Closer Look

MEMORANDUM

Pfizer 4Q13 - Progress on diabetic nephropathy candidates; ertugliflozin and PCSK9 inhibitor phase 3 programs underway - January 28, 2013

Executive Highlights

- Pfizer has received "encouraging" phase 2a data on its PDE5 inhibitor for diabetic nephropathy and plans to enter phase 2b; phase 2 CCR2/5 inhibitor being investigated for diabetic nephropathy and diabetic macular edema
- As we learned late last year, phase 3 programs were initiated in 4Q13 for the SGLT-2 inhibitor ertugliflozin (partnered with Merck) and the PCSK9 inhibitor bococizumab (programs includes two full CVOTs)

Pfizer CEO Ian Read led the company's 4Q13 and full-year 2013 financial update this morning. Excitingly (and the newest news of late related to diabetes with Pfizer), we learned that the company received promising data from a phase 2a study of its PDE5 inhibitor for diabetic nephropathy, and plans to move the candidate into phase 2b testing. Pfizer's other phase 2 candidate for diabetic nephropathy, a CCR2/5 dual inhibitor, is now being investigated for diabetic macular edema as well. Pfizer had announced during its 3Q13 update that its SGLT-2 inhibitor ertugliflozin (a partnered product with Merck) was advanced into phase 3 - we now see six phase 3 studies for the drug listed on ClinicalTrials.gov, including a cardiovascular outcomes trial and a trial in type 2 diabetes patients with chronic kidney disease. Finally, management commented on Pfizer's PCSK9 inhibitor for LDL cholesterol lowering, which is also in phase 3 (as was announced during Pfizer's 3Q13 update). Management stated during Q&A that the drug's phase 3 program should read out around the time of its main competitors' programs (Sanofi's alirocumab and Amgen's evolocumab are currently in phase 3 as well). Below are the top three highlights from the call, followed by a selection of relevant questions and answers.

1. We were excited to hear that Pfizer's PDE5 inhibitor for diabetic nephropathy (PF-00489791) continues to progress through phase 2. According to management, Pfizer has received promising phase 2a data on the compound, demonstrating "encouraging clinical performance" warranting further exploration in phase 2b. The company also continues to develop its phase 2 CCR2/5 inhibitor PF-04634817 for diabetic nephropathy, and today disclosed that it is investigating the candidate for diabetic macular edema as well. During Q&A, management commented that it sees important medical and commercial opportunity in renal diseases - both the PDE5 inhibitor and the CCR2/5 inhibitor are listed on the company's online pipeline as "Key Programs" in phase 2. Given the enormous unmet need for therapies for diabetic nephropathy, and the high-profile discontinuation of Abbot/Reata's bardoxolone methyl in 2012, we find this recent progress highly encouraging, even though phase 2 data remains fairly early stage..

2. Phase 3 testing is underway for Pfizer and Merck's SGLT-2 inhibitor ertugliflozin. The drug was advanced into phase 3 in early 4Q13 (initially announced during the company's 3Q13 update in October). There are currently six phase 3 trials for ertugliflozin listed on ClinicalTrials.gov (see bullet below). The worldwide collaboration (except for Japan) covers ertugliflozin monotherapy as well as two fixed-dose combinations (FDCs) with metformin and Merck's DPP-4 inhibitor Januvia (sitagliptin). During Pfizer's 3Q13 update, management disclosed that ertugliflozin's early clinical data suggest a potentially "best-in-class" portfolio of clinical characteristics that would be especially well suited for FDCs. SGLT-2/DPP-4 inhibitor FDCs have seen more development in recent months - Lilly/BI could file an empagliflozin/linagliptin FDC in 2014, and AZ is working towards a dapagliflozin/saxagliptin combination with data disclosure expected in 2Q14 and FDA submission in 4Q14. An FDC with the market-leading DPP-4 inhibitor Januvia could give

ertugliflozin a very competitive edge in an increasingly crowded SGLT-2 inhibitor market: J&J reported a strong US performance for Invokana (canagliflozin) in its recent 4Q13 update (the drug was also recently approved in Europe); AZ's Farxiga (dapagliflozin) received a US approval earlier this month and is already on the market in Europe; BI/Lilly's empagliflozin is nearing potential approval in the US and EU; Astellas/ Kotobuki's ipragliflozin was recently approved in Japan; Lexicon's SGLT-1/SGLT-2 dual inhibitor LX4211 will move into phase 3 contingent on partnership discussions; and Novartis' SGLT-1/SGLT-2 dual inhibitor LIK066 is in phase 2.

- **There are six phase 3 trials for the SGLT-2 inhibitor ertugliflozin currently listed on ClinicalTrials.gov -** All are currently recruiting except for MK-8835-006, which is not yet recruiting. Studies are listed in order of their estimated primary completion dates.

Study Name (Identifier)	Estimated Enrollment	Study Treatment	Primary Endpoint	Est. Primary Completion (as of publication)
MK-8835-003 (NCT01958671)	450 patients with type 2 diabetes	Ertugliflozin monotherapy vs. placebo or metformin	A1c change from baseline to week 26	August 2015
MK-8835-006 (NCT02036515)	405 patients with type 2 diabetes	Ertugliflozin vs. placebo as add-on to metformin and sitagliptin	A1c change from baseline to week 26	September 2015
MK-8835-007 (NCT02033889)	600 patients with type 2 diabetes	Ertugliflozin vs. placebo as add-on to metformin	A1c change from baseline to week 26	December 2015
MK-8835-001 (NCT01986855)	468 patients with type 2 diabetes and stage 3 chronic kidney disease	Ertugliflozin vs. placebo (with possible background therapy)	A1c change from baseline to week 26	July 2016
MK-8835-002 (NCT01999218)	1230 patients with type 2 diabetes	Ertugliflozin vs. glimepiride as add-on to metformin	A1c change from baseline to week 52	January 2017
MK-8835-004 (NCT01986881) [CVOT]	3900 patients with type 2 diabetes and established CV disease	Ertugliflozin vs. placebo (with possible background therapy)	Time to first MACE event	June 2020

3. The PCSK9 inhibitor bococizumab (indicated for the lowering of LDL cholesterol) was also advanced into phase 3 in early 4Q13 - news first shared during Pfizer's 3Q13 update. In Q&A, management noted that bococizumab's phase 3 program is expected to read out around the time of competitors' programs, which include Sanofi's phase 3 alirocumab and Amgen's phase 3 evolocumab. Pfizer's phase 3 program is designed for differentiation, and contains not one, but two full cardiovascular outcomes

trials (CVOTs). The first CVOT will enroll statin-intolerant patients, while the second will target more aggressive LDL-C thresholds - the applicability of this second study may have been thrown into question by the recent ACC/AHA guidelines that place less focus on specific LDL-C thresholds; however, if the trial successfully shows that targeting more aggressive LDL goals with a PCSK9 inhibitor improves outcomes, then the guidelines may need to be revisited. During Q&A, management commented that the results from these outcomes trials will be particularly important in determining the place for these agents in the hypercholesterolemia treatment paradigm. Management has previously guided for phase 2 data disclosure at the American College of Cardiology's 2014 conference in March.

Pfizer did not provide any further updates to its cardiovascular and metabolic pipeline during the call. According to the company's current online pipeline, PF-04937319, a hepatic glucokinase activator, remains in phase 2. Two small molecules (PF-05175157 and PF-06291874) as well as one biologic (PF-05231023) are in phase 1 for type 2 diabetes. A mystery undisclosed biologic for type 1 diabetes (PF-06342674) remains in phase 1.

Questions and Answers:

Q: Could you provide more color on the products in phase 2 outside of the products that you mentioned during the call today?

A: In renal diseases, we have seen positive phase 2a data on our novel PDE5 inhibitor. We also moved a CCR2/5 dual inhibitor into diabetic nephropathy and diabetic macular edema, underlying the medical and commercial opportunity we see in this disease.

Q: For the PCSK9 inhibitor, you're moving into phase 3, and obviously that involves a lot of studies and investment. Given that the new guidelines that place less of an emphasis on LDL target levels, how do you see the value of a PCSK9 program? Would you consider partnering with someone, given the amount that you will need to invest there?

A: We've initiated our phase 3 program. It's a broad program, with multiple lipid lowering studies. We decided to run two large outcomes studies to provide the broadest database of any of the PCSK9 programs in the most important patient populations that can benefit from this therapy. We believe that the results of these outcomes trials will determine the place for these agents in the management of patients with cardiovascular risk factors and high cholesterol levels. Our programs are designed to read out in a similar timeframe as our competitors' programs. We're off and running with our phase 3 program, and at this point we're going it alone.

-- by Manu Venkat and Kelly Close