Closer Look

MEMORANDUM

Concert Pharmaceuticals presents positive 48-week results from a phase 2 trial of CTP-499, a novel treatment for chronic kidney disease - July 13, 2014

Executive Highlights

- Treatment with CTP-499 appears to slow the rate of increase of serum creatinine levels in patients with chronic kidney disease.
- Treatment with CTP-499 reduced biomarkers of fibrosis, providing new insight into the drug's therapeutic mechanism.

Lexington, MA-based biopharmaceutical company Concert Pharmaceuticals recently announced promising 48-week results of its phase 2 clinical trial of CTP-499, its novel adjunct therapy for diabetic nephropathy and other forms of chronic kidney disease (CKD). The results suggest that CTP-499 may protect against loss of kidney function by reducing the progression of fibrosis, which would be a significant new mechanism for the treatment of CKD.

This phase 2 placebo-controlled trial involved three parts: i) a double-blind, randomized, placebo-controlled 24-week study evaluating the safety and efficacy of twice daily 600-mg doses of CTP-499 as measured by urinary albumin to creatinine ratio (UACR); ii) an optional blinded 24-week, placebo-controlled extension study, and iii) an ongoing open-label extension study of up to 48 additional weeks. After 48 weeks (parts 1 and 2), there was a 38% improvement in serum creatinine levels, a key secondary endpoint, in the treated group (n=65) compared to the placebo group (n=58) (an increase of 0.13 mg/dl vs. 0.21 mg/dl). This difference was not statistically significant (p=0.057), though we note that the trial was relatively small, so may have reached significance with larger numbers. Only 1.5% of patients in the treated group experienced an increase of ≥50% in serum creatinine levels, compared to 10.3% of patients in the placebo group, and this difference was statistically significant (p=0.026). In addition, there were statistically significant changes in the levels of two biomarkers of fibrosis; patients treated with CTP-499 had 52% less urinary fibronectin and 18% less plasma collagen IV after 48 weeks than patients receiving placebo. The trial did not meet its primary endpoint of a significant difference in UACR change after 24 weeks, but the difference did reach significance after 48 weeks. At that time the treated group had only a 24 mg/g increase in UACR from baseline compared to a 223 mg/g increase in the placebo group (p=0.097), which suggests that CTP-499 may have a long-term stabilizing effect on UACR. CTP-499 was generally well tolerated, with no adverse events judged to be related to the treatment.

An increase in serum creatinine levels is considered an indicator of declining kidney function, so these results suggest that CTP-499 may be able to reduce the rate of decline in patients with CKD. One of the investigators, Dr. Bhupinder Singh, noted that fibrosis is "believed to be a final common pathway for kidney failure" that occurs gradually over the course of the disease, so the fact that CTP-499 appears to target that pathway may explain why clinically significant effects did not become apparent until after a longer treatment period. CTP-499 is intended as an adjunct to treatment with angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), which are blood-pressure lowering agents and are considered the current standard of care for CKD. CTP-499's mechanism is not fully understood, but it is believed to involve inhibition of phosphodiesterases, enzymes that regulated cell-signaling pathways that increase inflammation and promote CKD. There is certainly a need for novel treatments in this area: the latest CDC statistics estimated that the number of patients on dialysis or with a kidney transplant due to diabetes rose 13% from 2008 (202,290) to 2011 (228,924).

- **AbbVie is also investigating a treatment for CKD; its candidate, atrasentan, remains in phase 3 trials.** Atrasentan is an endothelin-receptor antagonist and began its phase 3 SONAR trial in May 2013. The trial's primary completion date is estimated to be February 2017, and we assume that the earliest it could come to market would be 2018. Japanese company Kyowa Hakko Kirin also recently announced that it will resume development of Reata's failed CKD drug, bardoxolone methyl, which could potentially be a paradigm-shifting therapy if cardiovascular safety concerns are addressed. Bayer, Lilly, Pfizer, and Vascular Pharma are also investigating treatments for diabetic nephropathy in phases 1 and 2 (see our report for details).

-- by Emily Regier, Jessica Dong, and Kelly Close