Closer Look

MEMORANDUM

Ampio Pharmaceuticals releases positive phase 2 results for Optina (danazol), a twice-daily oral treatment of diabetic macular edema - August 19, 2012

Executive Highlights

- Ampio's oral treatment for diabetic macular edema, Optina (low-dose danazol), reduced retinal thickness and improved visual acuity in a 12-week phase 2 study (n=32).
- Ampio had a pre-IND meeting with the FDA in late July to seek approval for a phase 2/3 trial of Optina under the 505(b)(2) registration pathway.

Colorado-based Ampio Pharmaceuticals released select data last month from a phase 2 study of its oral treatment for diabetic macular edema (DME), Optina (twice-daily low-dose danazol). As a reminder, this study was ended early once the low-dose results were found to be similar to those of in vitro studies and consistent at four and 12 weeks - for more background on the early termination and Optina generally, see the May 17, 2012 Closer Look at http://www.closeconcerns.com/knowledgebase/r/e03dd6ed. The 12-week study enrolled adults with diabetic macular edema (n=32) who were randomized to receive one of three Optina dosages (10 mg, 30 mg, and 90 mg) or placebo. Interestingly, the effectiveness of the doses was strongly associated with BMI - 10 mg was most effective in people with lower BMI, and 30 mg was most effective in people with higher BMI (cutoffs unspecified). As only limited baseline data were provided, it was not clear from company materials which subgroup analyses were based on pre-assigned dosage groups and which were based on optimal-for-BMI dosage groups. The company did not respond to requests for further information, so we are unable to fully interpret the reported positive results on reduced retinal thickness (the study's primary endpoint), reduced retinal volume, and improved visual acuity. We hope to get a clearer sense of the trial's efficacy takeaways in subsequent Ampio presentations or other communications. In the safety analysis (n=34), three treatment-related adverse events (8.8%) were reported - one case each of peripheral edema, psoriasis, and worsening depression - all of which were deemed possibly (as opposed to probably or definitely) related to the investigational medical product. The study's two serious adverse events (5.8%) were a transient ischemic attack in the placebo group and a foot ulcer that was found unrelated to danazol dosage.

Ampio's next steps on the regulatory front were for a pre-IND meeting with the FDA in late July to discuss the company's combined phase 2/phase 3 trial, which is currently being designed. We have not learned any outcomes from this meeting as yet; as a reminder, Optina's development will potentially be streamlined by Ampio's use of the 505(b)(2) registration pathway. (The 505(b)(2) route allows companies to present previously conducted studies - in this case, of higher-dose danazol in non-DME indications.) We continue to think that an effective oral therapy for DME could be an excellent alternative (or adjunct) to today's more invasive therapies (laser eye surgery, intravitreal steroids, intravitreal anti-VEGF antibodies). We hope that the company's discussions with the agency were positive and look forward to details on study protocol as they become available.

- **Ampio has found that Optina's very low dose of danazol reverses the permeability of blood vessels around the retina.** The 12-week phase 2 study involved doses of 10 mg, 30 mg, and 90 mg, in contrast to the 200-800 mg doses of danazol currently used to treat endometriosis, fibrocystic breast disease, and hereditary angioedema. Ampio research suggests that small doses of danazol remodel the actin cytoskeleton (F-actin) of the endothelial cells that line retinal blood vessels. This change causes the adhesion molecules between these cells to be tightly bound to the peripheral actin thereby closing the gaps between the cells and reducing overall vascular leakage.

- **Ampio had a pre-IND meeting with the FDA in late July to plan out the next trial of Optina under the 505(b)(2) registration pathway**. This registration designation will allow Ampio to include previously collected data in its submission to the FDA. Notably, danazol has been a generic drug for several decades, but the ultra-low doses that Ampio has proposed to treat DME are protected in the United States, Canada and Hong Kong with allowed patents that will not expire until 2030. Ampio has also indicated interest in studying danazol as a treatment for diabetic kidney disease (proposed trade name Vasaloc) and wet AMD. For more information on Ampio and Optina, please see our May 17, 2012 Closer Look at http://www.closeconcerns.com/knowledgebase/r/e03dd6ed.
- **Close Concerns was not successful in reaching the company to discuss the questions below but we hope that we will be able to glean more on these questions moving forward**.

Close Concerns Questions

- **What were the baseline visual acuity and baseline A1cs?**
- **How long had participants had diabetes on average, and what was the range? How long had they had diabetic macular edema?**
- **We assume that the reason for using an alpha of 0.20 was small study size - is this correct?**
- **How strongly correlated were subfield central retinal thickness and visual acuity?**
- **How many patients were included in each dosage group?**
- **How many patients were included in the optimal dosage group as defined by BMI?**
- **What thresholds were used when defining BMI as high or low?**
- **What thresholds were used when defining A1c as high or low?**
- **In the A1c subgroup analysis referenced in the company's release, how was optimal dose defined?**
- **In the retinal-volume analysis referenced in the company's release, how was optimal dose defined?**
- **How many patients were included in the overall efficacy analysis?**
- **Which patients were included in the ICD-9-CM subgroup analysis? What were the treatment assignments of the other 10 patients?**
- **What is the status of Ampio's patents protecting ultra-low doses of danazol? Have they been officially issued? If not, what if any uncertainty remains as to whether they would be issued?**

-- by Hannah Deming, Joseph Shivers, and Kelly Close