Author's response to reviews

Title: Tolerability of NGX-4010, a capsaicin 8% dermal patch, following pretreatment with lidocaine 2.5%/prilocaine 2.5% cream in patients with post-herpetic neuralgia

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Author's response to reviews: see over
May 13, 2011

Dr Sonia Aguera
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Dear Dr Aguera,

Re: MS: 7004165884917692
Tolerability of NGX-4010, a capsaicin 8% dermal patch, following pretreatment with lidocaine 2.5%/prilocaine 2.5% cream in patients with post-herpetic neuralgia. Lynn R Webster, Margarita Nunez, Marvin D Tark, Edwin D Dunteman, Biao Lu, Jeffrey K Tobias and Geertrui F Vanhove

Thank you for the email communication of March 8, 2011 regarding the manuscript revisions necessary for publication. We have reviewed the manuscript with the comments from the reviewers and have modified the manuscript accordingly, with track changes to indicate changes from the previously submitted version. Listed below are the specific changes and comments made in response to the input from the reviewers. One reference has been added and the reference numbering adjusted in the text.

Reviewer 1: Vera Bril
The authors present an open study on the effects of lidocaine 2.5%/prilocaine 2.5% cream in reducing pain related to application of capsaicin 8% for PHN. The study is well presented, but an open-label trial. Still, the results are of interest.

1. My main comment is about the lack of any discussion about why this preparation would be used instead of lidocaine 4%. Both have similar benefits, but I did not observe any reason to choose the combination cream. Is the expense of both comparable? Is one option less costly to use? I think that the paper could be improved by some discussion of which option to choose.

RESPONSE
The reason the combination cream was studied was that lidocaine 4% cream is not available/approved in all countries in which NGX-4010 is approved.

The text in the second paragraph of page 5 has been changed to address this point (new text in red):

“The objective of the current study was to evaluate the tolerability of NGX-4010 after pretreatment with an alternative topical anesthetic, lidocaine 2.5%/prilocaine 2.5%
anesthetic cream, in patients with PHN, since 4% lidocaine cream is not available in all of the countries in which NGX-4010 is approved.”

Reviewer 2: Robert Johnson
Reviewer's report:
1. What is the purpose of this study? It does not compare treatments other than by historical control data and numbers are small. Is the eutectic mixture more readily available, easier to use or less expensive than the currently used lidocaine? MINOR ESSENTIAL REVISION

RESPONSE
Please see the response to Issue #1 of the previous reviewer.

2. The description of PHN is inadequate. It should include both continuous and paroxysmal spontaneous elements of pain as well as alodynia. MAJOR COMPULSORY REVISION

RESPONSE
The text in the first paragraph of the background (page 4) has been amended as follows (added text in red):

“PHN is caused by damage to the small-diameter sensory C and Aδ fibers within primary afferent neurons, which results in hypersensitivity and exaggerated responses to normally innocuous stimuli (evoked pain), as well as both continuous and paroxysmal spontaneous pain. Symptoms of PHN include pain from normally non-noxious stimuli such as the brush of clothing (alodynia), increased sensitivity to painful stimuli (hyperalgesia), intermittent stabbing or lancinating pain and constant deep burning.”

3. The statement regarding efficacy of 8% capsaicin in the Conclusions section should be modified to remove ‘… NGX-4010 is a treatment option for PHN that provides significant pain relief …’ and replace with ‘… may provide …’, or alternatively state figures for percentage gaining pain relief and its magnitude and duration. MAJOR COMPULSORY REVISION

RESPONSE
The text in the conclusion section has been modified (added text in red):

“In summary, NGX-4010 is a treatment option for PHN that may provide significant pain relief for up to 3 months from a single 60-minute application.”

Reviewer 3: Arnold Gammaitoni
Reviewer's report:
1. There is a lack of important information with regards to rescue utilization that is necessary to further put the results in context. The investigators state that patients had access to opioids for rescue and although they report the number of patients
that took opioid, they do not report the amounts taken and this severely limits how one judges the results. Its one thing to know that 42% of patient took opioid on the treatment day. It's another to know – How much? Was it 10mg of oxycodone, 60mg of oxycodone, 100mg??? Clearly this would impact the reader's opinion regarding tolerability on the treatment day and would provide a more complete picture along with the pain, AE, and BP data provided.

RESPONSE
We have added the opioid dose data to the methods and results section (added text in red).

Methods
“To determine the tolerability of NGX-4010 following pretreatment with the lidocaine 2.5%/prilocaine 2.5% anesthetic cream, the following were assessed: mean duration of patch application; mean changes in “Pain Now” NPRS scores from pretreatment values on the day of treatment; the proportion of patients using analgesic medication for treatment-associated pain during and following patch application on the day of treatment and on Days 0 to 7 and the mean daily dose; and the proportion of patients completing at least 90% of the intended patch application duration.”

Results
“A total of 10 patients (42%) received immediate-release, opioid-based analgesic medication (oxycodone or oxycodone-based medication), 3 patients (13%) received hydrocodone (or hydrocodone-based medication), and 1 patient (4%) received acetaminophen. The mean dose of opioid medication received on Day 0 was 11.5 mg for oxycodone and 15.0 mg for hydrocodone. The number of patients receiving medication for treatment-related discomfort decreased rapidly after the day of NGX-4010 treatment, with only 4 patients receiving medication on Day 1, 2 patients on Day 3, 1 patient on Days 5 and 6 and no patients on Day 7.”

2. Sample size – since there is previous data with the use of 4% lidocaine and the stated objective was to look at EMLA as an alternative to it; why then couldn't the investigators take a more rigorous approach to determining sample size. They state in the assessment paragraph on page 7 that this sample was deemed sufficient based on clinical judgment to adequately assess tolerability. I'm not sure what that means, especially since they then go on to rightly sight the sample size as a limitation in the discussion. If you know this going into the study then why not try to approach sample size differently. For instance, they could have selected one or more of the endpoints (pain, BP change, AE's) and then what they considered to be a clinically acceptable difference to conclude that EMLA provides similar tolerability. From this and using the variability data from the trials with 4% lidocaine, a sample size could have been estimated that would have better addressed the stated objective in my opinion.
RESPONSE
The objective of the current study was to evaluate the tolerability of NGX-4010 after pretreatment with an alternative topical anesthetic, lidocaine 2.5%/prilocaine 2.5% anesthetic cream, in patients with PHN and not to show that lidocaine 2.5%/prilocaine 2.5% is not inferior to lidocaine 4%. Using the approach suggested above would have led to a sample size that would have proved to be too large to make the study feasible. For example, a sample size based on showing non-inferiority based on a 10% difference in maximum increase in “Pain Now” on the treatment day between this study and historical data which showed a mean maximum increase of 2.8 (SD: 2.7) would have required 1275 subjects per arm based on 80% power and a type I error of 0.05. A 30% difference in maximum increase in “Pain Now” on the treatment day between this study and historical data would have required 512 subjects per arm based on 80% power and a type I error of 0.05.

Specific Comments:
1. Patient Demographics (Page 9)
It is stated that 1/3 of the patients in this trial were previous NGX-4010 users. Was there an attempt to look at whether or not these patients differed in terms of outcome vs. those that did not use the product previously? It would be interesting since previous users have knowledge of what the application will "feel" like, Are they more "tolerant"? Do they report lower pain scores? Do they use less rescue opioid? Your sample size is too small to say anything definitively but it would be interesting as a hypothesis generating exercise for future research.

RESPONSE
While this is a good and interesting idea, we do not feel such an analysis would be appropriate with the small number of patients who were previous NGX-4010 users. The tolerability to repeated NGX-4010 treatments has been described in a previous publication (Simpson et al 2010, Journal of Pain and Symptom Management) in patients with both PHN and HIV-DSP. These data showed that during four separate treatments with NGX-4010, approximately 50% of patients received oxycodone for treatment-associated discomfort. Likewise, a similar proportion of patients reported application-site pain after each of the four NGX-4010 treatments.

2. Pain associated with treatment section (Page 10)
I'm not sure why oxycodone or oxycodone based medication is separated out from hydrocodone or hydrocodone based medication. These are both opioids and should be grouped together when reporting proportion of patients that utilized "opioids".

RESPONSE
When we state on page 10 that “Half of the patients treated with NGX-4010 received medication on the day of application (study Day 0) for treatment-related discomfort,” this includes patients taking any medication for treatment-related discomfort including oxycodone hydrochloride and/or hydrocodone. The next sentence separates it out because, as described in the method section, oxycodone was administered in the clinic
during and shortly after the patch application procedure, while hydrocodone could be taken at home.

3. Figure 1 Change in Pain on the treatment day
The figure as it exists in the manuscript does not really present the data in what I feel is a meaningful way. Change scores in the absence of a starting point or the absolute scores leave out important information that the reader must then try to figure out as I have done above by adding the absolute pain scores for each timepoint in bold. In this case, I think the absolute pain scores provide a more complete picture. In essence these patients were experiencing moderate to severe pain during the first treatment day (during patch application and afterward). This is more impressive when you think about the fact that they were at about a 2.5 on average at the end of the EMLA application. Therefore you have a clinically meaningful change (≥2 points on a 10 point scale) for the entire treatment day after application. Indeed the swing from this low point to about an 8.0 at 55 min post NGX-4010 application also correlates with BP changes in Figure 2 below. So one could say they were "feeling it".

When I look at both pieces of information together I have to wonder how satisfied the patients were on the treatment day. Since there was no global satisfaction or global assessment reported by the patient we are left to wonder if this was acceptable to them.

RESPONSE
We have added the mean absolute NPRS scores to Figure 1 to address this point. Although the absolute NPRS score reaches 7.7, the data show that all patients completed at least 90% of the intended duration of patch application and none asked for early removal, indicating that the treatment was tolerable. Satisfaction surveys have been performed at the end of all studies. An integrated analysis of the four 12-week, randomized, controlled, double-blind studies showed that the majority of NGX-4010-treated patients (63%) reported that they would undergo treatment again and that only 12% of patients stated they preferred their previous treatments, while 48% of patients reported that they preferred NGX-4010 treatment over their previous treatments. These data were presented at the 13th World Congress on Pain in Montreal, Canada, August 29 – September 2, 2010 by Irving et al. (Quality of life measures in post-herpetic neuralgia patients treated with NGX-4010: Results of integrated analyses) but have not yet appeared in a manuscript.

The results section has been updated as following (added text in red):

“Pain Associated with Treatment
The mean absolute NPRS score was 4.7 before treatment, decreased following anesthetic application and then increased following application of NGX-4010 (Figure 1). A maximum mean increase in NPRS score of 3.0 was recorded just before removal of NGX-4010. The score quickly declined following patch removal to less than half the
maximum within 5 minutes of patch removal (+1.4) and returned to near pre-anesthetic levels (+0.7) within 85 minutes of patch removal (Figure 1).”

4. Conclusions:
I think the investigators need to support the following statement with data: "Results from the current investigation provide evidence that the tolerability of NGX-4010 following pretreatment with lidocaine 2.5%/prilocaine 2.5% cream is comparable with the tolerability observed in the clinical trials using 4% lidocaine…” Why? Perhaps they should pull some information into the discussion from those previous studies to show the pain levels, BP changes, AEs and opioid usage was similar. The reader cannot see this in the current manuscript without going and pulling those references. So some recap of that in your discussion would be quite helpful.

RESPONSE
We have added the following information into the discussion regarding opioid medication use, AEs, and BP from other studies with NGX-4010 (added text in red):

In the present study, the pain experienced during and following NGX-4010 treatment was transient, with mean NPRS scores returning to pre-anesthetic levels (+0.7, 95% CI: –0.68, 2.09) within 85 minutes of patch removal. This result is similar to that of a previous report also showing a transient increase in pain during NGX-4010 application, and a return of mean NPRS scores to pre-anesthetic levels (+0.4) by 85 minutes post-patch removal. The maximum mean increase in NPRS score of 3.0 (95% CI: 1.79, 4.21) observed just before removal of NGX-4010 in the present study was comparable with the mean NPRS score increases of 2.0 to 2.8 observed in a long-term safety study that included PHN patients.

The most common treatment-emergent AEs were application site-related pain and erythema. The incidence of application-site erythema in this study (100%) was similar to an incidence of 94% and 92% reported in previous studies of NGX-4010 in patients with PHN. Application-site pain was reported by 92% of patients in the current investigation and was slightly higher than an incidence of 56% and 63% of patients reported in two previous studies. However, despite this higher incidence of application-site pain, the pain increase and the use of medication for treatment-related discomfort was comparable, as described above.

Changes in blood pressure were associated with treatment-related changes in pain; in previous studies blood pressure increases were on average <10 mm Hg, while in the current study the maximum mean increase was 11.8 mm Hg (95% CI: 5.3, 18.3).

And we have adjusted the conclusion section as follows (added text in red):

Results from the current investigation provide evidence that the tolerability of NGX-4010 following pretreatment with lidocaine 2.5%/prilocaine 2.5% cream is comparable with the tolerability observed in the clinical trials using 4% lidocaine cream as pretreatment, in terms of intended application duration, extent of application site-related pain, use of
medication for treatment-related discomfort, dermal irritation, AEs, AE profile, and transient blood pressure changes.

**Editorial Requests:**

1) **Abstract:** please add your TRN as the last line of the abstract.

**RESPONSE**

We have moved the trial registration number to be the final sentence of the abstract. The trial was registered on Clinicaltrials.gov, which we have stated.

2) **Ethics:** please name the ethical body that gave approval for your study.

**RESPONSE**

Aspire IRB, LLC, 9320 Fuerte Drive, Suite 105, La Mesa, CA 91941, was the ethical body that approved the study. This has been added under the method section.

**New Reference**


Thank you for consideration of this manuscript. I look forward to receiving notification regarding this article submission.

Best regards,

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