properly power a phase 3 trial.

11. Safety Assessment and Monitoring

11.A. Pregnancies and Contraception Requirements for Females
For the purposes of this study, a female of childbearing potential is defined as any female who has experienced menarche and is pre-menopausal, unless permanently surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause in a previously menstruating female. We note that many adolescents with severe subtypes of epidermolysis bullosa have may significantly delayed age of menarche.

For the purposes of this study, all female participants of childbearing potential must use highly effective contraception (i.e. pregnancy prevention method with a failure rate of <1% per year) from the time of the Screening visit until 2 weeks after the last dose of study drug. This includes the use of one or more of the following acceptable methods:

1. Surgical sterilization (e.g., bilateral tubal occlusion or ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
2. Total (as opposed to periodic or cyclic) abstinence from heterosexual intercourse, only if planned for the entire duration of the study period and consistent with the preferred and usual lifestyle for the participant
3. Hormonal contraception associated with consistent inhibition of ovulation; these may include (but are not necessarily limited to) oral, intravaginal, implantable, injectable, or transdermal delivery methods
4. Intrauterine device/system
5. Exclusive (sole) monogamous intercourse with a sterilized (i.e., vasectomized) or otherwise non-fertile (e.g., castrated) male partner; the male partner must have received medical assessment of the surgical success

Any pregnancy occurring in a female participant or the female partner of a male participant, from the first study drug administration through the required follow-up visit will be reported within 24 hours of the investigator's awareness of the pregnancy. Any pregnancies that occur will be dated for time of conception through coordination with participants' family medicine or obstetrics provider based on ultrasound findings, quantitative serum BHCG results, last menstrual period, physical examination, and timing of coitus.

The investigators will follow the pregnancy to delivery or other pregnancy outcome. Pregnancy in a female clinical trial participant or female partner of a male clinical trial participant is not an SAE per se.

Any abnormal pregnancies that occur during the trial will be flagged as a serious adverse event and all available information will be captured as part of the CRF. Abnormal pregnancies include (but are not limited to): spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth).

Complications during pregnancies will be reported as such even if they occur after the Follow-up visit. All exposed infants will be followed and assessed at birth. Any congenital anomalies/birth defects will be recorded in the CRF and reported as SAEs.

11.B. Study Drug Discontinuation

Participants should be discontinued from study drug treatment in any of the following situations:

1. A female participant desires to become pregnant at the current time, stops contraception, expels her intrauterine device/implant, or becomes pregnant
2. A female participant has new breast findings (e.g. a palpable mass or abnormal mammography, discharge), or has abnormal vaginal discharge or bleeding
3. The participant decides to discontinue study drug treatment, or withdraws consent from the study
4. The participant receives a strong CYP3A4 inhibitor
5. Any medical condition that may jeopardize the participant's safety if study drug is continued, in the investigator's opinion; this may include the development of persistently (2 successive occasions) abnormal thyroid function tests (TSH >10, or TSH > 5 with low free T4; TSH <0.1, or TSH < 0.4 with high free T4); abnormal morning prolactin >100 ng/mL, cortisol, or corticotropin levels; or signs and symptoms of adrenal insufficiency. Participants with abnormal endocrine assessments will be referred to an endocrinologist for evaluation, which may include repeat laboratory assessment for participants with abnormal thyroid levels every 4-6 weeks until the abnormalities resolve.
6. Discontinuation is deemed to be in the best interest of the participant, in the investigator's opinion, including evidence that the participant does not meet inclusion/exclusion criteria intended primarily for safety reasons, or a persistent lack of adherence to study procedures

11.C. Definition of Adverse Events:

An adverse event (AEs) or suspected adverse reaction is considered "serious" (SAE) if, in the view of the investigator, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The Principal Investigator will provide oversight on monitoring safety/AEs/SAEs at this site. For data safety monitoring, the principal investigator, co-principal investigator, and any sub-investigators will formally meet monthly to review all new AEs, SAEs, and any safety concerns that arose in the past month.

11.C.i. Criteria for Unanticipated Problems:
The investigators as a group will assess whether the AE represents an unanticipated problem (UP) based on the following criteria:

Events (internal or external, deaths, life-threatening experiences, injuries, or other) occurring during the research study, which in the opinion of the PI meet ***all*** of the following criteria:

a) Unexpected in terms of nature, severity, or frequency, given (a) the research procedures described in the protocol-related documents, and (b) the characteristics of the participant population being studied; ***AND***
b) Related to participation in the research or there is a reasonable possibility or likelihood that the incident, experience, or outcome may have been caused by the procedures involved in the research; ***AND***
c) Harmful that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

11.D. Reporting Adverse Events:

11.D.i. Reporting UPs:
If the investigator determines that the AE represents a UP, the investigator will report the AE to the IRB **within 10 working days** from when the PI learns of the event.

If the adverse event does not qualify as a UP, the adverse event should be reported at continuing review.

11.D.ii. Reporting SAEs:
Unexpected deaths or life-threatening experiences **related** to the research will be reported to the IRB **within 5 working days** from PI learning of event.

Reporting any unexpected fatal or life-threatening suspected adverse reactions to the FDA will occur **no later than 7 calendar days** after initial receipt of the information.

Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to the FDA and all investigators will occur **no later than 15 calendar days** after determining that the information qualifies for reporting.

11.D.iii. Reporting AEs:
In this study, the occurrence of any AE from the time of informed consent until 4 weeks after the last dose of study drug will be reported to the Stanford IRB and the FDA.

Submission of annual progress reports will occur within 60 days of the anniversary of the date that the IND went into effect (date that clinical studies were permitted to begin).

11.E. Data Monitoring Plan:

Monthly to bimonthly, study staff will perform an internal quality control check of data to confirm that Good Clinical Practices are upheld and compliance with all regulations. This will include a review of source documents including the study paper chart, the informed consent, lab reports, physician notes, adverse event documentation, concomitant medication documentation, and online case report forms. CRFs may be used as source documents per PI discretion.

12. References:

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Appendix: Schedule of Events Table

	Screening		Double-Blind Phase				Optional Open-Label Phase				
	Pre-Screening	Screening	Baseline	Month 1	Month 2	Month 3	Baseline	Month 1	Month 3	Month 6[15]	Month 12[15]
	Phone Call	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call	Phone Call	Phone Call	Phone Call	Phone Call
Informed Consent		X									
Demographics	X	X									
Medical History	X	X									
Medication Review	X[1]	X[1]	X	X	X	X	X	X	X	X	X
Review Inclusion / Exclusion Criteria	X	X	X								
Vital Signs[2]		X	X		X						
Physical Examination		X	X		X						
Electrocardiogram (ECG)		X			X						
Target Wound Selection		X									
Target Wound Photographs[3]		X	X		X						
Target Wound Assessments[4]		X	X		X						
Questionnaire Completion[5]		X	X	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Dispense Study Diary(ies)[7]		X	X	X	X	X[14]	X	X	X	X	
Safety Laboratory Assessments[8, 9]		X[10]		X[11]	X[10]	X[10,11]	X[10,11]	X[11]	X[10,11]	X[11]	X[10,11]
Determination of Eligibility[12]			X								
Randomization			X								
Dispense Study Medication or Placebo			X	X							
Dispense Serlopitant						X[14]	X	X	X	X	
Review Adverse Events			X	X	X	X	X	X	X	X	X
Review Study Diary(ies)			X	X	X	X	X[13]	X[13]	X[13]	X[13]	X[13]

1: Includes a review of all medications taken within the previous 30 days
2: Includes height, weight, blood pressure, heart rate, temperature
3: Photographs only if participant has target wounds and has given consent for photography
4: Target wound assessment includes: average itch in past 24h, worst itch in past 24h, average pain in past 24h
5: Questionnaires include: Stanford EB Itch Survey, ItchMan, DLQI, ItchyQoL, Leuven Itch Scale, sPGAIS, PROMIS scales (pediatric versions for participants <18y), Itch Controlled Day Questionnaire.

6: Will also assess participant (pGICIS) and caregiver (cGICIS) impression of change in itch severity
7: Either electronic REDCap diary or paper diary. Completed paper diaries will be mailed back to Stanford; new paper diaries will be mailed to participant. Females of childbearing potential not on hormonal contraception will be given a menstruation diary in addition to the study diary.
8: Labs include: CBC, CMP, UA, UPT (if female of child-bearing potential)
9: Labs obtained from outside providers up to 60 days prior to Screening can be used as Screening labs for study purposes. as long as they contain the equivalent labs of interest
10: Additional labs obtained at Screening, Month 2, Month 3, Open Label: TSH, FT4, ACTH, cortisol, prolactin
11: Labs will be obtained at a local laboratory convenient for the participant, at +/- 10 days from target date of study visit.
12: Will determine if 30-day washout is needed from prohibited study medication
13: Open label phase diaries will be completed weekly
14: Will be performed only if participant elects to pursue optional open label phase
15: For participants enrolled prior to May 2020 who elect to continue in open label phase