Closer Look

MEMORANDUM

JDRF and iCo Therapeutics team with Johns Hopkins University to launch phase 2 iDEAL trial investigating iCo-007 in diabetic macular edema - April 6, 2012

Executive Highlights

- JDRF and iCo Therapeutics are recruiting patients for iDEAL, their phase 2 trial testing the diabetic macular edema (DME) compound iCo-007, to be conducted at Johns Hopkins University School of Medicine.

Global diabetes organization JDRF and Vancouver-based iCo Therapeutics have announced the preliminary study design for iDEAL, a yearlong phase 2 trial of iCo-007 (an antisense inhibitor of c-Raf kinase mRNA) for diabetic macular edema (see our October 26, 2011 report on the announcement of the JDRF and iCo Therapeutics partnership at bit.ly/seDOV5). The JDRF-supported study will be led by clinical scientists at Johns Hopkins' renowned Wilmer Eye Institute and will include 30 clinical sites across in the U.S. (clinicaltrials.gov identifier: NCT01565148).

The iDEAL trial will enroll up to 208 patients with diabetes (type 1 or type 2), DME with central subfoveal thickness greater than 250 microns (as measured by optical coherence tomography), and baseline visual acuity between 20/32 and 20/320 on the Early Treatment Diabetic Retinopathy Study (ETDRS) Chart. Patients will be randomized into one of two monotherapy arms (intravitreal dosing of iCo-007 at 350 or 700 micrograms [ug] at study start and month four) or into one of two combination arms (iCo-007 350 ug [months zero and four] plus laser photocoagulation [month zero, optional in month four] or iCo-007 350 ug [months zero and four] plus ranibizumab [months zero and four, each two weeks before the corresponding iCo-007 injection]).

The primary endpoint for iDEAL is change in visual acuity (mean change in number of letters) from baseline to month 8. Secondary endpoints include visual acuity at month 12, retinal thickness, durability of iCo-007 treatment throughout the year, and safety. Given C-raf kinase's important role in VEGF- mediated pathways, we especially look forward to hearing more about the efficacy of the iCo- 007/ranibizumab combination therapy and comparing it to that of iCo-007 monotherapy, Lucentis, and Roche's Avastin (bevacizumab, a Lucentis-like anti-VEGF therapy widely used off label to treat DME). An interesting wrinkle is that Lucentis' pivotal studies in DME used once-monthly dosing. If iCo-007 is found to enable less-frequent Lucentis dosing with similar efficacy, perhaps benefits could be seen in terms of cost and tolerability. Also, though it is far too soon to tell, we would be interested in knowing whether other potential adjuncts to anti-VEGF therapy, such as Lilly's Arxxant (ruboxistaurin), could add efficacy beyond iCo-007/ ranibizumab dual therapy.

iCo-007 will not be filed with the FDA for several years in the best-case scenario, given that phase 3 trials for DME therapies must have their primary efficacy assessment at two years or later. Thus the drug is well behind several other DME therapies, including Lucentis (under FDA review, decision slated for 1H12) and Regeneron/Bayer's Eylea (phase 3). JDRF's work in DME also includes a recently announced collaboration with KalVista to conduct late-stage preclinical research on KalVista's plasma kallikrein inhibitors (see the January 18, 2012 Closer Look at bit.ly/I0L5sQ).

- **As a reminder, iCo-007 was developed and designed by Isis Pharmaceuticals, which licensed worldwide exclusive rights of the drug to iCo Therapeutics in 2005.** iCo-007 is a second-generation antisense inhibitor that decreases intracellular concentrations of C-raf kinase

mMRNA. The C-raf kinase acts as an intermediate signaling molecule within pathways that regulate new blood vessel growth and vascular permeability, key factors of DME. Several key drivers of DME (e.g., VEGF) signal through C-raf kinase to promote abnormal blood vessel growth, fluid leakage from vessels, and the resulting retinal swelling. Thus, a drug that decreases C-raf kinase signaling can dampen the effects of VEGF and may enhance the efficacy of anti- VEGF antibodies such as ranibizumab (Roche's Lucentis).

- **The phase 1 trial for iCo-007 followed 15 patients with DME for 24 weeks across four clinical sites.** Data regarding safety were favorable: researchers reported no serious adverse events, no issues with ocular inflammation or intraocular pressure, and no systemic exposure issues. The trial showed some efficacy, with 69% of patients that completed the study's follow-up reporting stable or improved visual acuity. Notably, while a dose-dependent biologic effect was seen for the 110, 350, and 700 ug doses, the 1000-ug dose was less effective than the others. This most likely explains why iCo Therapeutics chose to include only the 350 and 700 ug doses in the iDEAL study.
- **One group of patients in the phase 2 iDEAL study will receive combination therapy of iCo-007 and Lucentis, which has already been well studied in DME.** As a reminder, in both of its pivotal US trials, RIDE and RISE (n=383; 377), Lucentis (intravitreal injections of0.3 mg or 0.5 mg) showed a very favorable benefit/risk profile. Roche filed a supplemental Biologics License Application (sBLA) for Lucentis in 2H11 with a decision anticipated by the end of 1H12. Pending approval, Lucentis would compete in the DME arena against Roche's Avastin, which is already widely prescribed off label for DME and has a much lower cost (roughly$50/injection for Avastin vs. roughly $2,000/injection for Lucentis). Lucentis' ability to gain traction in DME will depend on favorable reimbursement (which was not provided by the UK's NHS) as well as its relative safety and efficacy (which we think are generally viewed favorably by clinicians, though no prospective head-to-head data in DME will be available until a large trial that is expected to be run by the Diabetic Retinopathy Clinical Research Network [DRCR.net]). Another potential differentiator for Lucentis could be indications for use with adjunctive therapies like iCo-007, pending favorable results of combination therapy in iDEAL and subsequent studies. (Although iCo-007 would presumably act similarly in conjunction with either Lucentis or Avastin, we think iCo-007-plus-Avastin studies are unlikely in the near term.) Please see the October 13, 2011 Closer Look at bit.ly/sTclf3 for more thoughts on Lucentis-Avastin dynamics.

--by Nina Ran, Joseph Shivers, and Kelly Close