MEMORANDUM

Pfizer 2Q14 - Phase 3 continues to enroll for ertugliflozin, PCSK9 inhibitor; phase 2 trials terminated for acetyl-CoA carboxylase inhibitor - July 29, 2014

Executive Highlights

- Phase 3 trials continue to enroll for the SGLT-2 inhibitor ertugliflozin (partnered with Merck); management views fixed-dose combinations, including with Merck's DPP-4 inhibitor Januvia, as a central opportunity for ertugliflozin.
- Management reiterated that cardiovascular outcomes data on the PCSK9 inhibitor bococizumab should be available at roughly the same time as data from competitors.

Pfizer provided its 2Q14 financial update this morning in a call led by Chairman and CEO Mr. Ian Read. The company currently does not have any diabetes products on the market, but has a fairly robust pipeline of candidates for diabetes and its complications. Through the early portion of the year, Pfizer engaged in a series of attempts to acquire AstraZeneca (see our Pfizer 1Q14 Report), but the offers were repeatedly rebuffed. Below, we list the top three highlights from the presentation.

1. Phase 3 trial enrollment continues for Pfizer/Merck's SGLT-2 inhibitor ertugliflozin; management characterized the compound as a potentially best-in-class agent and commented favorably on potential fixed-dose combination, including with Merck's Januvia (sitagliptin).

2. The company has not yet updated its online pipeline, but three phase 2 trials for the acetyl-CoA carboxylase inhibitor PF-01575157 were terminated due to a safety concern in mid-May.

3. Enrollment continues for the broad phase 3 program for Pfizer's cholesterol-lowering PCSK9 inhibitor bococizumab; although a regulatory filing for bococizumab will likely come behind the filings for Amgen's evolocumab and Sanofi's alirocumab, outcomes data should be available at roughly the same time, according to Pfizer management.

Table of Contents

TOP THREE HIGHLIGHTS

1. Enrollment continues in the phase 3 program for the SGLT-2 inhibitor ertugliflozin, which Pfizer is co-developing with Merck - see the table below for a summary. While the majority of the trials were registered on ClinicalTrials.gov in late 2013 or in January 2014, one trial (MK-8835-005) was registered slightly later, in March, although from its current estimated primary completion date (October 2015) it should not hold up regulatory filing. The trial uses a factorial design to compare the co-administration of ertugliflozin and Merck's DPP-4 inhibitor Januvia (sitagliptin) - we imagine this will begin to lay the groundwork for a formal fixed-dose combination of the two compounds, which we believe will be an attractive product for Pfizer, Merck, and patients (see below).

- **There were no major changes to the estimated primary completion dates for any of the seven phase 3 trials -** the six non-CVOT trials should be complete by early 2016, while the CVOT will be complete in 2020.

Table 1: Phase 3 studies for ertugliflozin, arranged by estimated primary completion date

Study Name (Identifier)	Estimated Enrollment	Study Treatment	Primary Endpoint	Est. Primary Completion (as of May 9)
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
MK8835-005 (NCT02099110)	1,250 patients with type 2 diabetes	Ertugliflozin vs. sitagliptin when added to metformin	A1c change from baseline to week 26	October 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	October 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-8835-002 (NCT01999218)	1230 patients with type 2 diabetes	Ertugliflozin vs. glimepiride as add- on to metformin	A1c change from baseline to week 52	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	January 2016
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

- **Pfizer believes that ertugliflozin has plenty of potential for differentiating itself from the three currently (or almost) approved SGLT-2 inhibitors:** J&J's Invokana (canagliflozin), AZ's Forxiga/Farxiga (dapagliflozin), and Lilly/BI's Jardiance (empagliflozin). During Q&A, management commented that ertugliflozin is potentially a best-in-class molecule - Merck and Pfizer would need to have confidence in the compound's safety and efficacy to bear the costs of phase 3 development and CVOTs for a compound that will, at best, be fourth-to-market. Management also noted that the companies' strategy for ertugliflozin is highly dependent on the

prospect of fixed-dose combinations, especially with Merck's market-leading DPP-4 inhibitor Januvia (sitagliptin). Barring an unexpected development, an ertugliflozin/sitagliptin FDC would likely be the third SGLT-2 inhibitor/DPP-4 inhibitor FDC submitted for regulatory approval, behind Lilly/BI's Empa/Lina (filed in the US in 1Q14, EU filing planned for 2015) and AZ's Saxa/Dapa (filing planned for 4Q14). However, Pfizer/Merck's compound would have the advantage of featuring the most popular current DPP-4 inhibitor (Januvia), which might hold sway with patients and physicians (perhaps especially in primary care) due to the familiarity factor.

2. Pfizer has not yet updated its online pipeline, but as of early May, the company had a number of exciting candidates in development for diabetes and its complications - see the table below for a summary.

- **In less positive news, it appears that the phase 2 acetyl-CoA carboxylase inhibitor PF-05175157, which was advanced to phase 2 in 1Q14, is at risk -** the three phase 2 trials registered on ClinicalTrials.gov were recently prematurely terminated in mid-May due to an undisclosed safety concern in one of the trials. Fortunately (and we applaud the safety monitoring committee for being so on top of whatever issue arose), the other two trials were immediately halted before any dosing occurred. We hope to learn more about the issue that arose in the trial, and whether there is hope of pursuing the candidate at a different dose - we imagine that the updated company pipeline will at least be able to tell us if the candidate has been dropped completely.
    - **Acetyl-CoA carboxylase (ACC) is involved in the biosynthesis of fatty acids, and an ACC inhibitor would improve fatty acid oxidation.** The mechanism has shown positive effects on glucose homeostasis in preclinical testing. The competitive landscape for this class remains fairly uncluttered. Cambridge, MA-based biotech Nimbus Discovery has an ACC inhibitor in preclinical testing (ND-630). We found a publication on ACC inhibition from 2010 associated with Sanofi, and at GTC Bio 2011 we heard J&J Research Fellow Dr. James Lenhard discuss an investigation of an ACC inhibitor candidate.
- **The two phase 2 trials registered on ClinicalTrials.gov for the hepatic glucokinase activator PF-04937319 were completed in early 2013.** Since then, we have heard no further word on the candidate.

Table 2: Pfizer's diabetes drug pipeline

Drug Name	Class	Indication	Status/ Timeline
Ertugliflozin (PF-04971729)	SGLT-2 inhibitor	Type 2 diabetes	Phase 3
PF-00489791	PDE5 inhibitor	Diabetic nephropathy	Phase 2
PF-04634817	CCR2/5 antagonist	Diabetic nephropathy, diabetic macular edema	Phase 2
PF-04937319	Hepatic glucokinase activator	Type 2 diabetes	Phase 2
PF-05175157	Acetyl-CoA carboxylase inhibitor	Type 2 diabetes	Phase 2 (trials terminated)
PF-06291874	-	Type 2 diabetes	Phase 1
PF-06342674	Undisclosed biologic	Type 1 diabetes	Phase 1

- **Our eyes remain on Pfizer's two candidates for diabetic nephropathy, given the unmet need in that patient population.** The company's PDE5 inhibitor for diabetic nephropathy (PF-00489791) and its CCR2/5 antagonist for diabetic nephropathy and diabetic macular edema (PF-04634817) remain in phase 2. During the company's 4Q13 update, management shared the PDE5 inhibitor had demonstrated "encouraging clinical performance," warranting further exploration in phase 2b. Management had also then commented that it sees important medical and commercial opportunity in renal diseases. See our recent AbbVie 2Q14 Report for an overview of the current competitive landscape for chronic kidney disease drugs.

3. Management provided an update on bococizumab, the company's phase 3 PCSK9 inhibitor for LDL cholesterol lowering. The company believes that its phase 3 program is the broadest one available out of the field of competitors. For background, PCSK9 inhibitors are receiving a huge amount of attention for the 50-75% LDL reductions that some agents in the class have demonstrated in phase 3 (see our American College of Cardiology 2014 Full Report). Currently, the front-runners in the race are Amgen's evolocumab and Sanofi's alirocumab - these two candidates will likely be first to hit regulatory submission (Amgen just guided for US and EU filings in 3Q14). There has been some speculation on how the FDA will assess this drug class, especially with regards to a possible requirement for pre-approval outcomes data.

- **During Q&A, management expressed continued uncertainty over whether regulatory agencies will be looking for outcomes data pre-approval.** In Pfizer's view, given that the class has already clearly demonstrated strong LDL-lowering efficacy, the decision may come down to the readouts from studies that are looking at the correlation between LDL lowering through PCSK9 inhibition and improvements in CV outcomes. Management made the wise point that no matter what regulatory agencies require, CV outcomes data will be very important for payers, which will play a large role in determining the relative success of the different options within the class. For this reason, Pfizer continues to highlight the fact that while bococizumab will not be submitted at the same time as evolocumab or alirocumab (non-CVOT clinical trials end by early 2016), outcomes data should be available for all three agents at around the same time (roughly 2017).

QUESTIONS AND ANSWERS

Q: On ertugliflozin, how do you see yourself competing given that you will likely be fourth to market, and historically third or fourth entrants in these types of commoditized markets struggle to gain meaningful share?

A: We have a comprehensive program in partnership with Merck to develop ertugliflozin as a single entity and also in combination with Januvia and metformin. We will have an overall strategy that involves both the single entity and combination products as we make our way into that marketplace.

A: Of course, as you say, we will be fourth in, but it will ultimately depend on the quality of the clinical trial and the results. We believe that it is a potentially best-in-class molecule.

Q: We're seeing increased pricing pressure from PBMs translating into negative pricing dynamics in areas such as diabetes. GSK recently announced the pricing for their GLP-1 agonist at a 65% discount. To what extent do you think that aggressive pricing strategies like that may work for products that are late to the market?

A: Well PBMs are doing what they are constructed to do, which is to try and aggregate volume and achieve price discounts. This has been going on in the US market for many years now and I think that will continue to occur. It all depends on the value that you bring to the marketplace. [...] I can't really comment on GSK pricing. [...] Ultimately, efficacy and safety is the main deciding factor, and adoption is normally slow and driven by clinical data rather than pure pricing decisions.

A: Pricing and reimbursement in the US is very complex and fragmented. You are dealing not only with prices, but also with discounting, rebating, and tiered formularies. It is not as simple as saying that a price should be higher or lower. You need a strategic approach where you first and foremost build value for your product, then operate within the system that exists to derive maximum benefit.

Q: Could you update us on conversations you may have had with regulators in the last several months around the PCSK9 class? I know that Pfizer had spoken before about how you perhaps thought that outcome trials might be necessary prior to registration.

A: We have a very large clinical program that includes LDL lowering and a significant CV outcome study involving patients both above and below 100 mg/dl, and that includes primary and secondary prevention. We think it's the broadest program available, and that it should be able to bring real insight to patients, physicians, and regulators. It is difficult to speculate whether regulators will approve the class with LDL reductions alone or wait for outcomes studies. I think that it depends on the readouts from studies on the correlation between LDL lowering and outcomes. I would underline that in our view, what will really matter in terms of uptake in the marketplace is that payers will be looking at the outcome studies. We think we have a premier outcomes study program and we think it will deliver timely to competitors.

-- by Manu Venkat and Kelly Close