PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The neurokinin-1 antagonist orvepitant for EGFRI-induced pruritus in cancer patients: a randomised, placebo-controlled, phase II trial
AUTHORS	Vincenzi, Bruno; Trower, Mike; Duggal, Ajay; Guglielmini, Pamela; Harris, Peter; Jackson, David; Lacouture, Mario E.; Ratti, Emiliangelo; Tonini, Giuseppe; Wood, Andrew; Ständer, Sonja

VERSION 1 - REVIEW

REVIEWER	Laurent Misery University Hospital of Brest Brest France Galderma, Menlo, MSD,Trevi
REVIEW RETURNED	18-Mar-2019

GENERAL COMMENTS	Although results are negative, this is a very good paper and it is interesting to publish it for the knowldege of the medical community.

REVIEWER	Gil Yosipovitch University of Miami
REVIEW RETURNED	25-Mar-2019

GENERAL COMMENTS	Te authors present data of a randomised, double-blind, placebo-controlled study of a neurokinin-1antagonist Orvepitant for EGFRI-induced pruritus. The study was terminated because of challenges in recruiting cancer patients with significant itch . The number of participants enrolled was rather low 30 with drug and 14 with placebo. The results of the study demonstrate that the placebo was more effective in reducing itch than the 2 doses of Orvepitant . Although these are negative results it is important to share them with a with a selected group of oncologists and dermatologists who treat adverse targeted cancer treatments. However this would be of less interest to the readers of general medicine journal such as BMJ Open. Specific comments : The authors state that this is a safe drug and well tolerated I would be careful assuming this based on the data they present . There are also discrepancies between table 3 and what is written on safety and tolerability . Asthenia is stated only in those on drug in 8 of the patients but the table shows only 1

	patient? Anemia is stated in 3 patients on drug but it is not stated in table 3. Please check data for accuracy. No mention whether drug to drug interactions commonly noted in aprepitant were studied and pharmcokinetics of the drug that were performed based on the protocol attached) The explanation about the high expectations of the patients and placebo effect as the cause of failure of this trial are questionable as the high dose of drug did not show clinical meaningful itch reductions (the placebo did) . Furthermore there have been several trials with drugs for pruritus including NK-1 inhibitors.such as serlopitant that did show anti pruritic effect in patients with moderate to severe itch . See JAAD 2018). .Intro is written like a review and could be shortened. It would be more important to state what are the unique features of orvepitant in terms of its NK-1 inhibition for example comparison to aprepitant and its tissue affinity and CNS affinity. what is its half life, and drug to drug interactions.

REVIEWER	Ethan Lerner Massachusetts General Hospital, USA
REVIEW RETURNED	08-Apr-2019

GENERAL COMMENTS	The NK1 antagonist orvepitant was evaluated for the treatment of EGFRI-associated pruritus in a randomized, placebo-controlled Phase II trial. Orvepitant and not found to be efficacious. It is helpful to the scientific community to present negative results, as is done here. The data is presented clearly and I have only a few comments. 1) Please describe in more detail what is meant by pruritus of the head. Is this scalp pruritus, facial pruritus or something else? Was there an associated rash? Does this differ from the pruritus associated with checkpoint inhibitors? 2) The authors reference Gerber et al who note that mast cells accumulate in lesional skin. The authors use this reference to support the concept that substance P may activate mast cell NK1R to lead to pruritus. As it is now recognized that substance P activates MRGPRX2 (PMID: 28219706) which is expressed on mast cells, while at the same time activating central NK1R, it would be reasonable to note that targeting peripheral Mrgprs separately or together with central NK1R may be a future therapeutic approach.

REVIEWER	Stephanie Roll Institute for Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Germany
REVIEW RETURNED	02-Jul-2019

GENERAL COMMENTS	The authors present the results of a randomised, double-blind, placebo-controlled clinical trial to assess the effect of two different doses of orvepitant (30 mg or 10 mg) vs. placebo in patients with intense pruritus induced by epidermal growth factor receptor inhibitor. The manuscript is well written and illustrative. The study design and methodology seem generally sound.

	Comments 1) ABSTRACT, Primary and secondary outcome measures (page 2) Please state the primary endpoint as it is defined below (and in the study protocol). 2) Abstract, Conclusion (page 2) Please delete the last sentence. [Since efficacy (in a double-blind RCT) is measured as the difference between an intervention group and a control group, it measures the specific intervention effect in addition to other unspecific effects (such as the so called 'placebo effect', study participation effects, natural history of disease, and others); this is common methodology and true for every double-blind RCT.] 3) Study design and enrolment (page 4) Blinded analysis of data variance: Please explain how an analysis of variance can provide an indication of treatment benefit? Was the variance higher than expected and thus the assumed difference between treatment groups less likely to reach statistical significance? 4) Assessments (page 4) Please describe who assessed and graded the EGFRI-induced rash. 5) Endpoints (page 4) Sentence “Secondary endpoints were also evaluated: change from Baseline in mean patient-recorded NRS score (last 3 recordings) at Weeks 1, 4, 8”: please delete week 4 as this is already defined as the primary endpoint. 6) Statistical analysis (page 5) a) The definition of the intention-to-treat (ITT) population is not according to statistical guidelines. It should thus be labelled "modified ITT". b) Please describe more transparent which factors were included in the mixed-model repeated measures analyses. E.g. for the analysis of the primary outcome (change baseline to 3-day-mean) no repeated measures model would be needed. c) Please describe which other factors (besides treatment group) were included in the analysis models, eg. respective baseline value as covariate, stratification variable. Both variables should be included in all models. d) Please describe if all data from the three treatment groups (30 mg orvepitant, 10 orvepitantmg , placebo) were analysed together in one model or if separate analyses were performed (i) 30 mg orvepitant vs. placebo; ii) 10 mg orvepitant vs. placebo). e) Please describe if the study was designed as a confirmative or explorative trial. f) Please describe if there was any formal significance level, and if so its value. g) Please describe how multiplicity (due to the comparison of two treatment groups vs. placebo) was taken into account. 7) Table 2 (page 7) a) Please indicate more clearly the origins of the stated results, e.g. which results are from descriptive analyses and which results are from the models described in the 'Statistical analysis' section of the manuscript.

	b) For the SD, please show only 2 (not 3) decimal places (to be consistent with the notation of the mean). c) For the LSMEANS standard error, please show only 2 (not 3) decimal places. d) In the statistics column, row 'LSMEANS standard error (95% CI)' please delete the part '(95% CI)' as this is not shown. 8) Efficacy (page 7) Please include main results of Supplemental Table 1 directly into the manuscript (e.g. all secondary outcome measures listed in the abstract of the manuscript).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Laurent Misery

Institution and Country: University Hospital of Brest, Brest, France Please state any competing interests or state 'None declared': Galderma, Menlo, MSD,Trevi

Please leave your comments for the authors below

Although results are negative, this is a very good paper and it is interesting to publish it for the knowldege of the medical community.

Thank you for your review, and we agree with your comments. We believe that it is important that the RELIEVE 1 study and other clinical trials with NK1 antagonists are published because it builds the knowledge base and helps to define in which populations this class of drugs has the potential to deliver most benefit to patients.

Reviewer: 2

Reviewer Name: Gil Yosipovitch

Institution and Country: University of Miami Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

The authors present data of a randomised, double-blind, placebo-controlled study of a neurokinin-1 antagonist Orvepitant for EGFRI-induced pruritus. The study was terminated because of challenges in recruiting cancer patients with significant itch . The number of participants enrolled was rather low 30 with drug and 14 with placebo. The results of the study demonstrate that the placebo was more effective in reducing itch than the 2 doses of Orvepitant . Although these are negative results it is important to share them with a with a selected group of oncologists and dermatologists who treat adverse targeted cancer treatments. However this would be of less interest to the readers of general medicine journal such as BMJ Open.

Thankyou for your thorough review and the comments. NeRRe Therapeutics has pledged to publish all research and values the opportunity provided by BMJ Open to publish non-definitive studies. As noted previously, we believe that it is very important that the broader community are made aware of such results because it informs where NK1 antagonists can provide the most patient benefit and

undoubtedly stimulates discussion regarding the challenges of running such studies and the heterogeneity of the pathological mechanisms that may underlie the different itch complaints.

Specific comments : The authors state that this is a safe drug and well tolerated I would be careful assuming this based on the data they present . There are also discrepancies between table 3 and what is written on safety and tolerability. Asthenia is stated only in those on drug in 8 of the patients but the table shows only 1 patient? Anemia is stated in 3 patients on drug but it is not stated in table 3. Please check data for accuracy.

We double-checked this information. The data in both the text and Table 3 are accurate. Table 3 includes only AEs considered related to the study drug (as stated in the table title and in the sentence referencing it). Asthenia, for example, occurred in 8 patients but was considered related to the study drug in only 1 patient. We have edited this section to make is more clear and unambiguous and have further addressed the safety profile of orvepitant in the discussion section.

No mention whether drug to drug interactions commonly noted in aprepitant were studied and pharmcokinetics of the drug that were performed based on the protocol attached)

Drug-drug interactions were not specifically investigated in this particular early phase study, and a full assessment of clinical drug-drug interaction is yet to be completed. Sparse PK sampling was conducted in this study, but the planned exploration of the correlation of orvepitant plasma levels with clinical efficacy and secondary assessment scores was not conducted given the lack of efficacy observed. This point has been clarified in the manuscript.

The explanation about the high expectations of the patients and placebo effect as the cause of failure of this trial are questionable as the high dose of drug did not show clinical meaningful itch reductions (the placebo did). Furthermore there have been several trials with drugs for pruritus including NK-1 inhibitors such as serlopitant that did show anti pruritic effect in patients with moderate to severe itch . See JAAD 2018).

Reduction in patient-reported numerical reporting scale scores was seen in all 3 groups (orvepitant 30 mg, orvepitant 10 mg, and placebo) at the Week 4 primary endpoint. Mean reduction was largest in the placebo group, while median reduction was highest in the orvepitant 30 mg group. The reductions in NRS scores in the orvepitant groups were not statistically significantly different than those in the placebo group. As noted in the discussion, this study was under-recruited and therefore had a reduced sample size, making it difficult to determine a treatment difference. As also stated in the discussion, a placebo effect is commonly seen with subjective endpoints such as pruritus intensity, as shown in a recent meta-analysis of clinical trials in patients suffering from chronic itch. So, we believe one possible explanation for the RELIEVE 1 study outcome is the high expectations in this patient group that led to the notable placebo effect.

We acknowledge that significant results in reducing pruritus scores have been obtained with NK1 antagonists in other pruritic conditions such as chronic pruritus in general, prurigo nodularis, pruritus associated with atopic dermatitis and pruritus associated with psoriasis. However, these studies were in chronic pruritic conditions that are now considered to be neural hypersensitivity disorders. Orvepitant has now been shown to be active in a clinical study in another neural hypersensitivity disorder of chronic refractory cough. In contrast EGFRI-induced pruritus is an acute disease that

typically arises within the first 2 weeks of treatment. The pathological mechanism of EGFRI-induced pruritus also differs as it likely involves dermal mast cell accumulation and activation. This difference in itch pathophysiology may explain the divergent outcomes with NK1 antagonism therapy in these different pruritic conditions.

Another explanation is that the pruritus score reduction seen in all groups may be caused by the reported itch following initiation of EGFRI treatment not being sustained at the same intensity level over time.

Thank you for raising these important points. We have addressed them all in the discussion section.

Intro is written like a review and could be shortened. It would be more important to state what are the unique features of orvepitant in terms of its NK-1 inhibition for example comparison to aprepitant and its tissue affinity and CNS affinity. what is its half life, and drug to drug interactions.

We have condensed the original introduction section as suggested still allowing the readers to familiarise themselves with the context, prevalence, and importance of the topic.

We have added the requested information about the features of orvepitant and background on itch signalling mechanisms involving Substance P and the NK1 receptor to the introduction and have included the implications to the discussion section.

Reviewer: 3

Reviewer Name: Ethan Lerner

Institution and Country: Massachusetts General Hospital, USA Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below The NK1 antagonist orvepitant was evaluated for the treatment of EGFRI-associated pruritus in a randomized, placebo-controlled Phase II trial. Orvepitant and not found to be efficacious. It is helpful to the scientific community to present negative results, as is done here. The data is presented clearly and I have only a few comments.

1) Please describe in more detail what is meant by pruritus of the head. Is this scalp pruritus, facial pruritus or something else? Was there an associated rash? Does this differ from the pruritus associated with checkpoint inhibitors?

Thank you for the review and your comments.

Pruritus of the head means scalp pruritus (this detail has been added to the results section), and is not necessarily associated with rash. It is less frequently associated with rash than is seen with TKIs or monoclonal antibodies. This study was conducted before the introduction of checkpoint inhibitors into clinical practice.

2) The authors reference Gerber et al who note that mast cells accumulate in lesional skin. The authors use this reference to support the concept that substance P may activate mast cell NK1R to lead to pruritus. As it is now recognized that substance P activates MRGPRX2 (PMID: 28219706) which is expressed on mast cells, while at the same time activating central NK1R, it would be reasonable to note that targeting peripheral Mrgprs separately or together with central NK1R may be a future therapeutic approach.

The introduction has been edited to include information on the interaction of Substance P with the MRGPRX2 receptor on mast cells. Given the lack of observed efficacy with orvepitant, we felt it beyond the scope of the article to recommend a combination therapy or comment on MRGPRX2 as a monotherapy for this condition.

Reviewer: 4

Reviewer Name: Stephanie Roll

Institution and Country: Institute for Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Germany Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The authors present the results of a randomised, double-blind, placebo-controlled clinical trial to assess the effect of two different doses of orvepitant (30 mg or 10 mg) vs. placebo in patients with intense pruritus induced by epidermal growth factor receptor inhibitor. The manuscript is well written and illustrative. The study design and methodology seem generally sound.

Thankyou for your review and comments.

Comments

1) ABSTRACT, Primary and secondary outcome measures (page 2) Please state the primary endpoint as it is defined below (and in the study protocol).

The primary endpoint was edited as defined in the methods section. Secondary outcome measures were also clarified in the abstract and the methods section.

2) Abstract, Conclusion (page 2)

Please delete the last sentence.

[Since efficacy (in a double-blind RCT) is measured as the difference between an intervention group and a control group, it measures the specific intervention effect in addition to other unspecific effects (such as the so called 'placebo effect', study participation effects, natural history of disease, and others); this is common methodology and true for every double-blind RCT.]

This sentence has been deleted.

3) Study design and enrolment (page 4)

Blinded analysis of data variance: Please explain how an analysis of variance can provide an indication of treatment benefit? Was the variance higher than expected and thus the assumed difference between treatment groups less likely to reach statistical significance?

In accordance with the protocol, a blinded estimate of the standard deviation of the primary endpoint (NRS score) was calculated in accordance with Friede and Kieser (2013), Friede (2006) and Kiesser (2003) giving values of 2.6, 2.4, and 2.4, respectively. This blinded estimate of variance was greater than the original sample size assumptions. This information, coupled with the difficulties experienced in enrolling patients, led to the study being terminated prematurely.

- Friede T, Kieser M. Blinded sample size re-estimation in superiority and noninferiority trials: Bias versus variance in variance estimation. Pharmaceut Statist. 2013;12:141–6.
- Friede T. Sample size recalculation in internal pilot study designs: A review. Biom J. 2006;48:537–55.
- Kiesser M. Simple procedures for blinded sample size adjustment that do not affect the type I error rate. Statist Med. 2003;22:3571–81.

4) Assessments (page 4)

Please describe who assessed and graded the EGFRI-induced rash.

Assessment and grading was by the investigators. This sentence has, however, been deleted from the methods section because the results of this assessment were not part of any predefined endpoint and are not analysed in this paper.

5) Endpoints (page 4)

Sentence “Secondary endpoints were also evaluated: change from Baseline in mean patient-recorded NRS score (last 3 recordings) at Weeks 1, 4, 8”: please delete week 4 as this is already defined as the primary endpoint.

Corrected and other secondary endpoints clarified.

6) Statistical analysis (page 5)

a) The definition of the intention-to-treat (ITT) population is not according to statistical guidelines. It should thus be labelled "modified ITT".

b) Please describe more transparent which factors were included in the mixed-model repeated measures analyses. E.g. for the analysis of the primary outcome (change baseline to 3-day-mean) no repeated measures model would be needed.

c) Please describe which other factors (besides treatment group) were included in the analysis models, eg. respective baseline value as covariate, stratification variable. Both variables should be included in all models.

d) Please describe if all data from the three treatment groups (30 mg orvepitant, 10 orvepitantmg , placebo) were analysed together in one model or if separate analyses were performed (i) 30 mg orvepitant vs. placebo; ii) 10 mg orvepitant vs. placebo).

e) Please describe if the study was designed as a confirmative or explorative trial.

f) Please describe if there was any formal significance level, and if so its value.

g) Please describe how multiplicity (due to the comparison of two treatment groups vs. placebo) was taken into account.

a) As defined in our statistical analysis plan, the ITT population consists of all randomized patients who receive any dose of study medication (as recorded in the patient diary) and had at least one post-treatment efficacy assessment (ie, one valid patient-recorded NRS, Skindex-16 QoL, LSEQ, Clinic Visit NRS, or VRS score or pruritus intensity). This definition is in accordance with ICH E9, which defines the full analysis set as “the set of subjects that is as close as possible to the ideal implied by the intention-to-treat principle. It is derived from the set of all randomised subjects by minimal and justified elimination of subjects.” Regardless of that, all patients randomized were and are included in the ITT population; no randomized patients were excluded from the ITT population. Thus, we feel there is no justification to relabel the population.

b) In accordance with the Statistical Analysis Plan, the primary efficacy analysis (patient-reported NRS score) was analyzed as follows. The change in average daily pruritus score from Baseline over Weeks 1, 2, 3, and 4 was analyzed by mixed model repeated measures analysis, with the primary inference being the change from Baseline patient-reported NRS score (mean of last 3 days of each week) of the fourth week of dosing. The change from Baseline patient-reported NRS score (mean of last 3 days of each week) was fitted as the response variable in the mixed model. An unstructured correlation structure was assumed. Restricted maximum likelihood was used to estimate all parameters and was the basis for all hypothesis testing (this method is the default in SAS). No model convergence problems occurred. For the primary model including the interaction term, the hypothesis test to perform on the fixed effects was type III (SAS option htype = 3). SAS PROC MIXED applying kenward-rodgers degrees of freedom correction (ddfm=kr) was used for this. A two-sided test with $\alpha = 0.05$ was used to test the null hypothesis. Inference was made for each dose of orvepitant versus placebo using a model that incorporated all treatments. The model planned to include treatment group, study pooled site, study visit, protocol version, the interaction between study visit and treatment group, the interaction between study site and treatment group, the interaction between protocol version and treatment, the covariate (the baseline of the variable being analyzed), and the interaction between baseline covariate and visit. Formally, the model to be used was:

Model: $y_{ijkl} = \mu + x_{l(ij)} + T_i + S_j + V_k + P_l + TV_{ik} + TS_{ij} + TiPm + Vx_{l(ij)k} + \varepsilon_{kl(ij)}$

where: y_{ijkl} = efficacy variable being analyzed

μ = overall mean

$x_{l(ij)}$ = baseline covariate

T_i = treatment effect

S_j = study site effect

V_k = visit effect

P_m = effect of protocol version

TV_{ik} = treatment by visit interaction

TS_{ij} = treatment by study site interaction

TiPm = Treatment by Protocol version Interaction

$V_{xl(ij)k}$ = Visit by baseline covariate interaction

$\varepsilon_{kl(ij)}$ = error

i = 1,2,3 corresponding to the treatment groups

j = 1,2,... , s corresponding to the s study sites

k = 1, 2,... , v corresponding to the v study visits

l = 1, 2... p corresponding to the p patients within each study site by treatment group combination

m = 1, 2, 3 corresponding to the protocol version under which the patient was enrolled.

The primary efficacy endpoint was analyzed using the ITT population. No data imputation was performed. A least-squares means (LSMEANS) estimate of the treatment group differences (with 95% confidence intervals) was calculated for the difference between each dose of orvepitant and placebo for each week. The primary inference was taken for the treatment difference at Week 4 between 30 mg orvepitant and placebo. All other results taken from this model are secondary and exploratory.

A preliminary test was performed regarding the treatment by protocol version interaction. This term was found not to be statistically significant at the 0.10 level, and it was removed from the model. The factor protocol version was also found not to be statistically significant at the 0.10 level and was also removed from the model. Another preliminary test was performed regarding the treatment by study site interaction. It was also found not to be statistically significant at the 0.10 level and was removed from the final model used to analyze the primary efficacy endpoint.

Thus, the model used to analyse the primary efficacy endpoint included treatment group, study pooled site, study visit, the interaction between study visit and treatment group, the covariate, and the interaction between baseline covariate and visit. Formally, the model to be used was:

Sites were pooled to ensure sufficiently large pooled sites were created to enable the analysis to include pooled sites, while at the same time pooling sites no more than was strictly necessary. Site pooling was performed as detailed in the Statistical Analysis Plan such that Sites 06, 07, 14, 16, and 48 were pooled (N=12), Sites 09, 17, 18, 19, 20, 21, 22, 41, and 43 were pooled (N=15), and Site 01 was on its own (N=17). Relevant text has been added to the methods section, and an explanatory footnote has been added to Table 2.

c) See answer to b)

d) The 3 treatment groups were analyzed together in 1 model. Relevant text has been added to the methods section, and an explanatory footnote has been added to Table 2.

e) Exploratory – information added to the methods section

f) The significance level of the primary efficacy endpoint was 5% (ie, the primary test was to evaluate the efficacy of orvepitant (30 mg given once daily orally for 4 weeks) compared with placebo in reducing intense EGFRI-induced pruritus. All other analyses were secondary or exploratory. This information has been added to the methods section.

g) As this was an exploratory Phase 2 study, no account for multiple comparisons or multiple testing of the secondary or exploratory endpoints was made. This information has been added to the methods section.

7) Table 2 (page 7)

a) Please indicate more clearly the origins of the stated results, e.g. which results are from descriptive analyses and which results are from the models described in the 'Statistical analysis' section of the manuscript.

b) For the SD, please show only 2 (not 3) decimal places (to be consistent with the notation of the mean).

c) For the LSMEANS standard error, please show only 2 (not 3) decimal places.

d) In the statistics column, row 'LSMEANS standard error (95% CI)' please delete the part '(95% CI)' as this is not shown.

a) An explanatory footnote has been added.

b) Changed as requested

c) Changed as requested

d) Corrected as requested

8) Efficacy (page 7)

Please include main results of Supplemental Table 1 directly into the manuscript (e.g. all secondary outcome measures listed in the abstract of the manuscript).

Secondary outcome measures were clarified in the abstract and the methods section. EGFRI dose reductions and withdrawals from the study because of intense uncontrolled pruritus were added to the paragraph after Table 2 in the results section.

VERSION 2 – REVIEW

REVIEWER	Ethan Lerner Massachusetts General Hospital
REVIEW RETURNED	31-Oct-2019

GENERAL COMMENTS	The authors have been highly responsive.

REVIEWER	Stephanie Roll Institute for Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Germany
REVIEW RETURNED	31-Oct-2019

GENERAL COMMENTS	The authors have provided a sound and thorough revision of the manuscript. I only have a few minor comments. 1) Section „Patient and public involvement“

	Please delete the sentence "The primary endpoint was a patient recorded outcome". A patient reported outcome has nothing to do with "Patient and public involvement". Please change the sentence "There was no public involvement." to "There was no patient or public involvement in the planning of this trial." 2) Section „Study design and enrolment“ Please give the results of the blinded analysis of data variance. This is valuable information for the planning of future studies. 3) Section „Endpoints“ Please delete the newly included part "for orvepitant 30 mg versus placebo" in the first sentence (because this is a comparison, which is not part of an endpoint definition). 4) Section „Statistical analysis“ The definition of the intention-to-treat (ITT) population is not according to statistical guidelines. ICH-E9 states that „The intention-to-treat … principle implies that the primary analysis should include all randomised subjects“. The analysis population in the present study, however, consist of „all randomised patients who receive at least the first dose of study medication and had at least one post-treatment efficacy assessment.“ The analysis population in the present study should thus be labelled "modified ITT" or „Full analysis set“. 5) Please show results for the main secondary endpoints as defined in the study protocol (e.g. Skindex-16 QoL, LSEQ, Rescue medication usage) directly in the manuscript. 6) Please include Figure 1 into the material for review.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 4

Reviewer Name: Stephanie Roll

Institution and Country:

Institute for Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Germany Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below The authors have provided a sound and thorough revision of the manuscript. I only have a few minor comments.

1) Section „Patient and public involvement“ Please delete the sentence "The primary endpoint was a patient recorded outcome". A patient reported outcome has nothing to do with "Patient and public involvement".

Please change the sentence "There was no public involvement." to "There was no patient or public involvement in the planning of this trial."

A: We have revised the text as requested.

2) Section „Study design and enrolment“

Please give the results of the blinded analysis of data variance. This is valuable information for the planning of future studies.

A: We have included the results of the analysis.

3) Section „Endpoints“

Please delete the newly included part "for orvepitant 30 mg versus placebo" in the first sentence (because this is a comparison, which is not part of an endpoint definition).

A: We have revised the text as requested.

4) Section „Statistical analysis“

The definition of the intention-to-treat (ITT) population is not according to statistical guidelines. ICH-E9 states that „The intention-to-treat … principle implies that the primary analysis should include all randomised subjects“. The analysis population in the present study, however, consist of „all randomised patients who receive at least the first dose of study medication and had at least one post-treatment efficacy assessment.“ The analysis population in the present study should thus be labelled "modified ITT" or „Full analysis set“.

A: We have labelled this population as modified ITT.

5) Please show results for the main secondary endpoints as defined in the study protocol (e.g. Skindex-16 QoL, LSEQ, Rescue medication usage) directly in the manuscript.

A: We have included these results that were previously provided in a supplemental table in Table 3.

6) Please include Figure 1 into the material for review.

A: We have submitted Figure 1.