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Phase 2 Trial of a Neurokinin-1 Receptor Antagonist for the Treatment of Chronic Itch in Epidermolysis Bullosa Patients: A Randomized Clinical Trial

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PII: S0190-9622(19)32751-3

DOI: https://doi.org/10.1016/j.jaad.2019.09.014

Reference: YMJD 13825

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 13 April 2019

Revised Date: 19 August 2019

Accepted Date: 9 September 2019

Please cite this article as: Chiou AS, Choi S, Barriga M, Dutt-Singkh Y, Solis DC, Nazaroff J, Bailey-Healy I, Li S, Shu K, Joing M, Kwon P, Tang JY, Phase 2 Trial of a Neurokinin-1 Receptor Antagonist for the Treatment of Chronic Itch in Epidermolysis Bullosa Patients: A Randomized Clinical Trial, *Journal of the American Academy of Dermatology* (2019), doi: https://doi.org/10.1016/j.jaad.2019.09.014.

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Capsule summary

- Substance P/NK1R is key to the pathogenesis of itch. Recent trials have shown that antagonizing this pathway reduces itch in chronic pruritus, chronic prurigo, and cutaneous T cell lymphoma.
- This Phase 2 serlopitant study is the first randomized clinical trial for EB-related pruritus demonstrating safety and potential itch reduction.

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Article Type: Original Article

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Funding sources: EB Research Partnership (EBRP), EB Medical Research Foundation, Dermatology Foundation (support for AC)

Conflicts of interest: Kim Shu, Mark Joing, and Paul Kwon are employed by Menlo Therapeutics.

IRB approval status: Reviewed and approved by Stanford IRB; approval #37606

Clinicaltrials.gov listing: NCT02654483

Reprint requests: Albert Chiou, MD

Manuscript word count: 2497 out of 2500 words [excluding capsule summary, abstract, references, figures, tables]
Abstract word count: 200 out of 200
Capsule summary word count: 49 out of 50
References: 18
Figures: 2
Supplementary figures: 0
Tables: 3
Supplementary tables: 0
Attachments: CONSORT checklist, research protocol

Keywords: NK1 receptor; NK1 receptor antagonist; neurokinin 1 receptor; serlopitant; substance P; epidermolysis bullosa; drug response; chronic itch; pruritus

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Abstract

BACKGROUND:

Chronic pruritus causes major morbidity in epidermolysis bullosa (EB). The substance P-neurokinin 1 receptor (SP-NK1) pathway is a promising target for treating EB-related pruritus.

OBJECTIVE:

To evaluate the safety and efficacy of oral NK1 receptor antagonist serlopitant in treating moderate-severe pruritus in EB.

METHODS:

14 patients were randomized to serlopitant or placebo for 8 weeks, followed by a 4-week washout and optional open-label extension. The primary endpoint was change in itch as measured by a numeric rating scale (NRS). Secondary endpoints were change in: (1) itch during dressing changes and (2) wound size.

RESULTS:

We observed greater itch reduction with serlopitant, equivalent to a 0.64-point comparative reduction on the 11-point NRS by week 8, though this failed to meet statistical significance ($p=0.11$). More serlopitant patients achieved ≥3-point reduction compared to placebo (43% vs. 14%, $p=0.35$). In post hoc analysis excluding one subject with a concurrent seborrheic dermatitis flare, serlopitant achieved significantly greater median itch reduction from baseline by week 4 (-2 points vs. 0, $p=0.01$). We observed no statistically significant differences in secondary endpoints. Serlopitant was well-tolerated.

LIMITATIONS:

Small sample size due to disease rarity

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CONCLUSION:

The potential itch reduction with serlopitant observed in this trial will be pursued by a larger powered trial (NCT03836001).

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ORIGINAL INVESTIGATION

Introduction

Epidermolysis bullosa (EB) is a group of rare inherited skin disorders characterized by skin fragility and blistering due to mutations in keratin, laminin, or collagen genes. The EB population has reported itch to be the most distressing disease-related symptom, ranking higher than pain, difficulty eating, GI issues, and infections.[1-3] Itch coincides with wound location and severity and is exacerbated by activities such as dressing changes and bathing. Furthermore, it induces an itch-scratch-blister cycle which worsens skin injury.[4] Unfortunately current standard-of-care treatments such as topical steroids and antihistamines provide minimal palliative relief.[5] Despite this critically unmet need there have been no prior randomized controlled trials (RCTs) evaluating systemic therapies for EB-related pruritus, likely due to the low prevalence of this disease and lack of novel antipruritic therapies.[5,6] Any intervention that provides itch relief has the potential to be tremendously meaningful to patients with severely symptomatic EB subtypes.

Substance P (SP) is a potent neuropeptide of the tachykinin family that transmits nociceptive and itch signals by binding its receptor, neurokinin-1 receptor (NK1R). SP potentiates inflammation by inducing degranulation of mast cells, resulting in itch mediated by histamine, tumor necrosis factor-α, leukotriene B4, prostaglandin D2, and vascular endothelial growth factor.[7] There is an increased density of SP-positive nerve fibers in the dermis of atopic dermatitis and psoriasis, and scratching itself may upregulate NK1R expression.[7,8] Trials of the first NK1R antagonist aprepitant has shown promise in treating pruritic conditions such as cutaneous lymphoma and chronic prurigo.[9-12]

Most recently, the investigational NK1R antagonist serlopitant was evaluated in a 257-patient multicenter RCT for treatment of severe chronic pruritus. Serlopitant at the 1- and 5-mg doses demonstrated a significant dose-dependent reduction in pruritus at six weeks and was well

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tolerated.[13] The SP-NK1R pathway has never been evaluated as a target for EB itch, and it represents a potential avenue for improving the quality of life in a disease with severe dermatologic morbidity. We report the results the first RCT for EB-related pruritus evaluating the safety and efficacy of serlopitant in patients with EB.

Methods

Study Design

This Phase 2 study was a 12-week double-blind, parallel arm, placebo-controlled, randomized clinical trial evaluating the comparative effect of serlopitant 5-mg daily versus placebo for chronic pruritus in EB. Patients who completed the parallel arm portion were offered to participate in an open-label extension involving 8 weeks of serlopitant 5-mg and 4 weeks of washout for toxicity monitoring. This study was conducted at Stanford University Medical Center and Lucile Packard Children's Hospital. It was approved by the Stanford Institutional Review Board and registered on ClinicalTrials.gov (NCT02654483).

Study Population

Patients aged 13 and older with EB [dystrophic EB (DEB), EB simplex (EBS), or junctional EB (JEB) subtypes] and baseline Numeric Rating Scale (NRS) pruritus score ≥4 (out of 10) as reported on the Stanford EB Itch Survey for (1) average itch in the past 24 hours or (2) itch during bathing or dressing in the past 24 hours were eligible. Patients were required to have itch lasting ≥6 weeks and unresponsive to standard of care. Patients were excluded if there was evidence of chronic renal or liver disease, untreated hyperthyroidism, current hematologic malignancy or blood cell dyscrasia, pruritus of psychogenic or neuropathic etiology, pruritus from urticaria, drug allergy, infection, or other medical condition that in the opinion of the investigator would interfere with assessment of itch. Other exclusion criteria included exposure

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to ultraviolet B or psoralen and ultraviolet A treatment within 30 days prior to screening. Patients taking opiates were allowed to continue a stable dose.

Recruitment and Randomization of Participants

Patients were recruited from the Epidermolysis Bullosa Clinical Research Consortium (EBCRC) database, Lucile Packard Children's Hospital EB clinic, and REDCap database of EB patients who had consented to research recruitment. Patients were prescreened by phone or during routine clinic visits. Eligible patients were invited to a screening visit at Stanford involving the Stanford EB Itch Survey, which evaluates itch and quality of life, physical examination, baseline safety laboratory determinations, and baseline wound photography. Patients completed a Daily Itch Diary documenting itch severity NRS until next visit. Patients deemed eligible for enrollment upon review of laboratory results and medical history were randomized and mailed a one-month supply of serlopitant or placebo. Double-blinded randomization was performed using a randomly generated sequence with 1:1 allocation.

Interventions

On Day 1 of treatment, subjects received a loading dose of 3 tablets (15-mg), followed by 8 weeks of treatment with 5-mg serlopitant or placebo, and 4 weeks of washout. Patients were seen in clinic on weeks 4 and 8 for safety assessment and endpoint evaluation. Patients were contacted by phone at week 12 for final assessment with the Stanford EB Itch Survey. At completion, all patients were invited to participate in an open label extension study involving 8 weeks of serlopitant 5-mg daily and 4 weeks of washout for further toxicity monitoring. Study drug was provided by Menlo Therapeutics, Inc.

Outcome Measurements

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The primary statistical endpoint was comparative weekly change in NRS itch score over the 8-week active treatment. Because itch is subjective and varies day-to-day, patients recorded nightly NRS scores in Itch Diaries. Secondary endpoints were: (1) change in NRS during dressing changes and (2) reduction in selected wound sizes. Target wound areas were quantified via wound tracings performed with Canfield 3D photography and software at baseline and week 8. Safety was assessed by adverse events and laboratory monitoring.

Sample Size

Due to the rarity of EB, this study was powered to detect large differences in NRS score between groups. In power calculations, we assumed a mean NRS=8 for the placebo group versus NRS=5 for the active group with a standard deviation of 3, resulting in a sample size of 7 patients per treatment arm for 80% power and one-sided p-value of 0.05.

Statistical Analysis

Primary analysis was conducted on an intention-to-treat basis. A linear mixed model for repeated measures was applied to assess the comparative treatment effect on NRS between drug and placebo and to estimate weekly change. Statistical comparison of median reduction in target wound areas, median NRS scores, and proportion of subjects achieving specific NRS itch score reductions from baseline were performed using Wilcoxon's rank-sum test. Satistical comparisons were two-sided with p-value ≤0.05 considered significant. Analyses were performed using SAS (v9.4, SAS Institute Inc., Cary, NC).

Results

Between February 2016 and June 2017, 26 patients were screened and 14 patients were enrolled. All patients completed randomized treatment and washout. Both arms were similar in characteristics including gender, baseline NRS score, and EB subtype (Table 1). The

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serlopitant group was older (mean 27.6 years, SD 12.1) than placebo (mean 22.9 years old, SD 8.0), skewed by one older participant assigned to serlopitant. Most participants had recessive dystrophic epidermolysis bullosa (RDEB) (N=13), with one JEB patient allocated to placebo. Both groups had similar proportions of topical steroid, opioid, antihistamine, and anticonvulsant use at baseline, which remained unchanged during trial per protocol. In terms of pruritus-associated medication exposures, only one patient, randomized to serlopitant, was on concurrent antihypertensives (carvedilol, amlodipine). None were on concurrent statins, diuretics, allopurinol, or salicylates.

Clinical Response

All 14 patients were evaluated for the primary endpoint. Based on linear mixed model analysis of nightly NRS itch severity scores, the serlopitant group demonstrated a comparative weekly reduction in NRS relative to placebo (0.08-point/week comparative reduction, p=0.11) (Table 2). This reduction in favor of serlopitant corresponds to a 0.64-point reduction in NRS relative to placebo at 8 weeks of active treatment. We observed no statistical difference in comparative effect of serlopitant on itch associated with dressing change relative to placebo (0.01-point/week comparative reduction, p=0.85).

Spline visualization of averaged NRS scores by treatment group over time revealed day-to-day intra-group fluctuations (Fig. 1). For more intuitive evaluation of inter-group trends, we performed posthoc analysis evaluating the proportion of patients achieving 1, 2, and 3-point reductions in NRS score from baseline by the end of active treatment. Based on NRS scores reported during screening and week 8, 86% of the serlopitant group achieved at least 1-point reduction in itch from baseline compared to 57% of placebo (Fig. 2). More serlopitant patients achieved at least 3-point reduction in NRS from baseline (43%) compared to placebo (14%), though neither observation met statistical significance (p=0.35). In posthoc review, the sole

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placebo patient who achieved a 3-point NRS reduction was found to have been diagnosed with seborrheic dermatitis during trial and treated with hydrocortisone 2.5% lotion resulting in improved itch. Per protocol analysis excluding this patient showed that serlopitant achieved a statistically significant greater median reduction in itch from baseline by week 4 compared to placebo (-2 points vs. 0 on the NRS, p=0.01).

Target wound surface areas were quantified using Canfield software at baseline and week 8 to determine change in wound area. Median percent change in wound area for the serlopitant and placebo groups was -59% (range: -100% to 621%) and –47.2% (range: -100% to 331%), respectively, and the difference failed to meet statistical significance (p=0.85). We observed a wide range in wound area change across both groups, particularly in smaller target wounds measuring ≤10 cm^2, which represented 50% of the target wound population.

Safety

No subjects discontinued treatment due to adverse events (AEs). All subjects reported at least one AE, most mild to moderate in severity. Of the AEs related or possibly related to treatment, there were no new patterns discerned in AEs that occurred more frequently with serlopitant (Table 3). The most common AE was nausea, which occurred more frequently with serlopitant than placebo [2 patients (29%) vs. 1 patient (14%)]. No serious adverse events (SAE) were observed during the randomized period or washout. Three months after completing active treatment and prior to open label extension, one RDEB patient assigned to serlopitant was hospitalized for pulmonary embolism (grade III, severe) and diagnosed with heart failure with associated pleural effusion (grade III). Given the severe comorbidities associated with RDEB and temporal separation from study exposure, these SAEs were deemed unrelated to study drug. Another RDEB patient assigned to placebo was hospitalized for IgA nephropathy (grade III) on their first day of open label extension prior to receiving study drug. The patient ultimately

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expired months later from unknown causes (grade III). These SAEs were deemed unrelated to study medication as the patient had never received serlopitant. No significant trends in laboratory abnormalities were observed. Two RDEB patients on serlopitant demonstrated worsening anemia with >1 point drop in hemoglobin during treatment. This was not attributed to serlopitant given the high incidence of anemia in RDEB.

Quality of Life

In posthoc analysis, there was no difference in sleep quality metrics observed between the two groups by week 8. When asked at baseline how itching impacted their ability to fall asleep, 3 active (43%) and 2 placebo (28%) patients reported “a lot” which, by week 8, decreased to 1 patient (14%) in both groups. Similarly, both groups at baseline had 29% of patients (n=2) report “a lot” of evening wakings due to itching which, by week 8, fell to 0% in the active arm and 14% (n=1) in the placebo arm.

Discussion

Despite itch being the most burdensome symptom experienced by EB patients, there have been no prior RCTs evaluating interventions for EB-related itch. This study represents the first randomized, placebo-controlled trial to evaluate a novel NK1R antagonist in EB. Although this pilot study was powered to detect only large differences in NRS itch score between treatment groups, we still observed a small treatment effect in favor of serlopitant, though this failed to meet statistical significance (p=0.11). This benefit corresponded to a 0.64-point relative reduction in NRS by 8 weeks of treatment. In light of the significant morbidity associated with severe EB subtypes and lack of effective antipruritic treatments, even a small magnitude itch reduction can be clinically meaningful. The majority of patients (86%) in the active group showed at least 1-point improvement in NRS itch, and more patients in the active group achieved at least 3-point reduction in NRS by the end of treatment compared to placebo (43%

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vs. 14%), although these measures also did not meet statistical significance. These results provide the scientific basis to support further investigation into the treatment effect of NK1R inhibition in EB. A larger, stronger powered study is currently being pursued (NCT03836001). With a larger cohort, this trial will better quantify the effect size of serlopitant in treating EB itch.

We found on post hoc analysis that the sole patient on placebo who experienced a 3-point NRS reduction had received treatment for seborrheic dermatitis that likely interfered with itch assessments. EB-related itch is linked mechanistically to repeated cycles of healing and re-injury of fragile skin wounds. Future studies may benefit from capturing both global itch and itch specific to individual wounds, which may mitigate confounding itch from unrelated dermatoses such as seborrhea. We did not detect statistical differences in secondary endpoints of pruritus during dressing changes and wound size reduction between the two groups.

Serlopitant was generally well tolerated, with no new safety signals observed within the EB population. A high rate of mild to moderate AEs was observed in both arms, reflecting the comorbidities of EB. SAEs observed during this trial were deemed unrelated to study medication due to temporal separation from drug exposure. They serve as reminders of the significant medical challenges faced by patients with more severe EB phenotypes.

The enrolled cohort overwhelmingly represented RDEB, likely influenced by a combination of tertiary referral patterns and disease-specific factors including the increased severity and itch experienced by patients with DEB compared to EBS.[2] Enrolling more patients with other subtypes in future studies will improve generalizability within the EB population.

A dose-dependent response to serlopitant up to 5-mg was observed in chronic pruritus patients, however there are no published efficacy data regarding whether a higher dose improves itch

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reduction.[13] For many CNS-active drugs, clinical efficacy is associated with target receptor occupancy.[14,15] Based on pharmacokinetic data from aprepitant, serlopitant 5-mg is expected to achieve >90% CNS NK1R occupancy, which was the rationale for the dosage of this and preceding trials involving serlopitant. Beyond 5-mg, CNS receptor occupancy is expected to plateau, thus we speculate that increasing dosage would not have significant impact on itch.

A recent study has shown that RDEB patients have a high rate of pain with neuropathic characteristics, with evidence suggesting this may arise from small fibre neuropathy associated with severely reduced intraepidermal nerve fibre density secondary to chronic skin damage.[17] While the exact mechanism of EB-related itch remains unknown, one explanation may involve a similar neuropathic origin secondary to repeated wounding and skin regeneration. Interestingly, prurigo nodularis has a similar pattern of reduced intraepidermal nerve fibre density and serlopitant was recently found to significantly improve itch in prurigo nodularis.[16,18]

Chronic itch is detrimental to the quality of life of EB patients, and effective treatments for pruritus have the potential to provide greatly needed symptomatic relief. The promising results of this study suggest that the SP-NK1R pathway merits further evaluation as a potential target for this important patient population.

Acknowledgements

We thank the patients for granting permission to publish this information. This investigator-initiated study was enabled by a grant from the EB Research Partnership (EBRP) and Epidermolysis Bullosa Medical Research Foundation (EBMRF). AC was supported by a Dermatology Foundation Medical Dermatology Career Development Award. KS, MJ, and PK are employed by Menlo Therapeutics, Inc., which provided investigational drug. Design of the study, interpretation of the data, and drafting of this manuscript were performed independently

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by the Stanford-affiliated authors.

Abbreviations used:

AE: adverse event

DEB: dystrophic epidermolysis bullosa

EB: epidermolysis bullosa

EBCRC: Epidermolysis Bullosa Clinical Research Consortium

EBS: epidermolysis bullosasimplex

JEB: junctional epidermolysis bullosa

NRS: numeric rating scale

RDEB: recessive dystrophic epidermolysis bullosa

SAE: serious adverse event

SP-NK1R: substance P-neurokinin 1 receptor

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FIGURES

Figure 1. Spline Visualization of Average Itch Scores Over Time

Spline visualization of averaged numeric rating scale (NRS) itch scores by treatment group over time.

Figure 2. Proportion of responders by degree of improvement and treatment arm at 8 weeks

Proportion of patients achieving 1, 2 and 3 point reductions in numeric rating scale (NRS) itch severity from baseline at the end of week 8 by treatment arm.

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Table 1. Baseline Characteristics

	Total Patients (N=14)	Active (N=7)	Placebo (N=7)
Age (years)			
Mean (SD)	25.2 (10.2)	27.6 (12.1)	22.9 (8.0)
Median	24.5	26	19
Minimum	14	15	14
Maximum	53	53	37
Sex, N (%)			
Male	7 (50%)	3 (43%)	4 (57%)
Female	7 (50%)	4 (57%)	3 (43%)
Ethnicity, N (%)			
Caucasian	7 (50%)	4 (57%)	3 (43%)
Hispanic	4 (29%)	2 (29%)	2 (29%)
African American	1 (7%)	0 (0%)	1 (14%)
Other	2 (14%)	1 (14%)	1 (14%)
EB Subtype, N (%)			
EBS	0	0 (0%)	0 (0%)
RDEB	13 (93%)	7 (100%)	6 (86%)
DDEB	0	0 (0%)	0 (0%)
JEB	1 (7%)	0 (0%)	1 (14%)
Baseline NRS Itch Severity (SD)	6.6 (1.2)	6.6 (1.4)	6.6 (1.0)
Baseline NRS Dressing Change Severity (SD)	6.1 (1.9)	6.1 (1.9)	6.2 (2.2)

Baseline characteristics of patients in the active and placebo treatment arms. SD = standard deviation. EBS = epidermolysis bullosa simplex. RDEB = recessive dystrophic epidermolysis bullosa. DDEB = dominant dystrophic epidermolysis bullosa. JEB = junctional epidermolysis bullosa. NRS = numeric rating scale.

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435 **Table 2. Linear Mixed Effects Model Analysis Evaluating Daily Itch Journal**

Effect	Beta coefficient (95% CI)	p-value
Intercept	5.37 (3.82 - 6.92)	<.0001
drug, Active vs placebo	-0.62 (-2.82 - 1.57)	0.5482
week	0.02 (-0.05 - 0.09)	0.5537
week*drug	-0.08 (-0.18 - 0.02)	0.1081

436

437 Linear mixed effects model evaluating effect of treatment on itch over time over 8 weeks of

438 active treatment. Active = treatment with serlopitant 5-mg daily. CI = confidence interval.

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Table 3. Related and Possibly Related Adverse Events

	Placebo (N=7)		Serlopitant (N=7)	
Adverse Event	**Grade I/II**	**Grade III**	**Grade I/II**	**Grade III**
Nausea	1 (14%)	0 (0%)	2 (29%)	0 (0%)
Diarrhea	0 (0%)	0 (0%)	1 (14%)	0 (0%)
Headache	1 (14%)	0 (0%)	1 (14%)	0 (0%)
Rash	1 (14%)	0 (0%)	0 (0%)	0 (0%)
Otitis	1 (14%)	0 (0%)	0 (0%)	0 (0%)
Drowsiness	1 (14%)	0 (0%)	0 (0%)	0 (0%)
Dizziness	1 (14%)	0 (0%)	0 (0%)	0 (0%)
Wound infection	1 (14%)	0 (0%)	0 (0%)	0 (0%)
Worsening pruritus	1 (14%)	0 (0%)	0 (0%)	0 (0%)

All adverse events deemed related or possibly related to treatment by investigators observed during the 12-week parallel arm portion of the trial, including 8 weeks of randomized active treatment and 4 weeks of washout off treatment. Grading by severity based on judgement of investigators. Grade I = mild, Grade II = moderate, Grade III = severe.

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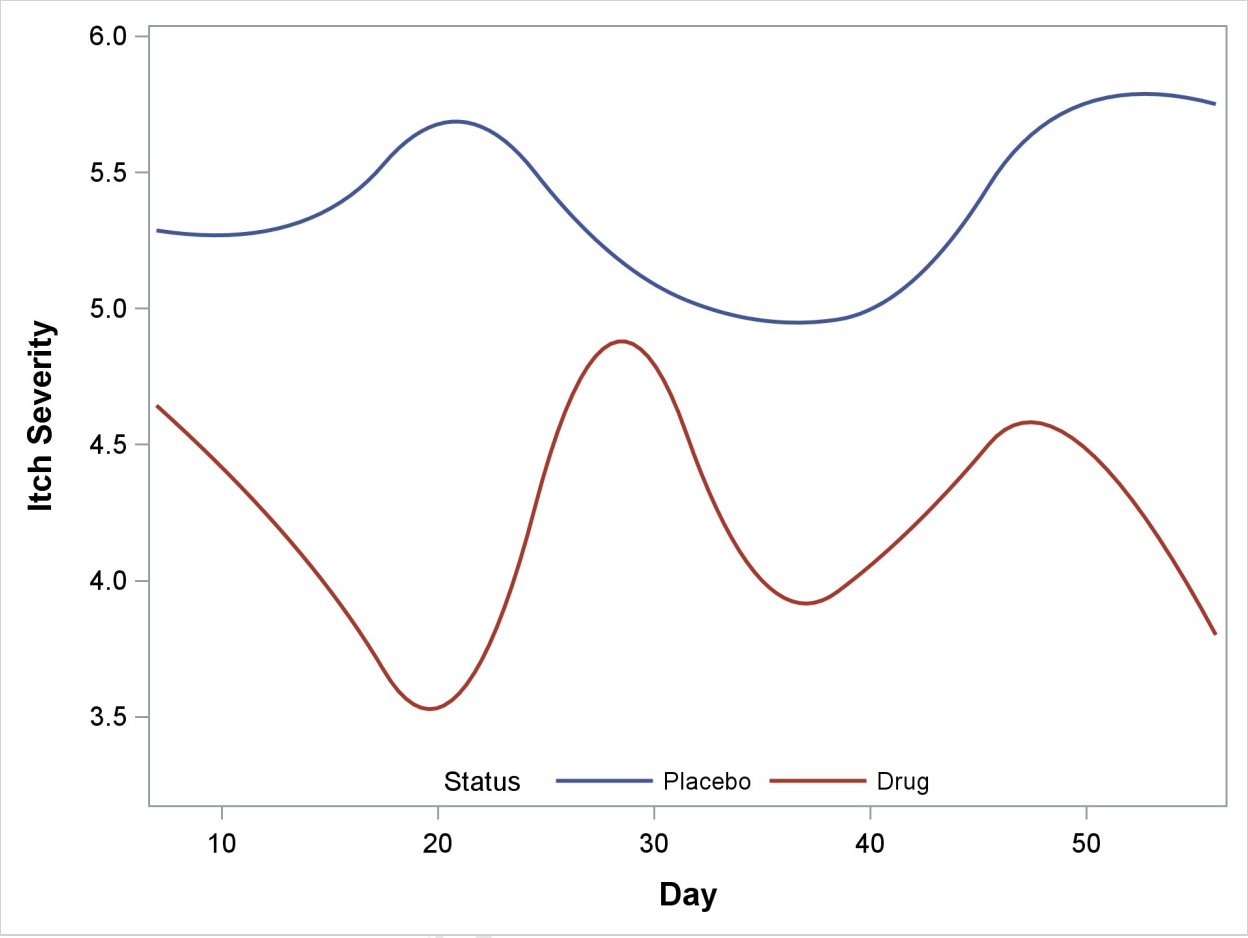
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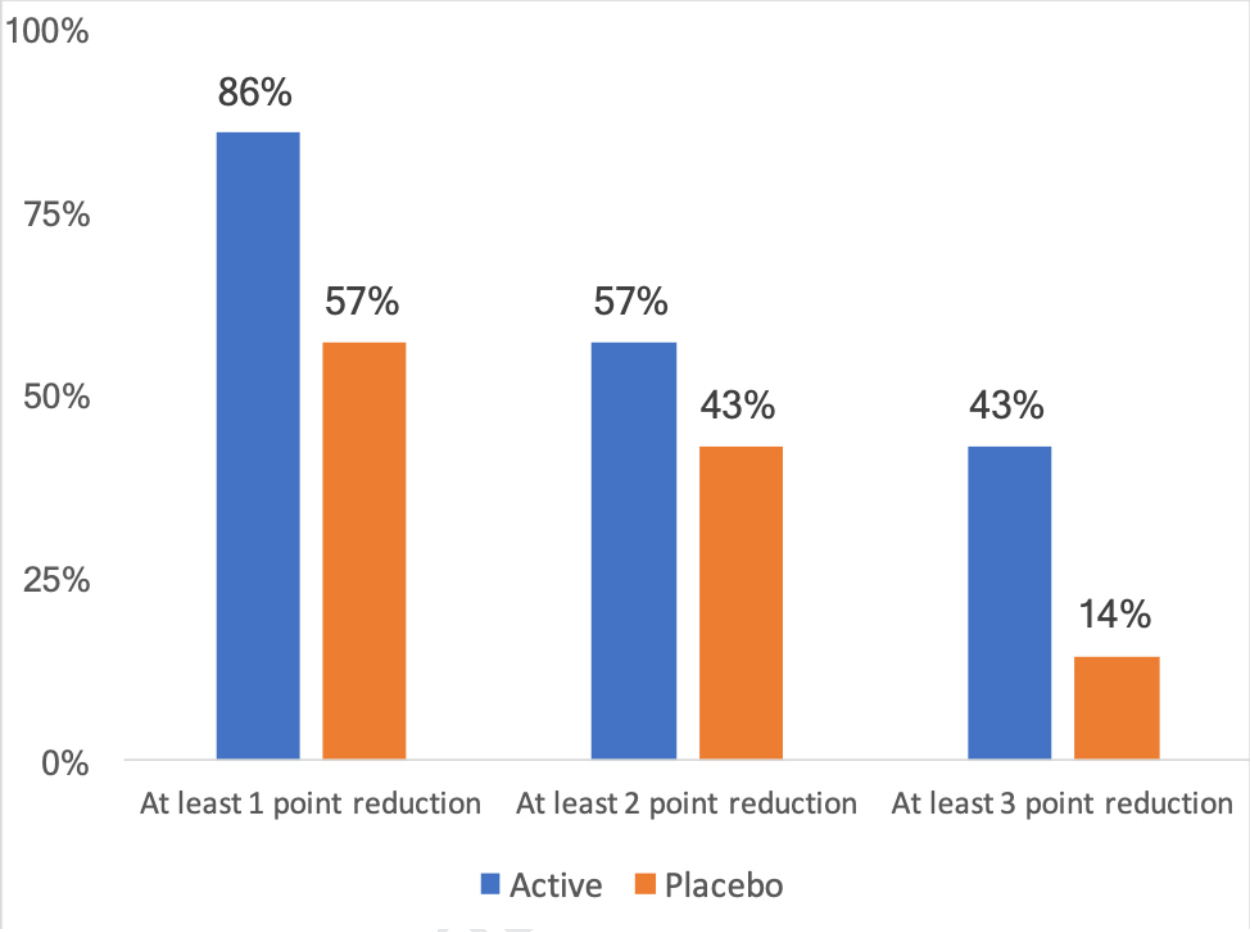
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At least 1 point reduction
At least 2 point reduction
At least 3 point reduction
Active
Placebo

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