MEMORANDUM

AbbVie 2Q14 - Chronic kidney disease candidate atrasentan remains in phase 3 - July 29, 2014

Executive Highlights

- Atrasentan, a candidate for chronic kidney disease candidate, remains in phase 3. There was no mention of the compound in the company's 2Q14 earnings call.

AbbVie reported 2Q14 financial results on Friday in a call led by CEO Mr. Richard Gonzalez. There were no updates on the company's chronic kidney disease (CKD) candidate atrasentan, which remains in phase 3. As a reminder, atrasentan is an endothelin-receptor antagonist and began its phase 3 SONAR trial (ClinicalTrials.gov Identifier: NCT01858532) in May 2013, and the trial is still recruiting. The trial's estimated primary completion date is February 2017 (which is consistent with estimates from early 2013), and we assume that the earliest it could come to market would be 2018. SONAR will serve as the single global registration trial for the compound.

SONAR's primary endpoint is time to first occurrence of a component of the composite renal endpoint: doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of end stage renal disease (chronic dialysis, renal transplantation, or renal death). Secondary endpoints include measures of albuminuria, estimated glomerular filtration rate (eGFR), and cardiovascular outcomes. The double-blind study will enroll an estimated 4,148 people with type 2 diabetes and eGFR between 25 and 75 ml/min/1.73 m² - patients with an eGFR above 60 will be capped at to 10% of the population. Notably, this trial is enrolling a slightly broader range of patients with earlier-stage CKD compared to the BEACON trial for bardoxolone methyl, which enrolled patients with eGFRs between 15 and 30 ml/min/1.73 m² - *BEACON was terminated in 2012 due to an excess of serious cardiovascular events, although we learned earlier this month that Kyowa Hakko Kirin in Japan has acquired rights to bardoxolone methyl and is restarting phase 2 testing*. Patients in SONAR will be randomized to receive a low dose (likely 0.75 mg, based on previous trials) of atrasentan or placebo once daily. *We hope that AbbVie's broader approach to enrollment may allow for subgroup analyses if a safety signal appears again in the highest-risk population. This outcomes trial should provide clarity on the benefits to renal function suggested by short-term phase 2 data, which only measured changes in albuminuria and not hard renal outcomes.*

There was no kidney-related Q&A.

- **Kyowa Hakko Kirin, Concert Pharmaceuticals, Bayer, Lilly, Pfizer, J&J, AZ, Daiichi Sankyo, NephroGenex, and Vascular Pharma are also investigating treatments for diabetic nephropathy.**

Table 1: Diabetic Nephropathy Competitive Landscape

Company	Drug Name	Class	Status/ Timeline	Other Remarks
AbbVie	Atrasentan	Endothelin-receptor antagonist	Phase 3	Primary completion expected 2017

J&J	Invokana (canagliflozin)	SGLT-2 inhibitor	Phase 3	Already marketed for type 2 diabetes; being investigated for diabetic nephropathy in CREDENCE trial
NephroGenex	Pyridorin	Oxidation inhibitor	Phase 3	Recently entered phase 3
AZ	Roxadustat	2-OG inhibitor	Phase 3	Recently entered phase 3
AZ	AZD1722	NHE3 inhibitor	Phase 2	Phase 3 expected in 2015
Bayer	Finerenone	MR (mineralcorticoid receptor) antagonist	Phase 2	Primary completion of safety/efficacy trial with different oral doses expected this month (Identifier: NCT01874431)
Concert Pharmaceuticals	CTP-499	Inhibitor of inflammation, oxidation, and fibrosis to be used with standard CKD therapies	Phase 2	Positive 48-week phase 2 results
Kyowa Hakko Kirin	Bardoxolone methyl	Inhibitor of inflammation	Phase 2	Reata's phase 3 BEACON trial terminated due to safety concerns; Kyowa Hakko Kirin recently acquired the candidate
Lilly	LY2382770	TGF-beta monoclonal antibody	Phase 2	Primary completion expected this month (Identifier: NCT01113801)

Lilly	LY3016859	TGF-alpha/epiregulin monoclonal antibody (inhibitor of two epidermal growth factor receptor ligands)	Phase 2	Currently recruiting, primary completion expected August 2015 (Identifier: NCT01774981)
Pfizer	PF-00489791	Phosphodiesterase inhibitor	Phase 2	Trial completed August 2013 (Identifier: NCT01200394); management mentioned "encouraging clinical performance" in 4Q13 update
Pfizer	PF-04634817	C-C chemokine receptor type 2/5 antagonist	Phase 2	Primary completion expected September 2014 (Identifier: NCT01712061); also being investigated for diabetic macular edema
Vascular Pharma	VPI-2690B	Targets insulin-like growth factor-1 signaling pathway	Phase 2	Initiating phase 2 trial in September 2014, according to company website
Daiichi Sankyo	CS-3150	Oral MR antagonist	Phase 2	Expected to enter phase 3 by early 2015
Lilly	Undisclosed small molecule	Undisclosed	Phase 1	None

- **Japan-based Kyowa Hakko Kirin announced on July 4 that it will resume phase 2 development for bardoxolone methyl.** Full results from the terminated BEACON trial were published late last year in *NEJM*. A detailed analysis of the trial presented at this year's European Renal Association-European Dialysis and Transplant Association Congress suggested that excluding a subset of patients with certain baseline risk factors (more advanced renal dysfunction, high fluid retention, and a prior history of cardiovascular disease) might have eliminated the increased risk of adverse events in the bardoxolone methyl arm. In light of this analysis, Kyowa Hakko Kirin has

decided to continue development "with a particular emphasis on patient safety." The company licensed bardoxolone methyl from Reata Pharmaceuticals and has exclusive rights to develop and commercialize the drug in Japan, China, Taiwan, Korea, and Southeast Asia.

- **Very interestingly, J&J hypothesizes that the SGLT-2 inhibitor Invokana (canagliflozin) might be able to slow the progression of diabetic nephropathy, a theory it is testing in the CREDENCE trial.** The study will enroll ~3,600 type 2 diabetes patients with renal impairment, with an expected end date in 2019.
- **NephroGenex announced the initiation of patient enrollment in the first of two phase 3 studies examining the safety and efficacy of its diabetic nephropathy drug Pyridorin on June 18.** This is one of the relatively few agents we have seen enter phase 3 for diabetic nepthropathy; notably, the FDA has granted Pyridorin fast-track status and approved a Special Protocol Assessment for the PIONEER trial program. The study (ClinicalTrials.gov Identifier: NCT02156843) has an estimated primary completion date of December 2017.
- **In other new news on the CKD front, Concert Pharmaceuticals announced positive 48-week results from a phase 2 trial of its CKD candidate, CTP-499, on April 25.** The amount of urinary albumin to creatinine ratio (UACR), the trial's primary endpoint, was not significantly altered for those taking CTP-499; however, there was a favorable trend toward a smaller ratio observed at 48 weeks.
- **There is certainly a need for novel CKD treatments, as currently available therapies can slow the course of the disease, but cannot reverse it.** 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). We hope very much some of the compounds now in development will change the course of the disease rather than just slow it or treat it. Our fingers are crossed and we salute the companies that are doing work on this front given that the regulatory landscape in particular is very challenging. We do have high hopes that reimbursement will be easier to garner in this area where there are so many unmet needs and so few alternatives for treatment.

-- by Emily Regier, Manu Venkat, and Kelly Close