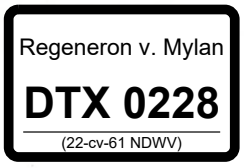
Date: Wednesday, April 4 2007 06:05 PM
Subject: Summary of issues for call: AMD P3 Planning
From: George Yancopoulos
To: Darlene Jody <Darlene_Jody@berlex.com>;
Attachments: Jody Call_040407.doc

please see enclosed outline for our discussions....



Darlene Jody Call / April 4, 2007

Dear Darlene:

Just a quick (albeit belated) pre-summary for our call – it has to do with planning for our AMD Phase 3 program.

Here at REGN, we like a top-down approach, in which major decisions are made by our Senior Management Team (following intense data review), and then "sold" down. We find this avoids a lot of unnecessary busy work and discord at the team level, which ultimately has a high chance of being obviated by the Senior Mgmt perspective anyway.

In this regard, after carefully reviewing the P2 data (as well as all prior P1 data, which is also quite relevant), our entire Senior Management Team is strongly united on the following AMD P3 program:

Two identical 1200 patient studies (the first led by REGN, the second by BHS), each with the same 4 arms, powered for NI to Lucentis control:

Lucentis Control (0.5q4w)
VT 0.5q4w
VT 2.0q4w
VT 2.0q8w (dose somewhat still undecided)

The rationale for this is that the data suggests that:

1. The higher dose (4.0) does not clearly provide further benefit at this time, so we would not use it unless something strongly changes with the maturing P2 data; we are a bit still struggling with the high dose to be used for the q8w interval
2. The quarterly dose groups slip more at 12w than at 8w, making NI a significant risk at 12w
3. Our commercial group assures us that the community would view a fixed dose regimen at 8w as a real big win in the marketplace, and that you are much better off having a strong 8w number than a weaker 12w number. In fact, any fixed dose regimen greater than every 4 weeks that doesn't require interim monitoring for visual acuity is seen as desirable among physicians.
4. The 0.5 and 2.0 monthly regimens provide best opportunity for best absolute efficacy, and also provide real opportunity for improved absolute efficacy compared to Lucentis (numerically if not statistically) which could convince physicians that our drug is the definitive better agent to be used regardless of dosing regimen and interval

(there is minor concern about tox coverage for the 2q4 group – while 10-fold tox coverage is standard, for 2q4w we have 6-fold coverage but have already given this to 30 humans in the P2, and can provide the additional tox during the P3 study, which we think is little risk since nothing has been seen tox-wise at the 4q4w in monkeys, and new study would be at 4q2w – we have previously negotiated similar solutions with the regulatory agencies)

I know there has been extensive discussion at the team level about the second study being a NI study using doses of VT q12w versus the Lucentis PIER regimen, which might suffice for EMEA and also simultaneously serve as a second study for the FDA based on using a separate Superiority analysis. Our view on this is that while such a second study is indeed likely to be NI to Lucentis PIER regimen, it is at high risk for not achieving Superiority and thus not being useful for the US approval in any way, and thus at high risk of seriously harming the global brand perception. Wiley has also told us in writing that he wants the labeled "optimal dose and regimen" reproduced, so even achieving Superiority in such a second study would probably not suffice for US approval. Finally, such a dosing regimen is unlikely to produce a benefit that favorably compares with monthly Lucentis dosing or unlabelled but published PRN approaches (which are being widely adopted as current standard of care), to which we are likely to be compared by physicians.

To summarize, 2 identical studies as suggested above provide full support for the TPP and global registration, as well as best chance of producing optimal data for VT, whereas a 4 arm + PIER design may provide an inferior label (and hence a weaker version of the TPP) AND unlikely to allow registration in the US.

There is also an issue of which formulation to use in the first study, which we can discuss as well.

Best,
George