Unknown

From: Street, Paul R
Sent: Monday, February 07, 2005 1:13 PM
To: Meulien, Didier; Jones, Martin AM (Seroquel)
Cc: Brecher, Martin; Stening, Göran K
Subject: RE: Seroquel France Feedback from Prof Montgomery

All

I just wanted to check if Idea B is consistent with Stuart's suggestion which (as I recall) was to define psychotic relapse in terms of PANSS score. He added it would be up to us to define the relapse criteria.

My (dumb) question is:

- In Idea B, would the 'proportion of these responders who did not relapse' be derived from PANSS scores?

Regards
Paul

-----Original Message-----
From: Meulien, Didier
Sent: 07 February 2005 15:47
To: Jones, Martin AM (Seroquel)
Cc: Street, Paul R; Brecher, Martin; Stening, Göran K
Subject: RE: Seroquel France Feedback from Prof Montgomery

Dear Martin
Thank you again. The IDEA A based on the analyses performed by Emma bring a good message. Let's confirm it and Let's also see the IDEA B.
Best regards
didier

-----Original Message-----
From: Jones, Martin AM (Seroquel)
Sent: den 7 februari 2005 16:40
To: Meulien, Didier
Cc: Street, Paul R; Brecher, Martin; Stening, Göran K
Subject: RE: Seroquel France Feedback from Prof Montgomery

Hi Didier

It's not explicitly stated, but I think it's >=40% reduction from baseline in derived BPRS. As I said, the numbers will need checking.

Martin

-----Original Message-----
From: Meulien, Didier
Sent: Monday, February 07, 2005 10:26 AM
To: Jones, Martin AM (Seroquel)
Cc: Street, Paul R; Brecher, Martin; Stening, Göran K
Subject: RE: Seroquel France Feedback from Prof Montgomery

Dear martin
Thank you again

in the email from Emma attached in your email under Idea A

what was the definition of the responder she is referring to ?
Was it this one

EXHIBIT 58
WIT: Meulien
DATE: 5-13-08
LINDA ROSSI RIOS

Brecher
EXHIBIT NO. 44
MH-5/29/08

41

Outpatient status
Total BPRS <= 36
All BPRS +ve items <= 4
meeting these criteria at week 12 ?

or another one ?

Thank you again
Best regards
Didier

-----Original Message-----
From: Jones, Martin AM (Seroquel)
Sent: den 7 februari 2005 16:20
To: Meulien, Didier
Cc: Street, Paul R; Brecher, Martin; Stening, Göran K
Subject: RE: Seroquel France Feedback from Prof Montgomery

Didier

Idea A

Ok, taking the logic that you can't relapse unless you've first responded, here is a table that looks at "maintenance of response" from week 12 to 52. N.B. The numbers will have to be checked.

<< Message: final database responders.xls >>

Idea B

One last(?) shot.

Define the proportion of responders @ week 12 using a % reduction from baseline.
Calculate the proportion of these responders who did not relapse over the following 40 weeks. (sort of the reverse of the previous approach)

Multiply the 2 percentages together and you'll get the proportion of the randomised population who can expect to have a good efficacy outcome after 52 weeks treatment.

Martin

-----Original Message-----
From: Meulien, Didier
Sent: Monday, February 07, 2005 10:12 AM
To: Jones, Martin AM (Seroquel)
Cc: Street, Paul R; Brecher, Martin; Stening, Göran K
Subject: RE: Seroquel France Feedback from Prof Montgomery

Dear martin
Thank you again for your input recommending to avoid the KM approach when it comes to splitt by reasons of dc. Looking at the informal KM curves this tells us not to take this way.
Best regards
Didier

-----Original Message-----
From: Jones, Martin AM (Seroquel)
Sent: den 7 februari 2005 15:45
To: Meulien, Didier
Cc: Street, Paul R; Brecher, Martin; Stening, Göran K
Subject: RE: Seroquel France Feedback from Prof Montgomery

Didier

One further point that you may be aware of. It's a bit statistechnical, but should not be forgotten.

Of all the KM curves in the attached file the most reliable one is the all cause curve. When you breakdown into separate reasons you need to remember that they are "competing" with each other i.e. a patient can't withdraw for more than one reason. This is important in this case, as the different causes have different time patterns, i.e. AEs happen before LOEs. This means that the LOE curve may not be truly representative, especially for haldol as they have lost more patients before the LOEs really start to happen. The impact of this is that the LOE curve is biased towards haldol.

One approach that I don't think has been used yet is a competing hazards survival analysis. This is not my area of expertise, but there are some excellent survival analysis statisticians in AZ. Not sure about Södertälje, but Kevin Carroll, John Armstrong, Rick Caplan or Mike Palmer may be able to help. REDACTED
REDACT

Martin

-----Original Message-----
From: Meulien, Didier
Sent: Monday, February 07, 2005 7:52 AM
To: Jones, Martin AM (Seroquel)
Cc: Street, Paul R; Brecher, Martin; Stening, Göran K
Subject: FW: Seroquel France Feedback from Prof Montgomery

I don't think that you received this email below

Hi Martin
You are probably busy on other important tasks, but you have probably a good memory on study 0050 and what has been produced as post oc analysis.
Could you please have a look at the different emails below including what we observe on the KM splitted by dc although this is an informal analysis in all patients).
Then we could try to discuss all of us over the phone prior a TC with Stuart.
Thank you in advance
Best regards
Didier

-----Original Message-----
From: Meulien, Didier
Sent: den 7 februari 2005 09:20
To: Brecher, Martin
Cc: Stening, Göran K; Street, Paul R
Subject: RE: Seroquel France Feedback from Prof Montgomery

Dear Martin,

- **Study 50**

I forward this email to Göran as there is a need to update him since his team is planning the extranalysis on study 0050.

Martin, we should also prepare our mind in case the results could bring a negative message, ie an advantage with hal on in study 50 on "psycotic relapse" and have an argumentation to dismiss this study as if was not primarily designed for answering to such an objective :a psycotic relapse trial, but still allowing to bring some information on long term efficacy and safety.

Attached below is an informal analysis looking at the KM splitted by reasons of dc in all patients (schizophrenic + schizo-affective) and you will see that the dc due to condition deteriorated is more important than in the hal group.
and we also know that schizo-affective respond better to Seroquel

<< File: KM0050.doc >>
Of course the real analysis need to be done by Göran team on the appropriate population (schizophrenics) and with applying different definition of psychotic relapses as suggested by you and Stuart Montgomery.

I will contact Göran this morning.

- **About another point that might come again: Short-term efficacy and comparability to other atypicals**

There was a very good piece of work in Seroquel Clarification Document - MR supporting documentation doc submitted to the Danish Agency, see answer to question 2.
Martin and Paul, should we prepare ourself to take this direction as it could appear to be an appropriate answer with statistical approaches ? the pb is there is only olanzapine ? Would this be enough ?

Best regards
Didier

-----Original Message-----
From: Brecher, Martin
Sent: den 4 februari 2005 23:15
To: Street, Paul R; Meulien, Didier; Melville, Margaret G; Koomen, Oscar; Hilton, Emma; Ostinelli, Juliette; Richard, Anne-Celine; Hache, Christine
Cc: McKenna, Kevin
Subject: RE: Seroquel France Feedback from Prof Montgomery

Didier, Paul,
I think we can look at all dc for loe pts for change from baseline and from previous visit on the PANSS positive subscale. I don't have an a priori view regarding how much of an increase is required to define a relapse and I suggest that we use a range of reasonable values. We need to have the mean change in these patients and the number of pts meeting criteria. Given the overall results on the PANSS positive and the KM curve for dc-loe we be can be hopeful if not optimistic.

Regardin amending the SR relapse trial-this seems to me to be a most a post approval commitment. We can of course provide them with the study
Martin

-----Original Message-----
From: Street, Paul R
Sent: Friday, February 04, 2005 9:02 AM
To: Brecher, Martin; Meulien, Didier; Melville, Margaret G; Koomen, Oscar; Hilton, Emma; Ostinelli, Juliette; Richard, Anne-Celine; Hache, Christine
Cc: McKenna, Kevin
Subject: Seroquel France Feedback from Prof Montgomery

All

Here is a brief summary of discussions between Stuart Montgomery, Meg, Oscar, Emma and I this morning, plus some suggested next steps.

Summary

Stuart strongly encouraged reanalysis of Study 50 to attempt to formulate arguments that Seroquel was as effective as haloperidol based on the incidence of psychotic relapse. His view was that arguments based on the strong safety profile would not be sufficient to allow approval in France. If arbitration was necessary to resolve issues after Day 90, AZ are unlikely to win. Stuart kindly offered to meet with the team again next week if necessary.

Main Discussion Items

- The requirements for long-term efficacy are clear, not just for schizophrenia but for all chronic diseases.
- AZ should focus on efficacy not just risk-benefit profile, hence Stuart has strongly recommended post hoc analysis Study 50 ('data mining') to focus on psychotic relapse. One suggestion was to determine the number of psychotic relapses by reviewing PANSS scores for patients who with drew for lack of efficacy.
- The SR relapse prevention study might help reassure AFSAPPS on some points, but FDA requirements may not match those in the EU. We may want to discuss the protocol with AFSAPPS and consider adding additional endpoints as necessary to meet their requirements?
- The EU regulatory environment, particularly the UK, is very hostile and AZ would probably loose any arbitration procedure (owing to lack of concordance with the guidelines). Potentially disastrous consequences could follow - other countries could revoke their licence (the cost of atypical is perceived to be burden)
- Dr Abadie is likely to uphold the decision of the AFSAPPS clinical assessment team
- The MEB may have limited influence over the French decision - but this would increase if additional data were available from a reanalysis of Study 50

Suggested Next Steps

- Determine what additional analyses of Study 50 are possible. Stuart would be available to discuss this issue in more detail next week if necessary
- Consider what additions (if any) could be made to the SR Relapse Prevention Study to address French concerns on psychotic relapse (A copy of the protocol will be sent Stuart for his comments)
- Invite Stuart to review any further regulatory responses before these are sent to AFSAPPS

Martin - As per my voicemail, do you think that Stuart's suggestions regarding reanalysis of Study 50 are feasible?

Thanks in advance.

Regards
Paul

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