Industry Note

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AMD Physician Conference Call: Lucentis is Promising But Bar is High

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SUMMARY

- On Friday, we held a conference call with three retinal experts to discuss their thoughts on Eyetech's Macugen, QLT's Visudyne, and Genentech's Lucentis. All physicians had substantial experience with these agents.
- Interest in Visudyne with triamcinolone remains strong and could entrench Visudyne against new anti-VEGF therapies when data from randomized studies is released in 2006. But physicians see little new growth prospects even if these trials are positive since this is already the standard of care.
- Macugen is expected to capture the occult and large lesions market where data has been superior to Visudyne, but dosing will be less frequent than per label.
- Lucentis could be more potent than Macugen but bar is high to bridge Macugen's first mover advantage. New liquid formulation of Lucentis causes less inflammation than the previous lyophilized one. While consequence of chronic pan-VEGF inhibition is unknown, Lucentis appears safe thus far.

OPINION

We hosted a conference call on Friday, April 29, with three retinal physicians to discuss market and scientific developments in age-related macular degeneration (AMD) ahead of the Association for Research in Vision and Ophthalmology (ARVO) meeting that will be held on May 1-5. These physicians had all participated in both Macugen's and Lucentis' clinical trials. All had clinical practices with significant volume and had access to numerous experimental therapies as part of ongoing clinical trials.

The call largely reaffirmed our ongoing thesis that Macugen will largely expand the wet AMD market by treating minimally classic and occult patients (approximately 75% of patients) were Visudyne has shown only equivocal results in the past. More so, the panelists echoed the opinion that Visudyne with intravitreal triamcinolone injection will remain the standard of care for predominantly classic lesions driven by strong efficacy and infrequent dosing (approximately 2 procedures per year).

While the panel have been concerned about the increased rate of intraocular pressure (that can cause glaucoma) and cataract formation when triamcinolone is used, they believe that the perceived benefits of vision stabilization and perhaps improvement with less frequent dosing (every 6 months vs. 3 months) justifies the higher toxicity. They cautioned, however, that data from large clinical studies evaluating the merits of this approach has not yet been released. But the physicians expect that these trials will likely substantiate the above-mentioned benefits seen in small clinical studies. Importantly, this data will be important to counteracting the emergence of competition from new anti-VEGF therapies, but is unlikely to result in higher utilization of Visudyne since it is already the standard of care.

Finally, the physicians also noted that based on their experience with Lucentis in both randomized and open-label clinical studies, they expect that Lucentis will prove to be a more potent agent than Macugen. In their view, Lucentis could result in better vision stabilization and even improvement over Macugen when data from the ongoing MARINA and ANCHOR

studies are released in the second and fourth quarter of the year, respectively. However, the bar for Lucentis is high given that it will come to market two years after Macugen.

Our conclusion from the call is that Macugen will continue to post a strong launch and expand the wet AMD market. Based on this call, we have increased our confidence that Macugen will be able to meet our $178 million estimate for 2005 sales (above management's guidance of $135-$150 million). We also expect that the drug will have only a modest impact on Visudyne sales and expect that Visudyne will meet our $507 million estimate, in-line with the $500-$530 million guidance. Finally, we note that Lucentis could prove to be superior to Macugen once clinical data from the Phase III MARINA study is released at a press release during the second quarter and full data is disclosed at the American Society of Retinal Surgeons (ASRS) meeting in July 16-20. However, given the ongoing weakness in Eyetech shares, we believe much of this competitive risk to Macugen is already priced into the stock.

VISUDYNE PLUS TRIAMCINOLONE DATA MAY ENTRENCH VISUDYNE BUT WON'T BOOST SHARE

In our view, one of the key takeaways from our conference call was that physicians continue to have enthusiasm for Visudyne with triamcinolone. As a case in point, 12% of all abstracts that will be presented at the ARVO meeting this week (159 of the 1,338 abstracts) will discuss the merits of the combination of Visudyne plus triamcinolone. On the call, two of the three physicians noted using these two drugs in all AMD subtypes, but especially in predominantly classic lesions.

While many of these abstracts show that this approach results in superior results over Visudyne alone, these studies are small and will not offer definitive prove. Our panelists noted that several trials are ongoing to answer this question and expect preliminary data from the VISTA and RETINA studies (see Figure 1) by the end of the year. However, since Visudyne with triamcinolone has become the standard of care, enrollment in these studies is slow and final data might not be available until 2006. The prevailing consensus view on the call was that these studies should demonstrate significantly better efficacy for this approach and entrench Visudyne's role in this disease against the new anti-VEGF therapies. However, the panelists also agreed that this data, even if positive, is unlikely to drive increased use of Visudyne, but will merely convert the minority of physicians who are still using Visudyne alone.

FIGURE 1: VISUDYNE COMBINATION TRIALS

Name	Sponsor	Size	Subtypes	Analyses	Status/Data Timing
VISTA	Manhattan Eye and Ear Infirmary (Spaide)	120	All	12 months	60/120 patients enrolled Preliminary data end 2005
RETINA	Independent Canadian investigators	60	Predominantly classic	12 months	H2 2005
National Eye Institute	QLT/ NVS	300	All	12 and 24 months	Interim data H2 2006
VISIT	Novartis	300	All	6, 12 and 24 months	H2 2006
Johns Hopkins Trial	Johns Hopkins investigators	60	All	12 months	Subtenon administration H2 2006
VERITAS	QLT Inc	300	Predominantly classic	12 and 24 months	Start H2 2005, enrollment complete H2 06, first data H2 2007

Source: Company presentations

OCCULT LESIONS GIVE MACUGEN PLENTY OF ROOM TO GROW

On the call, the physicians noted that Macugen will be used across all lesions types due to its broad label and reimbursement. However, Macugen is expected to dominate the occult lesion market segment (most prevalent form) specifically due to its favorable activity. In their view, there is also plenty of room for Macugen to be used also in minimally classic lesions albeit there is slightly more competition from Visudyne in that segment. The low penetration of Visudyne in minimally classic and occult lesions is due to lack of Medicare reimbursement until April 2004 and equivocal clinical results.

As Macugen has only been on the market for 14 weeks, it is still too soon to see what the real world results will be as compared with the pivotal trials. The physicians expect to treat patients in line with the label (every 6 weeks) during the first several cycles and then re-evaluate patients for response. In their view, compliance will be high in patients who respond to the therapy, but expect that patients will not opt to remain on this inconvenient regimen if their disease continues to progress despite treatment.

RETINAL PHYSICIANS ARE LIKELY TO DOSE MACUGEN AND LUCENTIS ON AN AS-NEEDED BASIS

Retinal physicians have gotten used to using Visudyne on an as needed basis and only treat patients when there is evidence of neovascular leakage from optical coherence tomography (OCT) or fluorescein angiogram imaging. Our consultants plan to do the same with Macugen and Lucentis, despite data presented by Eyetech suggesting that efficacy decreases if the every-6-weeks dosing schedule is not followed. We are concerned that this may actually blunt Macugen's efficacy and consequently lead to even lower compliance.

Interestingly, data that will presented at ARVO by Heier from long-term follow-up from Genentech's Lucentis Phase I/II study suggests that Lucentis' efficacy is maintained with less frequent doses (0.20 doses every 4 weeks vs. current schedule of 1 dose). If this is borne out by the ongoing PIER (every 3 months dosing) and PRONTO (dosing as needed) trials, than Lucentis will have the inside edge over both Macugen and Visudyne in the marketplace.

LUCENTIS' EFFICACY IS EXPECTED TO BE SUPERIOR TO MACUGEN

The call also focused on Genentech's Lucentis, a promising new anti-VEGF therapy in pivotal studies. The physicians concurred that present therapies were an advance but left plenty of room for improvement since Visudyne and Macugen's predominant result is vision stabilization as opposed to improvement. Based on early experience with Lucentis, there is widespread optimism that this agent will deliver superior results to the 6% rate of >3 lines vision improvement offer by the currently available agents.

Despite being blinded in several Lucentis trials, our consultants have seen rapid but significant vision improvements that are unlikely caused by the sham injections. This suggests that Lucentis has a powerful effect on retinal swelling, as visual improvements of that magnitude do not occur in untreated patients. Additionally, since Lucentis has also posted encouraging activity in several open-label studies, our consultants believe that it will results in encouraging results.

However, questions remain as to whether this anecdotal experience will be confirmed when results from the large, randomized studies are published. On the call, there was general agreement that Phase III data almost always falls short of earlier clinical results. Given that Lucentis will be not be approved until early 2007, two years behind Macugen, the panel noted that the bar for Lucentis is high.

Also on the call, two physicians cautioned that while Lucentis' head-to-head trial versus Visudyne (ANCHOR) is widely expected to favor Lucentis, this would not necessarily

change practice patterns since the trial is not using Visudyne in combination with triamcinolone, the current standard of care. Therefore, we conclude that the Street may be overestimating the vulnerability of Visudyne to the new anti-VEGF therapies, and not appreciating the significance of these combination trials in shaping the market.

WHILE SAFETY ISSUES ARE HARD TO PREDICT, LUCENTIS APPEARS CLEAN

The panel noted that inflammation has not been an overarching concern in the ongoing Phase III Lucentis trials since the new liquid formulation is used. Previously, inflammation was commonly reported when the old lyophilized formulation was employed. More so, whereas in the early clinical studies patients were seen in the first week after dosing, physicians do not see participants in the current studies until the next dose is given one month later. As a result, the reported rate of inflammation is likely to decrease dramatically since these occurrences were transient in earlier studies.

The issue of the safety of pan-VEGF inhibition has also been hotly debated, as Macugen favors specific VEGF165 inhibition whereas Lucentis offers pan-VEGF blockade. On the call, one of the physicians raised the theoretical concern that chronic pan-VEGF inhibition may be harmful to the optic nerve over the long run. Thus far this evidence is restricted to animal studies, and there is no human evidence to support this theory in clinical studies. At ARVO several abstracts will be presented which describe the treatment of AMD with systemic Avastin. Besides hypertension, the therapy was surprisingly well tolerated, and there were no episodes of thrombosis or hint of toxicity to the retina.

In conclusion, the panelists noted that while the safety of Lucentis is hard to predict from anecdotal experience in ongoing studies, no obvious concerns have been raised thus far.

Companies mentioned in this note:

Eyetech (EYET–$22.99; 2S)

Genentech (DNA–$70.84; 1H)

QLT Inc. (QLTI–$10.72; 3H)

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