Author’s response to reviews

Title: A randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of neramexane in patients with moderate to severe subjective tinnitus

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Author’s response to reviews: see over
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MS: 2317521433587717: A randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of neramexane in patients with moderate to severe subjective tinnitus

Dear Dr Shipley,

Please find attached the above manuscript revised in line with peer review comments received. We outline below, point-by-point, how we have responded to peer review comments.

We have ensured that the manuscript conforms to the journal style. I certify that all forms of conflict of interest by all authors have been clearly identified in the text.

We want to thank you for the time and effort expended in reviewing our submission and value the feedback received. We look forward to hearing whether our revised manuscript is now suitable for publication.

Yours sincerely,

Markus Suckfüll
(corresponding author)
Reviewer 1: Carlos Herraiz

Reviewer’s report with responses
This paper presents the efficacy and safety of a new developed drug (neramexane) for tinnitus. The question posed by the authors is well defined and the objectives of the trial are clearly described and achieved.

Method:
Discretionary revision: The method is well defined. The authors explain the inclusion and exclusion criteria, the study flow chart and the efficacy endpoints. The up-titration period and the fixed-dose treatment period is well described, but I have the doubt if there is also a down-titration period or the drug was stopped completely after the fixed-dose period.
Response: The sentence describing the design of the follow-up phase has been modified as follows:

After the treatment phase, administration of study medication was ceased immediately and patients were followed-up for further four weeks with no active treatment and with restrictions on concomitant therapy. [Page 9]

Could the authors describe the method used for the “interview-based investigator’s clinical impression of change (CGIC)?
Response: The following has been included in the methods section:

The CGIC (item 27 of the tinnitus follow-up interview) was assessed by the patient according to a 7-item Likert scale ranging from 1 (very much improved or disappeared) to 7 (very much worse). [Page 10]

There is a lack of audiological data concerning to percentage of patients with hearing loss included in the study, hearing thresholds, etc. Although I do not consider these data absolutely necessary for the study. I would be interesting to describe them. The efficacy of neramexane could be associated to the presence and degree of hearing loss. Sub-typing tinnitus (presence of hearing loss or normal hearing) could increase the significance of the results for one of these groups.
Response: Hearing loss, puretone hearing thresholds, masking levels and tinnitus matching at screening have now been included in Table 1 [Page 27] and 2 [Page 28]. In regards to the efficacy of neramexane according to the presence and degree of hearing loss, the following text was added to Page 13:

Changes in THI-12 total score were stratified by hearing impairment at Screening and analyzed per treatment group. Due to low patient numbers with severe or profound
hearing loss in the low frequency and in the high frequency group, no statistical significant differences could be shown.

There is a writing mistake. Results (paragraph number 5): It says Table 3 and it has to be changed to Table 2.
Response: Citation of tables within the text has been updated

The abstract, references and title convey the objective of the study and the writing is acceptable. Data reporting is correct and it follows the relevant standards. The writing is acceptable.

Discussion and conclusions
They are well balanced and supported by the data. References to other works are well documented

Reviewer 2/3: Ana Elgoyhen / Berthold Langguth

Reviewer's report with responses
Suckfull et al, report the results of a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of neramexane in patients with moderate to severe subjective tinnitus. Tinnitus is a pathological condition for which no approved drugs are on the market. Therefore, any new compound to treat this condition can potentially make a huge difference for treatment. However, some major issues described below concerning the present work, should be addressed.

Major
Page 5, Line 2, Tinnitus is not a physiological phenomenon.
Response: Reference to tinnitus as a physiological phenomenon has been removed.
The sentence now reads as follows:

Subjective tinnitus is commonly referred to as any sound experienced by a patient without recognizable source. It can be heard by most persons in absolute quietness. Intermittent tinnitus not in quietness… [Page 4]

Page 5, last sentence, the statement that tinnitus sensation/perception as measured by pitch, maskability and loudness – do not correlate with tinnitus severity should be referenced.
Response: This statement [Page 4] has been referenced to the following papers:


Page 6 first line, In addition to their presence in the auditory pathway, NMDA receptors are also present on inner hair cells. NMDA receptors are not present on inner hair cells, they are expressed by afferent fibers of the auditory nerve in certain conditions like trauma.
Response: NMDA receptor presence on hair cells has now been removed. The sentence now reads as follows:

The clinical observation that tinnitus sensation/perception – measured by pitch, maskability, and loudness – do not correlate with tinnitus severity in patients suffering from clinically important tinnitus [4–7] strongly supports the thesis that brain structures other than the auditory pathway must be involved.
In addition, NMDA receptor antagonists have been reported to afford protection from hearing loss caused by free-radical-induced damage to the hair cells [8]. [Pages 4/5]

Page 6, Reference 5 does not relate to the sentence, correct references are Elgoyhen et al, 1994, Elgoyhen et al PNAS 2001.
Response: The following references have now been incorporated on Page 5.


Page 6, second paragraph, Outer hair cells known to tune the electromechanical transmission of sound in the cochlea are directly involved. I would change this phrase to: Activation of a9a10 receptors inhibits mechanical amplification brought about by the activity of outer hair cells.
Response: This change has been incorporated as shown below:

Activation of α9α10 receptors inhibits mechanical amplification brought about by the activity of outer hair cells. [Page 5]

Response: The following references have now been incorporated on Page 5.


Page 8: second paragraph: the description of the patient sample is insufficient. More information about the diagnosis of subjective tinnitus is required. It is commonly accepted that there exist different forms of tinnitus which respond in different ways to specific treatments. Therefore a detailed description of diagnostic procedures performed in each patient and a more detailed description of patient characteristics is mandatory.

Response: More information has been included about how patients were diagnosed with subjective tinnitus on Page 7:

Patients 18 to 65 years of age at screening with a clinical diagnosis of persistent, subjective, moderate to severe, uni- or bilateral tinnitus present for at least 3 months but not more than 18 months were included. Diagnosis of these patients included a complete physical and ear, nose and throat examination and also included psychoacoustic measures and questionnaires including the Tinnitus Interview.

Tinnitus can never be diagnosed by a score in a tinnitus questionnaire: this sentence should be modified in the sense that the severity of tinnitus was assessed by the TBF-12.

Response: This change has been incorporated on Page 7:

Subjective tinnitus severity was graded using a 12-item German version (THI-12, German:TBF-12) of the 25-item English ‘Tinnitus Handicap Inventory’ (THI) patient questionnaire [18] and the physician’s Clinical Global Impression of Tinnitus Severity (CGI-S) scale. Each question of the THI-12 can be answered by the patient with either ‘often’ (2 points), ‘sometimes’ (1 point) or ‘never’ (0 points) with a maximum total score of 24 indicating most severe suffering from tinnitus. The CGI-S asks physicians to rate their patients’ tinnitus severity based on their past experience with other patients with the same diagnosis and ranges from 1 (normal, not at all ill) to 7 (extremely ill).

Information should be provided about the diagnostic procedures which were performed to exclude objective tinnitus. Were patients with puls-synchronous pulsatile tinnitus included?

Response: The following text has been included on Pages 7 and 8:

All patients included in the study were considered to have moderate to severe subjective tinnitus according to a THI-12 total score ≥9 and a CGI-S score of ≥4 at both screening and baseline. Patients had to have a body mass index (BMI) ≥18 kg/m² and ≤32 kg/m² and no clinically relevant abnormalities following physical examination and laboratory evaluation. Women of childbearing potential were required to practice adequate contraception. All patients provided written informed consent.

Patients were excluded if they presented with intermittent or pulsatile tinnitus or tinnitus as a concomitant symptom of another otological/neurological condition (e.g. otitis media). Patients with conductive hearing impairment were also excluded (air conduction threshold >20 dB worse than bone conduction threshold in at least two tested frequencies).
In addition, patients with epilepsy, acoustic neuroma, multiple sclerosis, serious head/cervical trauma with residual deficits, anamnestic HIV infection or any other clinically relevant neurological or psychiatric disorder or systemic disease (e.g. cardiac disease) following physical examination or assessment of medical history were excluded. Patients could not have received any other concomitant pharmacologic or non-pharmacologic treatment for tinnitus in the 28 days prior to screening (30 days if an investigational drug), including sound generators, counseling, behavioral therapy and psychotherapy. Pregnant and breastfeeding women were excluded.

Patients who met the inclusion criteria and none of the exclusion criteria were randomized to one of four treatment groups: neramexane 25 milligrams per day (mg/d), 50 mg/d or 75 mg/d or placebo. Treatment was administered over a 16-week period consisting of a 4-week up-titration period and a 12-week fixed-dose treatment period, with twice-daily dosing during both treatment periods.

If yes, which tests were performed in order to exclude an internal sound source such as a vascular anomaly in these patients? Further it should be described whether patients with treatable hearing disorders (e.g. conductive hearing loss) or with severe sensorineural hearing loss were included.

Response: A description of procedures for the diagnosis of unilateral, conductive, or sensorineural hearing loss has been included on Page 7:

In order to differentiate and characterize tinnitus patients in more detail, study recipients were subjected to pure tone audiometry, tinnitus pitch and loudness matching and tinnitus masking. An auscultation around the ear and neck to check for vascular turbulences, inspection of the ear canal and the tympanic membrane, cranial nerve testing, observation for nystagmus and tuning fork testing according to Weber and Rinne for unilateral, conductive, or sensorineural hearing loss were also performed.

Patients with severe hearing loss were included and hearing status at baseline has been incorporated in Table 1 [Page 26].

Also information is required about the laterality of the tinnitus and its pitch. All this information and information about the mean tinnitus duration and the hearing status of the participants in the different groups should be added to table 1.

Response: This data has now been incorporated into Table 1 [Page 26] and Table 2 [Page 27].

It is evident that only patients who fulfilled all inclusion criteria and did not meet exclusion criteria were included. However a detailed description of inclusion- and exclusion criteria is mandatory. Which comorbidities were excluded? Were comorbidities which frequently occur together with tinnitus such as depression, anxiety, insomnia, hyperacusis, phonophobia or severe hearing loss excluded? How were these exclusion criteria diagnosed?

Response: Inclusion and exclusion criteria have not been included on Pages 7 and 8 (see above). Information about how comorbidities were diagnosed has also been included in greater detail on Pages 7 and 8 (see above).
Which concomitant treatments were allowed? In Germany and Austria hearing aids, noise generators, counseling and a modified form of TRT are frequently used. Were these concomitant treatments excluded? Which comedications were allowed?

Response: This information has now been included as follows on Page 8:

Patients could not have received any other concomitant pharmacologic or non-pharmacologic treatment for tinnitus in the 28 days prior to screening (30 days if an investigational drug), including sound generators, counseling, behavioral therapy and psychotherapy.

It should be explained why the change in the TBF-12 was chosen as the primary outcome parameter. Other questionnaires are much better established and more widespread used, in Germany mainly the Tinnitusfragebogen Goebel and Hiller, internationally the THI. Why were these established questionnaires not used? The use of the TBF-1 has the inconvenience that treatment results are not comparable to other studies and it is extremely difficult to judge which change on the score is clinically meaningful.

Response: The following text has now been included on Page 9:

The primary efficacy endpoint was the absolute change in THI-12 total score from baseline to the endpoint visit (Visit 6, i.e. Week 16, or early termination). The THI-12 is derived from the 25 item version of the Tinnitus Handicap Inventory. The scale is easily administered and is a psychometrically robust and reliable tool to assess the different aspects of tinnitus suffering [18]. Although initially validated in German language only, it has meanwhile shown intercultural validation [19] which makes it a suitable tool for further international studies.

A methodological paper on the THI-12 (“Assessment of tinnitus-related impairments and disabilities using the German THI-12: sensitivity and stability of the scale over time”) has been submitted and is currently under review. In the absence of any therapeutical gold-standard, the question of clinical relevant changes had been addressed to an expert panel who considered a difference of 1 score point between treatment groups as clinically meaningful.

Some information should be given concerning which were the most frequent reasons for screening failures.

Response: The follow text has now been included on Page 13:

Patient disposition is summarized in Figure 2. Overall, 628 patients were screened from October 2005 to March 2007, although 197 of these patients were screened but not enrolled. The main reasons for screening failure included abnormal ECG, abnormal liver function, THI-12 score <9 and treatment with other concomitant medication (e.g. benzodiazepines).

The authors mention that a dose reduction was possible during the trial. They should report in how many patients/group the dosage was reduced during the trial.

Response: Table 5 [Page 30] has been included to show the percentage of patients with treatment-emergent adverse events leading to dose reduction. In addition, the following text has been included on Page 15:
As shown in Table 5, the percentage of patients with treatment-emergent adverse events leading to dose reduction increased with neramexane dose. Dizziness, vertigo, nausea and fatigue were the most common treatment-emergent adverse events leading to dose reduction.

Page 10, statistical analysis. It is not clear why the THI-baseline value was entered as covariate in the ANCOVA. First, I see no reason for this procedure, since the THI baseline score was similar in the different treatment groups. Second ANCOVA assumes that the covariate is unrelated to the independent variable in the model (Yzerbyt et al. (2004) Adjusting researchers’ approach to adjustment: On the use of covariates when testing interactions. Journal of Experimental Social Psychology, 40, 424-431).

The baseline of the primary variable was included as covariate in the model following the EMEA guidance “Points to Consider on Adjustment for Baseline Covariates (CPMP/EWP/2863/99)”. This analysis was defined a-priori in the study protocol as recommended in the guidance document (II.7)

Page 12: The authors report that 61 of the randomized patients were excluded from the TPP population. However the patient flowchart mentions 109 patients as “withdrawn” after randomization

Response: The treated-per-protocol (TPP) population included all patients of the ITT population who had no major protocol violations. Although 109 patients were withdrawn following randomization only 61 patients exhibited major protocol violations that excluded them from the TPP population. Therefore if patients were withdrawn that did not mean they were not part of the TTP population as they could have received all study medication but may have withdrawn consent or if they developed ECG abnormalities etc.

Page 13: second paragraph: Table 2 instead of Table 3.

Response: Citation of tables within the text has been updated.

Treatment effects on puretone threshold, tinnitus pitch, loudness match, minimum masking levels and HADS scores should be reported in detail. Also the effect on laboratory values, EC and vital signs should be described in more detail.

Response: Screening audiometric and psychoacoustic measurements have now been included in Table 1 [Page 26] and 2 [Page 27]. In addition the following text has been included:

No relevant changes were observed in either treatment group for puretone threshold, tinnitus pitch, loudness match, or minimum masking levels. [Page 14]

No relevant change of the HADS score was observed. Decreases in the depression score (means ranging from –1.6 for placebo to –2.4 for the 50 mg/d group) were small and did not show a clear dose-dependency. This supports the hypotheses that neramexane specifically improves tinnitus symptoms and does not act through an antidepressant or anxiolytic effect. Patients without symptoms of anxiety or depression (HADS anxiety or HADS depression subscore < 10) benefited from neramexane treatment, whereas subjects with symptoms of anxiety or depression did not benefit. The estimated treatment difference for patients in the 50 mg dose group with a baseline depression subscore < 10 was 1.2 score points on the THI-12 (p =
and 1.3 score points (p = 0.030) for those patients with a baseline anxiety subscore < 10. [Pages 14 and 15]

There was no relevant influence of the study medication on laboratory values, ECG or vital signs. No clinically meaningful changes in hematology, clinical chemistry or coagulation values were apparent from screening to week 8 or week 16 (or early termination) in any of the treatment groups. For the vast majority of patients, the ECG was assessed as normal. Furthermore, none of the abnormalities assessed as clinically relevant by the investigator fulfilled the criteria for potentially clinically significant PR, QRS or QTcB intervals. Mean and median values of blood pressure, pulse rate and weight were similar across all treatment groups and were stable throughout the study. [Pages 15 and 16]

Page 15, first, paragraph. Suggest evidence is not correct
Response: The sentence has been amended.

15: last paragraph: the explanation for the improvement of tinnitus at the follow-up visit, 4 weeks after stopping the study medication is not really satisfying. Other potential mechanisms (e.g. effect of drug withdrawal, effects in nonauditory brain areas) should also be discussed. Interestingly similar effects were observed in some tinnitus patients, which were treated with memantine (Figueiredo et al. 2008).
Response: we agree that we currently do not know the reason for this phenomenon. Therefore, a longer wash-out period of 3 months has been introduced to one of the Phase 3 studies. Figueiredo et al. 2008 is now discussed further below. (The text has been modified as follows [Page 16]:
As the elimination half-life of neramexane is 30–45 hours, this further improvement is very unlikely to be attributable to a direct effect of the substance. As only one post-treatment measurement was performed in this study, this post-treatment effect is further investigated in an ongoing Phase 3 trial.

Page 16: Accuracy and reliability of the questionnaire which has been used as primary outcome measure are critical for the interpretation of data. It is problematic if data about the accuracy and reliability of this instrument is not yet published. Citing a paper “in preparation” is insufficient.
Response: The following references have been included to support THI-12 as a valid and reliable instrument [Page 18]:


A methodological paper on the THI-12 (“Assessment of tinnitus-related impairments and disabilities using the German THI-12: sensitivity and stability of the scale over time”) has been submitted and is currently under review

Page 16, second paragraph, this paragraph describes results and should be in the Results section.
Response: This change has been incorporated.
Page 16, third paragraph, This finding is consistent with publications confirming that the tinnitus suffering as perceived is not systematically dependent on audiometrically derived measures of tinnitus loudness and pitch, references are needed. Response: This statement [Page 18] has been referenced to the following papers:


Page 17, first paragraph, references are needed. Response: The statements in this paragraph have now been referenced.

Page 17. other NMDA antagonists have been tested in the treatment of tinnitus in the past both in humans and in animal studies. Especially the results of trials investigating memantine should be discussed, since neramexane and memantine seem to be very similar in their mechanism of action. Response: Animal studies with memantine were performed in salicylate- and quinine-induced tinnitus models, whereas neramexane was investigated in noise trauma induced tinnitus models. Full publications of preclinical data with neramexane are not available yet, therefore the authors restrained from further discussion. The results of Figueiredo et al have now been implemented:

A placebo-controlled crossover study with memantine, an NMDA antagonist with moderate affinity, did not show a significant difference between memantine and placebo treatment on tinnitus suffering as assessed with the 25-item version of the THI [24]. However, as the authors conclude, the study had some methodological weaknesses (dose limitation, duration of wash-out phase) and the negative results do not generally exclude the usefulness of substances with NMDA antagonistic properties for the treatment of tinnitus.

Conclusions
Post-hoc analyses revealed that reducing the tinnitus duration to 12 months, excluding patients with clinically relevant symptoms of depression or anxiety, weight-adjusted dosage and other aspects could be associated with a further enhancement of the effect of neramexane. These data is not shown. Therefore, it should be withdrawn from conclusions or shown on the Results section Response: This passage has been deleted.

Additional minor comments
Page 1. list of authors: (markus.suckfuell@med.uni-muenchen.de), superscript should be deleted Pawel J. Jastreboff³(pjastre@emory.edu), a space is missing
Response: These changes have been incorporated.

Page 3
background: a9/10 should be changed to a9a10 and throughout the manuscript
nicotinergic should be changed to cholinergic nicotinic line 2, receptor should be
changed to receptors
Response: These changes have been incorporated.

Page 4 Line 1, in respect on should be deleted
Response: This change has been incorporated.

Page 5, Line 7, German population suffer, change suffer to suffers
Response: This change has been incorporated.

Page 5, Second paragraph, glutamatergic transmission have been implicated in
various disorders of the central nervous system (CNS) disorders, disorders should be
deleted once.
Response: This change has been incorporated.

Page 7 Line 1: occurring during, change to involved in
Response: This change has been incorporated.