From: Lind, Tore
To: Leff, Richard L
CC: Levine, Doug; Magner, David; Sostek, Mark
Sent: 5/31/2006 8:11:39 AM
Subject: RE: Platinum (confidential)

Hi Rich,

I've seen the comments in several mails this week and find them adequate although sometimes speculative which also is adequate as long as we don't have adequate data.
I've touched base with Kerstin Röhss, our clinical pharmacology expert. I did a couple of studies in the mid 80th on omeprazole and "cytoprotection" with no such signs and we have at least three additional in-house studies of interest incl. uncoated omeprazole. We are chasing these reports.
According to timelines addressed in your previous mail, a phase 3 program with Nexium-Meloxicam (I've not seen any timelines for a Naproxen-combo except for in the US program, study start mid 20011) could start at the earliest late 2010, probably the year after. /tore

-----Original Message-----
From: Leff, Richard L
Sent: 31 maj 2006 03:01
To: Lind, Tore
Cc: Levine, Doug; Magner, David; Sostek, Mark
Subject: FW: Platinum (confidential)
Sensitivity: Confidential

Tore,

Mark Sostek and David Magner went to do some information gathering on Friday last week, and yesterday (Monday) was a holiday in the US. Their **DRAFT** notes are below.

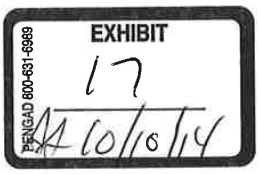
Basically, there was variable PK and PD without buffering or enteric coating the PPI for lanzoprazole 15 mg + EC-naproxen 500 mg BID given for up to 14 days to normal volunteers (I think administered fasting).

The Medical Science view coming from that visit is thus that without some protection of the PPI, a combination with Naproxen (or any NSAID) would be inferior to buffered or enteric coasted PPI. Without such formulation, the combination would probably be superior to naproxen alone, but on a background of LDA compared to celecoxib it is not as certain. Arthritis and other pain patients usually take their NSAID with food. Also, in the real world patients don't take their NSAID every day (even if told to do so by their physician, which technically is not the FDA's recommendation); thus, for those taking the combination once a day or sometimes skipping a few days, we're thinking that an optimal formulation of the PPI is best. Which, from what I understand, is consistent with the Nexium rationale and messaging.

If you have any questions, please let Mark and/or I know.

Take care.

Rich



-----Original Message-----
From: Magner, David
Sent: Saturday, May 27, 2006 1:42 PM
To: Sostek, Mark; Helm, Jim
Cc: Levine, Doug; Watson, Chris; Goode, Denise E; Anson, Lisa LM; Gibbs, Mike; Leff, Richard L; Jones, Derek
Subject: RE:
Sensitivity: Confidential

Mark,

Thanks for the summary of our meeting with Pozen. I'd just like to add a couple of other comments, specific to dose and the comparators in their studies.

Their pilot study (for each PPI) compared the PN product to naproxin and the PPI (I'll call it N+P) given separately. The PN product had the advantage, by design, of delivering the PPI twice, whereas the N+P only had the PPI given in the am. Given

Mark's comments relative to availability of the PPI from the PN product, this looks a lot like a comparison of a "half dose" of the PPI in the PN formualtion, given bid, as compared to the "full dose" of the PPI in the N+P dose. They claim that differences between PN and N+P are due to the local effect of the PPI (as Mark stated, there is no clear evidence of that currently). It may also be possible that it is due to a bid dosing regimen of the PPI, and that being unprotected is not necessary at all. If they are right, and there is a local effect, it is good for their product. If there is no local effect though, it may be possible to get a similar effect with bid dosing for naproxin and a PPI.

We spoke a little about a potential eso POC study, if we are to move forward with eso. They would propose a study similar to the ome and lanso POC studies. We should consider if using a bid eso dose in the N+P arm would be justified - it could either prove/disprove the need for the unprotected eso.

I believe that there is also a risk regarding the dose. The piolt studies were run in healthy volunteers and for 14 days. Extrapolating that to 6 months in patients is not without risk. Pozen's position is that they may not have the best dose, but they are confident of positive results since the FDA has allowed them to move forward with a single dose. If we move forward with this project, I think we should consider the risks and rewards of adding a second (higher) dose to the Phase 3 studies. It may be that a higher dose is needed either for 1)patients, as opposed to HVs, or 2) to keep patients ulcer free for 6 months, as opposed to 14 days.

Dave

-----Original Message-----
From: Sostek, Mark
Sent: Saturday, May 27, 2006 10:10 AM
To: Helm, Jim
Cc: Magner, David; Levine, Doug; Watson, Chris; Goode, Denise E; Anson, Lisa LM; Gibbs, Mike; Leff, Richard L; Jones, Derek
Subject:
Importance: High
Sensitivity: Confidential

Dear Jim:

Dave and I spent a very interesting day at Pozen yesterday. We look forward to discussing further with you on Tuesday. I thought that I would send you a few "top line" bullets that we came away with regarding the Pozen formulation and planned development program.

The CEO, Marty Reese and some of their other top executives were gracious enough to answer all of our questions and allowed us to look at anything we requested.

Here are some points we learned.

- The "unprotected" immediate PPI release formulation results in approximately 50-60% of the PPI being degraded in the stomach on DAY 1, before it is absorbed. With each successive day as the gastric pH is increased somewhat less gets degraded on each successive day. By steady state approximately 30% is being degraded. So the pharmacodynamic efficacy gradually increases on each successive day until steady state is reached

- The steady state pharmacodynamics of the PPI in the Pozen formulation is therefore equivalent to less than the initial dose (e.g. lansoprazole 15 mg gets degraded to the point where its acid control is perhaps equivalent to only 10 mg). The bid dosing overcomes this somewhat...but omeprazole 20 mg bid in this formulation is probably more consistent with omeprazole 10 or 15 bid.

- The current Pozen formulation with omeprazole will be unproven for treating GERD symptoms (due to degradation of parent compound), therefore this formulation may be suboptimal for patients who need to be treated for GERD

- POZEN is postulating that a "local" non acid inhibitory effect is partially responsible for the ulcer protection that they have seen. Specifically they cite the possibility that the PPI could act as a local free radical scavenger on the gastric mucosa. However there is no good, recent or solid data to support this and therefore at this point this can only be categorized as pure speculation.

- The postulated "beneficial impact" of the PPI being released first before the naprosyn will only matter if there is a "local PPI effect". Since this is unproven, I doubt this could be promoted. Although data displays of the

pharmacokinetics without attached claims could be possible.

- They have not done any studies in actual patients, reflecting the true target population and have not done any pilot studies longer than 14 days duration. Therefore the results of the pivotal studies of 6 months duration and in a different population are not necessarily a slam dunk...although I believe it is better than 50:50 that they would be successful.

- I think that it is clear, that the current formulation is NOT optimal from an acid suppression standpoint (because of PPI is degradation in the stomach), but they characterize it as a good first attempt, with further refinements and modifications possible later

- The GI black box will still be present for this product, as well as the CV black box.

- It could be difficult to explain to physicians why PPI "protection" is not necessary for this product unlike all other PPIs.

Kind Regards,

Mark