1) **Title:** A Phase 2 trial of Neurokinin-1 Receptor Antagonist for the Treatment of Itch in Epidermolysis Bullosa patients

2) **PI:** Jean Tang, MD, PhD

3) **Funding:** Epidermolysis Bullosa Research Partnership (SPO # 117763)

4) **Fund sources for this project**:
Epidermolysis Bullosa Research Partnership (EBRP) – provided funding
Menlo Therapeutics, Inc. – provided study medication

5) Specific aims:
This study aims to determine the safety profile of Serlopitant (or VPD-737) in children (>13 y.o.) and adults with pruritus associated with epidermolysis bullosa (EB). This study also aims to determine the efficacy of Serlopitant (5 mg) compared with placebo on reducing EB itch as measured by patient self-reports using a numeric rating scale (NRS) for itch severity and the Stanford EB itch questionnaire. A secondary aim of this study is to determine whether Serlopitant when compared with placebo reduces EB wounds and promotes healing as determined by serial photographs.
It is our hope that Serlopitant will reduce itch in adolescents and adults with EB.

6) **General background**:
NK1 receptor antagonists (Aprepritant and Serlopitant) were originally tested in clinical trials as an antiemetic and a medication to treat overactive bladder. Since 2005, NK1 receptor antagonists have been evaluated in 13 completed Phase I studies and two Phase 2b studies (N=300 subjects). Serlopitant has been well tolerated in young men at a single dose of 400mg, and in the elderly at a dose of up to 20mg. Repeat dosing of up to 50 mg a day for 4 weeks was well tolerated in young adults and elderly males. There were no drug-related serious adverse events (SAE) in these Phase I studies.

In a double-blinded, 6-week randomized trial of 257 adults with chronic pruritus, Serlopitant was shown to decrease itching significantly in a dose-dependent manner (submitted NEJM, clinicaltrials.gov NCT01951274). 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 5mg daily, and there were no treatment related serious adverse events. Based on this data, we have chosen to compare 5mg serlopitant vs. placebo. When assessing pruritus with a visual analog scale (VAS), symptoms were reduced in a statistically significant manner in both the 1mg ($p = 0.001$) and the 5mg ($p = 0.002$) dose groups when compared to placebo. After 6 weeks of treatment, nearly 70% of participants taking 5mg of serlopitant reported a 2-point reduction in VAS while nearly 50% of participants reported a 4-point decrease in VAS.

In a Phase 2 dose-ranging study of 557 subjects examining treatment of overactive bladder, the most common clinical AEs across all treatment groups were headache (5.7%), diarrhea (5.2%), urinary tract infection (4.7%), dry mouth (4.5%), nasopharyngitis (4.5%), upper respiratory tract infection (4.3%), fatigue (4.1%), dizziness (3.8%), back pain (2.9%), nausea (2.3%), and peripheral edema (2.2%).

Serlopitant has been more recently evaluated in a Phase 2 study of 257 adult subjects 18-65 years of age with chronic pruritus (TCP-101). In this study, treatment-emergent AEs (TEAEs) were reported in 25.4% of subjects in the placebo group and in 31.3%, 36.9%, and 37.5% of subjects in the serlopitant 0.25 mg, 1 mg, and 5 mg groups, respectively. Two severe TEAEs were reported: hypothyroidism in one subject in the serlopitant 0.25 mg group and peripheral neuropathy in one subject in the serlopitant 5 mg group. Both of these events were considered not related to study treatment.

Treatment-related TEAEs were reported in 7.9% of TCP-101 subjects in the placebo group and in 10.9%, 13.8%, and 12.5% of subjects in the serlopitant 0.25 mg, 1 mg, and 5 mg groups, respectively. “Nervous systems disorders” was the SOC with the highest incidence of treatment-related adverse events.

One SAE (spontaneous abortion) occurred in a TCP-101 subject in the serlopitant 1 mg group. This event was considered not related to study treatment. Five subjects (three in the placebo group, one in the serlopitant 1 mg group, and one in the serlopitant 5 mg group) discontinued the study as a result of a TEAE. Two of these subjects had events considered not related to study treatment (pruritus in 2 subjects) and three subjects had events considered to be treatment related (headache in one subject; diarrhea in one subject; and symptoms of a panic attack in one subject).

There was no evidence of meaningful trends in laboratory abnormalities or changes in vital signs in the TCP-101 study. Two subjects had a clinically significant change in an electrocardiogram (ECG): 1 subject in the serlopitant 0.25 mg group changed from normal to abnormal (clinically significant), and 1 subject in the serlopitant 5 mg group shifted from abnormal (not clinically significant) to abnormal (clinically significant).

Overall, the nonclinical and clinical studies to date have demonstrated that serlopitant has an acceptable safety and pharmacokinetic profile, and they support the further evaluation of Serlopitant in pruritus-related indications.

Overall, headache was the most commonly reported TEAE in TCP-101, reported in 6.3% of subjects in the placebo group and in 1.6%, 4.6%, and 1.6% of subjects in the serlopitant 0.25 mg, 1 mg, and 5 mg groups, respectively. Somnolence and diarrhea were the TEAEs with the highest overall incidence in the active-treatment groups. Somnolence was reported in 1.6% of subjects in the placebo group and in 1.6%, 4.6%, and 4.7% of subjects in the Serlopitant 0.25 mg, 1 mg, and 5 mg groups, respectively. Diarrhea occurred in 1.6% of subjects in the placebo group and in 0%, 6.2%, and 3.1% of subjects in the serlopitant 0.25 mg, 1 mg, and 5 mg groups, respectively. Most of the TCP-101 TEAEs were mild or moderate in severity.

Overall, the nonclinical and clinical studies to date have demonstrated that serlopitant has an acceptable safety and pharmacokinetic profile, and had been supported for further evaluation of Serlopitant in pruritus-related indications. Moreover, existing nonclinical data in adult animals and cumulative clinical data in adults support clinical trials in adolescents.

7) **Preliminary unpublished data**:

There is a trend towards greater reduction in itch severity as measured by daily self-reported NRS itch severity for serlopitant 5 mg as compared to placebo during the two month active trial period, though this was not statistically significant.

8) **Experimental design and data analysis**:

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 (DEB, EBS, or JEB).
4. Subjects must have pruritus of at least 6 weeks duration
5. History of chronic pruritus
6. On the Stanford EB Itch survey, subject must have a Screening Visit (Visit 1) NRS pruritus score of at least 4 on either (1) average itch score in the past 24 hours or (2) bathing/dressing itch score in the past 24 hours.
7. Female subjects must be of non-childbearing potential (ie, post-menopausal for at least 1 year, had a hysterectomy, or had a tubal ligation) or, if 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. Effective contraception is defined as follows: oral/implant/injectable/ transdermal contraceptives, intrauterine device, condom with spermicide, or diaphragm with spermicide. Abstinence or partner's vasectomy is acceptable if the female agrees to use effective contraception if she decides to discontinue abstinence or to have sexual intercourse with a non-vasectomized partner.
8. 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 subject to travel to Stanford or to undergo study procedures or to give informed consent.
2. Have a history of sensitivity to any components of the study material.
3. Are 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 subject at undue risk.
5. Have chronic renal disease, ie, serum creatinine greater than 2 times the upper limit of normal.
6. Have chronic liver disease, ie, AST or ALT greater than 2 times the upper limit of normal. Subjects with hepatitis B and C who have normal liver function may be enrolled.
7. Have a current malignancy (such as Hodgkin's lymphoma, B or T cell lymphoma, or myeloma) or blood cell dyscrasia (eg, polycythemia or myelofibrosis) that would lead to systemic chronic pruritus.
8. Subjects with untreated hyperthyroidism.
9. 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).
10. Have pruritus due to urticaria, drug allergy, or infection (such as pityriasis rosea or tinea or active human immunodeficiency virus [HIV]). Note: Subjects with HIV who have undetectable viral load, CD 4 counts >200 cells/cc, and stable retroviral therapy may enroll.
11. Have taken investigational medications within 30 days prior to Screening.
12. Are unwilling to discontinue specific pruritus medications for at least two weeks 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).

13. Within in the past 12 months, have expressed suicidal ideation with some intent to act.
14. Started or changed medications, creams, or emollients including over-the-counter (OTC) preparations or bath oil treatment for relief of pruritus within 3 months prior to Screening.
15. Have any social or medical condition (e.g. alcoholism, drug dependency, psychotic state) that, in the investigator's opinion, might interfere with the subject's ability to comply with the requirements of the protocol.

Statistical basis for the number of subjects to be enrolled:
This 14 patient clinical trial is powered only to determine large differences in the placebo (N=7) vs. 5 mg (N=14) groups. In power calculations, we assumed a mean of 8 NRS for the placebo vs. 5 NRS for the active with a SD of 3, and p-value of 0.05 (one sided).

Two-sample t test with equal variances						
	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
x	14	5	0.8017837	3	3.267852	6.732148
y	7	8	1.133893	3	5.225463	10.77454
combined	21	6	0.7121396	3.263434	4.514503	7.485497
diff		-3	1.38873		-5.906646	-0.0933544
Diff= mean (x) – mean (y)					t = -2.1602	
Ho: diff = 0					Degrees of freedom = 19	
Ha: diff < 0			Ha: diff != 0		Ha: diff > 0	
Pr(T < t) = 0.0219			Pr(|T| > |t|) = 0.0437		Pr(T > t) = 0.9781	

Statistical plan for analyzing at least the primary hypothesis:
The sample size is powered to detect small differences in NRS score. Because itch is subjective and varies daily, subjects will be asked to keep an itch diary every day. For each subject, 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 mix effects (GLM, SAS) to track the change in itch in each of the groups from baseline. This study will provide the effect size, standard deviation and range of itch scores in EB patients in order to properly power a larger phase 2 trial. This study can detect large differences in itch scores should Serlopitant decrease itch from severe to low-none at 1 and 2 months. At the 3 month follow up, we will measure the durability and length of response.

Matrix showing procedure plan for each study visit:

	Schedule of Events for Phase 2 Serlopitant						
	Screening period		Treatment period			Follow up	
	Phone call	**Visit 1**		**Visit 2**	**Visit 3**	**Phone call**	**Early Term**
	Screening call	**Screening visit**	**Determination of Eligibility**	**Month 1**	**Month 2/EOT**	**Month 3**	
Examination	**Day -60 to -30**	**Day -44* to -1**	**Months 6 to 0**	**Day 30 ±14**	**Day 60 ±14**	**Day 90 ±14**	
Informed consent/ Photographic consent		X					
Demographics		X					
Medical history		X	Review				
Prior[a] & current medications	X	X		X	X	X	X
Abbreviated physical examination		X			X		X
Vital signs		X		X	X		X
Urine pregnancy test (UPT)[b]		X	Review results	X	X		X
Inclusion/exclusion criteria	X	X					
Blood samples for clinical laboratory tests[c]		X[c]	Review results	X[c]	X[c]		X[c]
Randomization			X[h]				
NRS[d] & Stanford EB survey		X		X	X	X[e]	X
Photograph the affected area[f]		X		X	X		X
Dispense study medication			X[h]	X			
Dispense subject diary		X	X[h]	X	X[g]		
Review/collect diary with subject				X	X	X	X
Review and record adverse events				X	X	X	X

Note: NRS = numeric rating score.
* Includes up to 30 day washout from prohibited medications. The study medication and diary dispensation are to occur no more than 1-2 weeks after Screening Visit.

a: all medications taken within 30 days prior to screening.
b: for females of child-bearing potential.
c: all subjects: hematology, serum chemistry will be measured at Screening, Month 1, and Month 2/EOT or early termination (ET).
d: NRS recorded by subject daily, using diary, from screening visit through the end of the study; NRS is included in the Stanford EB Itch survey.
e: the Stanford EB survey will be administered over the phone by a member of the research staff.
f: photographs taken only if patient has signed photography consent
g: a return envelope will be provided for the patient to return the study diary to Stanford after the follow up phone call

	Schedule of Events for Phase 2 Serlopitant						
		Screening period		Treatment period		Follow up	
		Phone call	Visit 1		Visit 2	Visit 3	Phone call	Early Term

h: Patient letter of enrollment and study medication will be mailed to patient after determination of eligibility following the Screening Visit

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Each subject will be un-blinded individually after completing 3 months of study period. All patients who complete the study will be offered a 2-month trial on active drug. Patient who received active drug in the first phase will be contacted and asked if they would like to continue on active drug for an additional 2 months. Patients who received placebo in the first phase will be contacted and asked if they would like to repeat the study on open label for 2 months.

When this occurs, the schedule of events will be as follows:

Patients who would like to continue with the treatment for the open-label extension portion of the study will be provided with the research medication and research daily diary. They will be followed up by phone at baseline, 1 month, 2 months, and 3 months (wash out). In addition, they will go to an external lab near their home for lab monitoring that will occur once a month for the two months they are on active drug.

Data Monitoring Plan:

The Principal Investigator will provide oversight on monitoring safety/AEs/SAEs at this site. While there is not Data Safety Monitoring Board, the PI will act as the medical expert who answers safety/medical questions and who will provide medical expert opinion on this study. All AEs will be regularly reviewed and evaluated. The investigator will assess whether the AE represents an unanticipated problem (UP). If the investigator determines that the AE represents a UP, the investigator will promptly report the AE to the IRB. If the adverse event does not qualify as a UP, the adverse event should be reported at continuing review.

FDA Reporting:

In this study, the occurrence of any SAE 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 within 24 hours of coming to the attention of the investigator.

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 serious, unexpected suspected adverse reactions, 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.

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).

9) **Significance**:
Management of chronic pruritus is notoriously challenging for patients with 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 anti-histamines and topical steroids only minimally relieve itch.[3]

It is our hope that serlopitant will reduce itch in EB adolescents and adults. However, in the process of conducting this clinical trial, we will obtain critical FDA feedback on the development of novel itch endpoints, valid instruments to measure itch, and an orphan drug disease product designation – all of these important milestones will reduce the regulatory hurdles for future clinical trials in EB itch and stimulate more drug development in this unmet area.

10) **Key references**:
1. Danial C AR, Gorell ES, Lucky AW, Paller AS, Bruckner A et al. Prevalence and Characterization of Pruritus in Epidermolysis Bullosa. Pediatric Dermatology 2015;32:6.
2. Goldschneider KR, Lucky AW. Pain management in epidermolysis bullosa. Dermatol Clin 2010;28:273-82, ix.
3. Danial C AR, Gorell ES, Lucky AW, Paller AS, Bruckner A et al. Evaluation of Treatments for Pruritus in Epidermolysis Bullosa. Pediatric Dermatology 2014.