

From: Veltri, Enrico [Enrico.Veltri@spcorp.com]
Sent: Tuesday, July 17, 2007 10:56 PM
To: J.J.P. Kastelein
Cc: Strony, John
Subject: RE: RE: ENHANCE

John, thank you for the note. I frankly understand the frustration, but this has been a long and painful process for all involved in this nightmare of a journey. The bottom line however is we all aspire to have quality and credible data, and results that we can stand behind-- whatever the 'truth'. I have been involved in over 20 clinical megatrials, with >200,000 patients enrolled, both positive and negative, stopping early for benefit and stopping early for harm, but I must say ENHANCE has been the most frustrating and, I likewise don't have a good sense of control of the process of data cleanup. You should be aware that the decision not to submit an abstract was a decision based on our concern (both Merck and Schering-Plough) that the quality, ie clean up, and the completed work received to date was not where it needed to be, and a high probability of indeed the withdrawal of the 'bland- no results' abstract, not something we wanted to do, ie yet again try to explain why we submitted then withdrew. In distinction, we would rather try to get it on the program later if and when we had greater confidence, this approach having been accomplished in the past, albeit not the usual path. John Strony did try to contact you but you were on vacation. Anyway, the issue at hand remains the quality of the data, we are analyzing the most recent submitted blinded database, and will be providing you our assessment and thoughts in the next few days. Best regards, Rick.

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

From: J.J.P. Kastelein [mailto:j.j.kastelein@amc.uva.nl]
Sent: Friday, July 13, 2007 8:12 AM
To: Veltri, Enrico
Cc: Strony, John
Subject: RE: RE: ENHANCE

Dear Rick,

I am glad you took the trouble of providing me with such a long answer.

The raging part of my former emails comes from an enormous amount of frustration and a feeling that I have no control whatsoever on anything that relates to ENHANCE. As you know, in my normal state of mind, I am a controlled individual and I am not hard to work with.

However, in all my previous experiences as a member of a Steering Committee or as a PI, I felt I was in control. With ENHANCE, that is totally the opposite.

The database is at SP, consultants like Gene Bond are in my opinion impossible to work with and never agree with me, Bo Yang has made several crucial mistakes on the way that costs us 9 months, Eric is a nightmare to work with in terms of organization and I can go on and on. The last example of this "never working with me" is the fact that you have decided to withdraw the abstract. This is not necessary. You could have sent in an empty abstract that as my friend at AHA told me can be filled with data one week before AHA itself and if you were too late, you simply withdraw it. One phonecall to me would have cleared all of this. This is exactly what I have done with Pfizer for the Torcetrapib latebreakers at ACC this year. The data were ready 3 days before ACC.

Also, I am constantly under pressure from Merck to plan all sorts of activities, before, at and after AHA. Because I !!! will be the one who has to stand up and present and defend the data, and I would deeply appreciate being involved again and not just simply at the end of a long decision line.

Regards, John

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-----Oorspronkelijk bericht-----

Van: Veltri, Enrico [mailto:Enrico.Veltri@spcorp.com]
Verzonden: maandag 9 juli 2007 19:08
Aan: J.J.P. Kastelein
CC: Strony, John
Onderwerp: RE: RE: ENHANCE

John, we (collectively) have always stated that our intent was to present ENHANCE at AHA, but with the caveat that we needed quality and complete data. Both CEOs- Fred Hassan at SP, and Dick Clark at Merck- have gone on record publically to state that we would present ENHANCE results at a scientific forum later this year, BUT they have also stated that the quality of the data needs to be paramount to any presentation, and this call is left to me- and Liz Stoner, my counterpart at Merck. Liz and I met with you as you know earlier this year to convey this commitment, and there is much progress made, but as John outlined to you, we have some delays, yet I believe not insurmountable to still make a presentation at AHA. So these are the facts-

1) the carotid imaging, our primary endpoint, is not yet complete, we hope to have more information on the batch 3 issue this week. The blinded QCed imaging database did not get to us in time for a late-breaker abstract, and was so delayed, the WWOC meeting June 22nd did not feel confident of submitting an abstract without having the queried database QC. Indeed SP received the final batch database late July 2nd, instead of the promised 1 week before late breaker deadline of June 29th. I do not see what you are raging about-- Editors, FDA etc, --the database is not QCed, not lock ready, and it remains blinded. So we are behaving in the highest scientific integrity, we want the data to be correct, whatever the result may be.

2) the femoral imaging is part of a key secondary endpoint, and not 'exploratory' and it should not be new to you that we decided to have all imaging data locked. All those involved with the Operations calls- SP, Merck, outside consultants, CEL know that this is the case, we have been planning this, and indeed I gave the go-ahead to start the femoral readings 'at risk' July 2nd once we had received the carotid database in an effort to make a expeditious transition. As John mentioned, SP SOPs are clear on these database matters.

Thus, we must work together to complete the outstanding database cleanup and readings in a rigorous manner and not short cut for the sake of presentation. Having said that, even though we 'missed' the AHA late-breaker deadline, we have all been in the situation to attempt to get important scientific and clinical data on late-breaker sessions 'after' the formal deadlines. We must be more certain however that the data will be available however, and then we can work collectively to approach the scientific session chairs perhaps to get on the agenda.

I trust that you would be in agreement with a continuing effort to get quality and complete data for an AHA presentation, for I truly believe we will have very important results to share, and the trial and wait will have been worth it. The final chapter may well be a happy ending.

Hope you enjoy the rest of your vacation. Rick.

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

From: J.J.P. Kastelein [mailto:J.J.Kastelein@amc.uva.nl]
Sent: Saturday, July 07, 2007 9:11 AM
To: Strony, John
Cc: Veltri, Enrico
Subject: Re: RE: ENHANCE

I have been travelling half the globe in the last 6 months to a number of large and important meetings at the strong wish of Merck to chair them or to present ezetimibe data. At every single one of them I was cleared to say that ENHANCE would be presented by me at AHA .

There is no reason whatsoever to include femorals; you will be seen as a company that tries to hide something and I will be perceived as being in bed with you !

John

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

From: "Strony, John" <john.strony@spcorp.com>
Date: Friday, July 6, 2007 4:36 pm
Subject: RE: ENHANCE

> With regards to the below stated matter, I have been trying to call
> you including that of cell phone and office.
>
> It is true that the executive management of SP AND Merck through the
> auspices of the WWOC (World wide Operations Committee) have placed a
> hold on abstract submission. I immediately attempted to call your
> office but there was no answer and no machine to leave a message. I
> also called your mobile and I successfully left a message for you to
> call leaving my
> cell phone number (which I always answer). After 36 hours and not
> hearing from you I sent you an e-mail.
>
> The decision to hold submission was based on several factors:
>
> 1) The primary data, namely that of the carotids, is undergoing the
> query process. In parallel, the database has been migrated to a
> commercially available, validated system. We lost 3 weeks doing so. The

> data in the CEL was scattered throughout various computers and lap
> tops making
the
> process more complex than anticipated.
>
> 2) Collin and Jim are now auditing the image data base starting with
> batch 5 and working backwards. When they hit Batch 3 they identified
> 150 extraneous image values from that batch. The origin of these
> values are now being looked into. If the entry dates are after those in

> the current file then, by convention, the more recent entries are
> deemed valid. This would subject batch 3 to a potential re-query
> process. This could cost several weeks. (As an aside, it was Batch 3
> that was the last

> batch accepted during the December crunch and it appears to
> contain a
> unique problem, namely 29% of the queries were answered by the
> replacement of image values with an unreadable code - the average is
> <3%). They have not audited batches 1, 2 or Vanguard, so brace
> yourself for potentially more issues.
>
> 3) Schering SOP's (the database resides in SP) forbid the locking and
> relocking of any database. A deviation requires signatures from the
> highest levels of management. Given the emphasis on compliance upper
> management decided not to take that risk which could in the eyes of a
> hard lined regulatory agency potentially invalidate the entire data
> base. We recognize that the Femoral and m-modes are exploratory
> but that
> makes no difference. (we have in our more recent trials made
> exploratory image analyses separate studies with unique databases
> thus avoiding such
> issues).
>
> 4) The timeline for the reading of the femorals alone has been a
> moving target. First it was 8 weeks, then 12, and then 16. This is
> under the assumption of having 4 readers. However, one of the four has

> failed qualification and now we are down to three. If all runs
> smoothly (which has never happened in ENHANCE) we are told it will take

> 17 weeks for the
> primary readings. Don't forget the querying process and clean-up
which
> is still not factored.
>
>
>
> I share your disappointment(s) and frustrations for this trial from
> hell. However, in the face of all this I have to say that we are
> proceeding in a positive direction; there is much confidence in the 2
> managers who are handling the operations and data base, and that
> in the
> end all involved in the trial could stand proud and say that the
> results are valid with no cause for second guessing.
>
> John
>
>
>
> -----Original Message-----
> From: J.J.P. Kastelein [mailto:J.J.Kastelein@amc.uva.nl]
> Sent: Friday, July 06, 2007 4:46 AM
> To: Strony, John
> Subject:
>
>
>
> Dear John ,
>
> is it correct that SP has decided not to present at AHA , but to await

> the two other , completely unvalidated , endpoints , which analysis is

> going to take us straight into 2008 ?!?!?
>
> If this is true , SP must have taken this decision without even the
> semblance of decency to consult me as PI of the study. I can tell
> you
> that if this is the case , our collaboration is over and I will

> take
> the appropriate steps to get in touch with the Editors of major
> Journals as well as with the FDA . This starts amelling like
> extending
> the publication for no other then political reasons and I cannot
> live
> with that .
>
> This is the second day of a long overdue holiday after a terrible
> year, thank you very much for yet another terrible chapter of this
> trial
>
> John
> *****
> This message and any attachments are solely for the
> intended recipient. If you are not the intended recipient, disclosure,
> copying, use or distribution of the information included in this
> message is prohibited -- Please immediately and permanently delete.
>
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