Closer Look

MEMORANDUM

Phase 3 BEACON Trial for Reata/Abbott's bardoxolone methyl Terminated - October 18, 2012

Executive Highlights

- The phase 3 BEACON trial for bardoxolone methyl has been terminated due to an excess of mortality and serious adverse events.

In a profoundly disappointing turn of events, the phase 3 BEACON trial for Reata/Abbott's chronic kidney disease (CKD) candidate, bardoxolone methyl, has been terminated due to an excess of serious adverse events (SAEs) and deaths in the bardoxolone arm. Discouragingly, Reata's statement indicates that all other ongoing trials with bardoxolone methyl in CKD will also be terminated. There had been tremendous enthusiasm for this candidate because of the current lack of effective treatment options for CKD and because of bardoxolone's potential disease-modifying anti-inflammatory mechanism, so this news comes as a major setback for CKD patients as well as payors hoping that the compound would ben the cost curve. It has been widely viewed that bardoxolone could hit blockbuster status and Abbott had partnered with the company last year, investing $450 million for rights in most international markets (followed by a later investment of $400 million for a follow-up portfolio).

Results from the phase 2 BEAM trial seemed especially promising because gains in eGFR for the mid- and high-level doses tested persisted for the entire 52 weeks of treatment and even after treatment discontinuation, suggesting that the drug was disease-modifying and could reverse CKD (see details in bullets below). Abbot had just announced yesterday during its 3Q12 earnings call that the BEACON trial had recently completed the expanded enrollment of 2,000 patients with stage 4 CKD and type 2 diabetes. We don't yet know what the excess deaths and SAEs in BEACON were attributed to, but we speculate below about some differences between the BEAM and BEACON studies. It appears that bardoxolone did cause an increase in albumin excretion in phase 2b, which is associated with adverse outcomes. As we understand it, the largest risk was this increase in urinary albumin-to-creatinine ratio (UACR); we are looking to understand this element of the side effect profile better.

Broadly, we wonder to what extent the patients selected were the best patients to show benefit with little chance of risk. We are unsure if the generally high mortality rate for patients with stage 4 CKD resulted in an imbalance of events or if patients with stage 4 CKD were perhaps too ill to handle the treatment. Given that no glaring safety signals were apparent in the phase 2 BEAM study with stage 3 and 4 CKD patients (though we note this was a much smaller study of 227 patients), we wonder if Reata/Abbott will still attempt to develop the drug for less severe CKD.

The result by the data safety monitoring board raises a variety of questions. To start, is enough known to assess whether enrolling a differently designed follow-on trial possible, given the unmet need? While we assume the safety signal must have been quite robust to stop BEACON, we wonder if a decision to enroll patients that were less sick to start (and less at risk of other co-morbidities including death) would have yielded a different result. Such a result could have taken longer to reach but could possibly have provided an indication for a broader group of patents. Reata chose the riskiest and highest-need population to treat - this is logical as these are the patients at highest need. In hindsight, we wonder if trying the compound in healthier (relatively) patients could have made a difference.

Next, we wonder about the chances that unlucky statistical variance could have played a role, especially in very sick stage 4 CKD patients who could (by luck) have been more susceptible to death from other causes. While it is a foregone conclusion from our view that the imbalance in the trial could not be ignored, we

wonder what role chance could have played in creating those statistics and if that would have been different in other groups of less risky patients. (Other large trials like PROTÉGÉ and ACCORD also "failed" though possibly different clinical trial design could have changed the outcome.) We also are curious simply what the statistics show (hazard ratios, p values etc.) Given the massive unmet need associated with CKD and huge potential shown for bardoxolone in phase 2, we hope that such questions are thoroughly addressed by the company and advisors and independent experts in CKD. We acknowledge, of course, that a risk that could not be foreseen simply arose in this trial that makes future development untenable.

We will await word on what Reata's plans are and what the fate is of Abbott's $450 million investment and its follow on investment in Reata's pipeline. We assume there are resources to re-assess bardoxolone and other candidates, and will look forward to learning more about this, especially given Dr. Janet Woodcock's (FDA) strong stated interest in serving the highest risk patients.

Historically, bardoxolone carried so much optimism on its shoulders, and ultimately, we sincerely hope that it could possibly still find a place in the treatment of CKD. The stakes were very high for bardoxolone since nothing of its kind is currently available and it would have offered a sorely needed treatment for a very ill population. Abbott continues to develop atrasentan (ABT-627; phase 2) and ABT-614 (phase 1b) for CKD. We discuss details on these two candidates and other CKD candidates in development later in this report. More discussion is also available in our Abbott 3Q12 report at http://www.closeconcerns.com/knowledgebase/r/54fc41b3.

As context for how grave a condition stage 4 CKD is, a 2004 longitudinal study on CKD outcomes in the Kaiser Permanente network found that the five-year mortality rate of patients with stage 4 CKD was 46%-worse than many cancers. Furthermore, patients with stage 4 CKD were twice as likely to die during stage 4 as they were to progress to ESRD and dialysis (Keith et al., Arch Intern Med 2004). We hope that some further development in this sphere will emerge.

- **Results of Reata's phase 2 BEAM trial had been very promising. In the 52 week trial, bardoxolone produced significant gains in estimated glomerular filtration rate (eGFR), with sustained improvements after the treatment stopped** - this suggested that the drug was actually disease modifying and could, unprecedentedly, reverse the course of chronic kidney disease (CKD). The study randomized 227 adults with chronic kidney disease (mean eGFR ~32 ml/min/1.73 m2) to receive placebo or bardoxolone methyl 25, 75, or 150 mg once daily. At the end of the 52-week study, patients who received placebo experienced an average decline in eGFR of -1.1 ml/min/1.73 m2, whereas patients receiving bardoxolone sustained improvements in eGFR of +4.7, +9.4, and +8.1 ml/min/1.73 m2 for the 25, 75, and 150 mg bardoxolone groups, respectively. eGFR in patients on the 75 and 150 mg doses maintained improvement throughout the 52-week study, whereas at the lower 25 mg dose there was some loss of eGFR from week 24 to week 52.
- **In the phase 2 BEAM trial, the biggest adverse event imbalances seen between the placebo and 75 mg bardoxolone arms (75 mg is closest to the dose utilized in the phase 3 trial) were in muscle spasms (18% vs. 61%), arthralgia (12% vs. 21%),hypertension (11% vs. 21%), nausea (9% vs. 26%), hypomagnesemia (5% vs. 25%), and decreased appetite (4% vs. 23%).** No imbalances of greater than 4% were observed for any serious adverse event (SAE), but the trial was likely too small to detect statistical significance.
- **The phase 3 BEACON study quickly over-enrolled, prompting Reata to expand the trial from 1,600 to 2,000 participants.** BEACON was an event-driven outcomes study that sought to examine bardoxolone methyl's ability to delay end stage renal disease (ESRD) or cardiovascular death for patients with stage 4 CKD. The main differences we could glean from the BEAM and BEACON trials were the patient population and change in drug formulation - we wonder if either of these had an effect on drug safety:
    - **The drug used in the BEACON trial was a different formulation of the drug used in the BEAM trial.** Reata changed the formulation of the drug to improve its bioavailability after studying the comparative activity of both formulations. The phase 2 BEAM trial utilized a crystalline formulation whereas the phase 3 BEACON trial utilized an

amorphous formulation that improved bioavailability. The doses used in the BEAM trial were 25, 75, and 150 mg of the crystalline form, whereas the dose used in the BEACON study was 20 mg of the amorphous form. Reata management stated that this was equivalent to about 80-85 mg of the crystalline form used in the BEAM study.

    - **Another difference between the BEAM and BEACON studies was the CKD status of participants.** The patients in the BEAM study had an average eGFR of ~32 ml/min/1.73 m2 + ~7 ml/min/1.73 m2 (indicating they were likely a fairly even mix of stage 3 and stage 4 CKD patients) whereas the BEACON study enrolled only patients with stage 4 CKD and type 2 diabetes. We wonder if patients with more advanced disease were more susceptible to adverse effects.

- **CKD is categorized into five stages of severity, sorted by estimated glomerular filtration rate (eGFR),** with stage 5 being end stage renal disease (ESRD). To our knowledge, no other study has specifically targeted the fragile stage 4 CKD population. As context for how grave of a condition stage 4 CKD is, a 2004 longitudinal study on CKD outcomes in the Kaiser Permanente network found that the five-year mortality rate of patients with stage 4 CKD was 46%- worse than many cancers. Furthermore, patients with stage 4 CKD were twice as likely to dieduring stage 4 as they were to progress to ESRD and dialysis (Keith et al., *Arch Intern Med* 2004).
- **As we understand it, the formulation of bardoxolone was changed for the phase 3** BEACON trial in order to increase bioavailability. An amorphous drug formulation was used rather than the crystalline formulation used in phase 2; we assume this made no difference but are not certain of this fact.
- **Before today's news, Reata and Abbott had the most advanced diabetic nephropathy pipeline of any company. In addition to their agreement, AbbVie has a license with Zealand for ZP 1480, an MSH receptor agonist for the treatment of renal failure, about to begin further Phase 2b studies. Other companies investigating therapies for diabetic nephropathy include Concert Pharmaceuticals and Vascular Pharma.** Concert Pharmaceuticals' candidate (CTP-499) is in phase 2; results are expected in mid-2013. Notably, the target patient population is somewhat different - Concert's study includes mild/moderate (stage 2/3) CKD patients whereas BEACON enrolled significantly more advanced CKD patients. Vascular Pharma is advancing its preclinical diabetic nephropathy candidate, VPI- 2690B, into phase 2 testing with funds secured through the company's Series A round of financing; the company expects to file for investigational new drug (IND) approval in 2H13. Vascular Pharma is developing this candidate in partnership with Janssen Biotech, a subsidiary of J&J; Janssen has exclusive rights to acquire the company pending trial results. For more detail on Concert's CKD programs, please see our April 13 *Closer Look* at http://www.closeconcerns.com/knowledgebase/r/cfbe27f2. Additional discussion on VascularPharma is available in our September 27 *Closer Look* at http://www.closeconcerns.com/knowledgebase/r/e3c2a11e.

Close Concerns Questions:

What were the overall rates of mortality and SAEs in the bardoxolone and placebo arms? What were the hazard ratios for mortality and SAEs?

What were the p values associated with the results? What SAEs were most common?

Could this have been attributed to the switch to the amorphous drug formulation rather than the crystalline formulation used in phase 2?

What was the average time to mortality or SAE in each arm?

What was the duration of stage 4 CKD in each arm prior to randomization? Has any other study has examined a stage 4 CKD treatment?

Will Reata/Abbott be able to pursue development in patients with less severe CKD (e.g., in stage 3 patients instead of stage 4) or with more targeted stage 4 patients?

Are there any CKD candidates in the second-generation anti-inflammatory modulator (AIM) portfolio that Abbott and Reata commenced collaboration on in 2011?

-- by Jessica Dong, Adam Brown, and Kelly Close

The Close Concerns team expanded this report on October 19, following the original report being published very late the evening of October 18.