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

Authors:

Lynn R Webster (lrwebstermd@gmail.com)
Margarita Nunez (mnunez@cnsmail.com)
Marvin D Tark (mtark@drugstudies.net)
Edwin D Dunteman (edunteman@aapain.net)
Biao Lu (biao_lu_2002@yahoo.com)
Jeffrey K Tobias (jtobias@neurogesx.com)
Geertrui F Vanhove (TVanhove@neurogesx.com)

Version: 3 Date: 6 December 2011

Author's response to reviews: see over
December 6, 2011

Philippa Harris, Ph.D.
Executive Editor
BMC-series Journals
BioMed Central
Floor 6, 236 Gray's Inn Road
London, WC1X 8HL

Dear Dr. Harris,

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 November 6, 2011 regarding further manuscript revisions necessary for publication. We have reviewed the comments from the editorial board and have modified the manuscript accordingly, using yellow highlighting to indicate changes from the previously submitted version. Listed below are the specific changes and comments made in response to the input from the editorial board.

Editorial board comments
We think that your manuscript requires greater detail on the limitations of the study, especially in the discussion section. In particular the limitation that this is an open, non-controlled study should be discussed in detail.
The Procedures section of the Materials and Methods have been amended to include “non-controlled, non-randomized” to the description of the trial, as detailed below.

This was a 7-day, open-label, non-controlled, non-randomized, multicenter study with a total of three visits—Screening, Day 0 (treatment day), and Day 7.

The limitations of the study have been discussed further within the Discussion section of the manuscript, as detailed below.

The major limitation of this study was that it was an open-label, non-randomized trial that did not include a control arm or a comparator arm for the tolerability of NGX-4010 treatment following pretreatment with lidocaine 2.5%/prilocaine 2.5% cream. Therefore, direct comparisons between the tolerability of NGX-4010 treatment following pretreatment with lidocaine 2.5%/prilocaine 2.5% cream or 4% lidocaine cream cannot be drawn. This means that it is not possible to confirm whether NGX-4010 treatment is equally tolerable following pretreatment with either topical anesthetic cream. As there was no control arm, it is also not possible to compare directly the tolerability of NGX-4010 after lidocaine 2.5%/prilocaine 2.5% cream pretreatment with the tolerability after no anesthetic cream pretreatment. Consequently, it is not possible to determine whether pretreatment with lidocaine 2.5%/prilocaine 2.5% cream is essential for the tolerability of NGX-4010 treatment. However, the objective of this study was to investigate the tolerability of NGX-4010 treatment following pretreatment with lidocaine 2.5%/prilocaine 2.5% cream, because 4% lidocaine cream is not available in all of the countries in which NGX-4010 is approved. Despite the limitations of an open-label, non-randomized study, these objectives were met, with the data showing that NGX-4010 is a tolerable treatment following pretreatment with lidocaine 2.5%/prilocaine 2.5% cream. Other limitations of this study included the small sample size and lack of long-term follow-up. However, all application-site AEs in this study were short term and transient,
resolving within 7 days and longer follow-up would not have provided additional tolerability information.

Based on the mode of action of lidocaine and prilocaine, it is not surprising to find that the tolerability of NGX-4010 following pretreatment with lidocaine 2.5%/prilocaine 2.5% appears to be similar to that seen when 4% lidocaine is used as a pretreatment.

RESPONSE
To further address the comments from the editorial board, we have also amended some of the text in the Abstract and the Conclusions section, as detailed below.

Abstract
The tolerability of the patch application appeared comparable with that seen in other studies that used 4% lidocaine cream as the pretreatment anesthetic.

Conclusions
Previous clinical trials utilized 4% lidocaine cream as pretreatment; however, other topical anesthetics may also be used. Results from the current investigation provide evidence that NGX-4010 is tolerable following pretreatment with lidocaine 2.5%/prilocaine 2.5% cream. Moreover, tolerability appears 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, AE profile, and transient blood pressure changes.

FURTHER CHANGES
In addition to the above amends made in response to comments from the editorial board, we have also updated a sentence in the Background section to illustrate that the antidepressants are analgesic, and the Competing Interests have been updated, as detailed below.
Background

Neuropathic pain therapies include adjunctive analgesic antidepressants and anticonvulsants, as well as opioids and various topical treatments such as lidocaine or low-concentration capsaicin [8,9].

Competing interests

Lynn R Webster is a consultant for NeurogesX Inc and Astellas Pharma Europe Ltd. Biao Lu, Jeffrey K Tobias and Geertrui F Vanhove are former employees of NeurogesX Inc and own NeurogesX Inc stock.

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

Best regards,

Lynn Webster, M.D.
Medical Director, Lifetree Clinical Research
(801) 892-5140
LRWebsterMD@gmail.com