

Amendment 046 - Final Prescribing Information, June 20, 2011 - Laviv

From: Schneider, Bruce
Sent: Monday, June 20, 2011 1:44 PM
To: Tull, Lori
Cc: Zhu, Yao-Yao
Subject: FW: BLA 125348 Amendment 046 - Final Prescribing Information

Attachments: emfalert.txt

From: Kevin Hennegan [mailto:khennegan@cbrintl.com]
Sent: Sunday, June 19, 2011 10:45 AM
To: Jeanne Novak; Schneider, Bruce
Cc: Zhu, Yao-Yao; Lee Buttrill; Jay Merritt; Dana Weinberger
Subject: RE: BLA 125348 Amendment 046 - Final Prescribing Information

Dear Bruce,

As a follow up, here are the definitions of the various populations analyzed in the IT-R-005 and -006 studies, copied verbatim from the IT-R-005/006 Statistical Analysis Plan. The relevant ITT and Safety population definitions are highlighted.

As the 81 yo subject from IT-R-006 did not receive any study injections, he was included only in the ITT population and was excluded from the Safety population.

Best regards,

Kevin
Population
Subjects Included

Intent to Treat (ITT)
Subjects who were randomized to the study and are summarized according to the group to which they were randomized.

Efficacy Evaluable
Subjects who were randomized and received three injections of the study treatment, met

inclusion/exclusion criteria relevant to efficacy, and did not have a major protocol deviation (as determined by the sponsor).

Modified Intent to Treat (MITT)

Subjects who were randomized to study treatment and received at least one treatment.

Safety

Subjects who received at least one treatment summarized according to the treatment they actually received.

Kevin Hennegan, MA
Senior Managing Consultant
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-----Original Message-----

From: Jeanne Novak
Sent: Sunday, June 19, 2011 8:11 AM
To: Schneider, Bruce
Cc: Kevin Hennegan; Yao-Yao.Zhu@fda.hhs.gov; Lee Buttrill; Jay Merritt; Jeanne Novak; Dana Weinberger
Subject: RE: BLA 125348 Amendment 046 - Final Prescribing Information
Importance: High

Hi Bruce,

In short, the data in the PI are correct. It turns out that the populations described for the ISS and ISE in the PI are different. I will explain this

below.

At the time of the analysis for efficacy for the 005 and 006 studies, the FDA asked that we use the ITT definition (not MITT which was defined as having received at least one injection) for the analysis of efficacy. As such, the ISE population is based on subjects who were "randomized." Therefore, the ISE population includes subjects who received no treatment, including the 81 yo (male).

The ISS in the current package insert is a combined data set from seven studies; 001, 002, 003a, 003b, 005, 006 and 007.

While the 005/006 had a total number of 421 subjects included in the ISE, only a subset of the 421, (just 372 treated subjects) were actually included in the ISS (Table 1, page 6). Again, to your earlier point, the population analyzed for this ISS is as follows: "includes 508 subjects who received at least one treatment of LAVIV and 354 subjects who received a vehicle-control"

Thus, the subjects from 005/006 included in the safety population are, in fact, only a subset of the ITT efficacy population described on page 8 since the ISS (Table 1) required receipt of at least one injection. It should also be noted that only the 005 and 006 studies were included in the ISE while SEVEN studies were included in the ISS.

We (Kevin) have reviewed all of the tables and listings supporting the generation of the ISS and the ISE. We have reviewed the data in the 005 and 006 CSRs, and we have located and identified that the 81 yo male who was "randomized" but not treated. We are confident in the data and can provide any additional details upon request. We can also have a call if you determine this is necessary.

I believe this resolves the issue. In our opinion, the PI is correct and requires no revisions.

Please let me know if this is an adequate explanation. I can be reached at
----(b)(6)-----.

Sincerely,

Jeanne

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-----Original Message-----

From: Schneider, Bruce [mailto:Bruce.Schneider@fda.hhs.gov]
Sent: Sunday, June 19, 2011 7:08 AM
To: Jeanne Novak; Dana Weinberger
Cc: Kevin Hennegan; Zhu, Yao-Yao; Lee Buttrill
Subject: RE: BLA 125348 Amendment 046 - Final Prescribing Information
We can speak today if you wish.

-----Original Message-----

From: Jeanne Novak [mailto:jnovak@cbrintl.com]
Sent: Sunday, June 19, 2011 8:50 AM
To: Schneider, Bruce; Jeanne CBR; Dana Weinberger

Cc: Kevin Hennegan; Zhu, Yao-Yao; Lee Buttrill

Subject: Re: BLA 125348 Amendment 046 - Final Prescribing Information

Hi Bruce,

We believe we can explain the difference. It has to do with the population definitions. I am on my cell phone in St Louis and arranging to get a dial in number so we can have a conference call with you and others if needed. A full summary of our review will follow. We propose a conf call at 830 am Mtn time or later.

My cell number is ---(b)(6)---. So feel free to call me at ANY TIME

Jeanne M. Novak, Ph.D.

CEO and President

Principal Consultant

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Sent wirelessly via BlackBerry from T-Mobile.

-----Original Message-----

From: "Jeanne Novak" <jnovak@cbrintl.com>

Date: Sun, 19 Jun 2011 06:06:44

To: Schneider, Bruce<Bruce.Schneider@fda.hhs.gov>; Jeanne
CBR<jnovak@cbrintl.com>; Dana Weinberger<dweinberger@cbrintl.com>

Reply-To: jnovak@cbrintl.com <'jnovak@cbrintl.com'<jnovak@cbrintl.com>; Dana

Cc: Kevin Hennegan<khennegan@cbrintl.com>; Zhu,

Yao-Yao<Yao-Yao.Zhu@fda.hhs.gov>; Lee Buttrill<lbuttrill@cbrintl.com>

Subject: Re: BLA 125348 Amendment 046 - Final Prescribing Information

Hi Bruce

Kevin has been doing a review of the database. I will be able to access tomorrow am. We will go over this and your comments. I am sure we can get this resolved tomorrow

Jeanne M. Novak, Ph.D.

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Principal Consultant

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-----Original Message-----

From: "Schneider, Bruce" <Bruce.Schneider@fda.hhs.gov>

Date: Sun, 19 Jun 2011 00:50:10

To:

Weinberger<dweinberger@cbrintl.com>

Cc: Kevin Hennegan<khennegan@cbrintl.com>; Zhu,

Yao-Yao<Yao-Yao.Zhu@fda.hhs.gov>; Lee Buttrill<lbuttrill@cbrintl.com>

Subject: RE: BLA 125348 Amendment 046 - Final Prescribing Information

Page Last Updated: 07/19/2011

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