Closer Look

MEMORANDUM

## Pfizer 3Q13 - Ertugliflozin enters phase 3; PCSK9 inhibitor advanced to phase 3, clinical trial program details - October 29, 2013

**Executive Highlights**

- Pfizer and Merck have advanced their SGLT-2 inhibitor ertugliflozin to phase 3; management remarked that the candidate has potentially "best-in-class" characteristics.
- Pfizer announced the advancement of bococizumab (RN-316), its PCSK9 inhibitor candidate for LDL-C lowering, to phase 3.
- Bococizumab's phase 3 program is designed for differentiation and will involve two full CVOTs, including one in patients uncontrolled on statins.

*Pfizer CEO Ian Read led the company's 3Q13 financial update this morning. As was mentioned by Merck management in its 3Q13 update yesterday, Pfizer announced that the two companies have advanced their SGLT-2 inhibitor candidate ertugliflozin into phase 3 clinical testing. Pfizer and Merck's worldwide (except for Japan) collaboration covers ertugliflozin monotherapy as well as two fixed-dose combinations (FDCs) with metformin and Merck's Januvia (sitagliptin). During Q&A, management mentioned that phase 2 data indicates that ertugliflozin is highly selective for the SGLT-2 receptor, is highly potent, and requires a low dose, a "best-in-class" portfolio of characteristics that also make ertugliflozin ideal for fixed-dose combinations with compounds like Januvia. Neither Merck nor Pfizer has provided timeline forecasts for ertugliflozin, but an FDA submission in 2016 appears likely. If approved, ertugliflozin would enter a crowded SGLT-2 inhibitor market: J&J's Invokana (canagliflozin) has seen promising early growth after its US launch this past spring and an EU decision is expected this year; BMS/AZ's Forxiga (dapagliflozin) has launched in Europe and was recently resubmitted to the FDA; Lilly/BI filed empagliflozin in the US and EU in March. Other SGLT-2-based candidates include Astellas/Kotobuki's ipragliflozin (filed in Japan earlier this year), Chugai's tofogliflozin (phase 3 in Asia, but dropped by Roche for development elsewhere), Lexicon's SGLT-1/SGLT-2 dual inhibitor LX4211 (phase 3 expected later this year), and Novartis' SGLT-1/ SGLT-2 dual inhibitor LIK066 (phase 2). On the FDC front, Lilly recently forecast that a regulatory submission for an empagliflozin/Tradjenta (linagliptin) FDC could occur as early as 2014.*

*Excitingly, management announced that its PCSK9 antibody candidate bococizumab (the proposed generic name for RN-316) is beginning phase 3 testing this month for the lowering of LDL-C. The company is completing the final analyses of its phase 2b studies, and plans to present the findings at the American College of Cardiology's March 2014 meeting in Washington, DC. Management provided some very interesting information and commentary on the design of the phase 3 program, which is designed to differentiate the product. Notably, Pfizer will conduct not one, but two full cardiovascular outcomes studies for bococizumab. The first will enroll patients who were unable to achieve LDL levels lower than 100 mg/dl on statins, a high-risk population that would likely be a key target demographic for the PCSK9 class. A second outcomes trial will study the effect of reducing LDL-C to levels well below the thresholds recommended by current guidelines in terms of additional CV benefit. During Q&A, management stated that it is possible that the FDA will want, in addition to LDL-C lowering, a robust clinical safety database and cardiovascular outcomes data for approval. Other companies developing PCSK9 inhibitors include Amgen (AMG 145, phase 3), Roche (RG7652, phase 2), Lilly (LY3015014, phase 2), and Catabasis (CAT-2003, phase 2 andCAT-2054, preclinical). Interestingly, Pfizer has another PCSK9 candidate in its pipeline, RN-317 (PF-05335810, phase 1); we had initially wondered whether the addition of that candidate*

*to the pipeline indicated a lack of confidence in RN-316 (now bococizumab), but it now appears that was not the case.*

*No updates were provided on the rest of Pfizer's pipeline during the call. The most recent version of Pfizer's online pipeline (updated August 9th) shows that the company's two candidates for diabetic nephropathy, PF-04634817 (a chemokine CCR2/5 antagonist) and PF-00489791 (a PDE5 inhibitor) are still in phase 2. Additionally, Pfizer has two small molecules (PF-05175157 and PF-06291874) as well as one biologic (PF-05231023) in phase 1. We are interested to know more about PF-06342674, a phase 1 biologic for type 1 diabetes that was added to the pipeline in recent months.*

*As a reminder, the company announced during its 2Q13 update that it plans to separate company operations into two units for branded products and a third unit for generics. An eventual spin-off of the generics business could presumably follow at some future point. This new structure should help the company focus on innovation and product development, which should benefit the company's relatively early-stage cardiometabolic portfolio. During the 3Q13 call, management forecast that the new commercial structure would be formally implemented at the start of fiscal year 2014.*

**Questions and Answers**

**Q: Can you help us understand what the points of differentiation are for the SGLT-2 candidate, especially given that there are three other entrants potentially to the market before you enter. Also, can you comment on a combination strategy that you might have with Januvia?**

A: In terms of ertugliflozin, we have entered a worldwide collaboration except for Japan with Merck to develop and commercialize ertugliflozin and our fixed-dose combinations with metformin and Januvia. We are initiating phase 3 clinical trials with our partner Merck. I certainly don't want to comment in detail about competitors in this class other than to say that our two lead competitors have had a troubled regulatory pathway in the US and Europe, and we believe that the dialogue we've been able to have with the FDA, as well as the strength of the molecule, certainly has enabled us to put together a development program that, combined with the strength of our partnership with Merck, gives us a very good runway into the marketplace.

A: Ertugliflozin is a highly selective molecule, and if you explore the class you see that there are differences in selectivity among the molecules. It's highly potent, it's a very low dose, which is a key characteristic when you aim to combine with other drugs such as the market-leading Januvia and metformin. It performed very well in phase 2 studies with robust lowering of A1c and also effects on blood pressure. So we think, really, these unique characteristics of a best-in-class molecule combined with the long experience with Januvia allows for a very favorable and long-term opportunity there.

**Q: To the extent that there are a couple other PCSK9 inhibitors out there, can you talk about what you need to see in phase 2 to make this large investment and potentially how your product is differentiated beyond the clinical trial differences you highlighted?**

A: Well clearly we've seen phase 2 data of sufficient quality to encourage us to enter in to phase 3, and we believe we will have a highly competitive product.

A: First of all, we think we have a great antibody, which came out of our labs in San Francisco. And I think in addition to having an excellent substrate to take into clinical development, we think we've been able to put together a very differentiated clinical program. Our program will be the only program investigating both high-risk primary and secondary prevention populations, and when you begin to look at the program in more detail, it includes a dedicated CV outcomes study in patients who can't achieve LDL levels lower than 100 mg/dl despite the use of statins, which is a very high-risk patient population with a great deal of unmet need, and patients who represent a tremendous cost to the healthcare system, so positive outcomes in that population would be very significant, we believe. And we also combine in our program a second phase 3 outcomes trial that will address whether driving LDL levels well below levels recommended by current guidelines will lead to a further reduction in cardiovascular events. Lastly, I think that compared to other programs, our phase 3 program enrolls the broadest range of high-risk patients, in need of improved cholesterol management; uniquely, it includes high-risk primary and secondary intervention patients. So overall, we believe that the

combination of a good basic antibody combined with a clinical program that has the ability to demonstrate real differentiation across patient populations with significant unmet need will enable us to bring a very competitive profile to what is a potentially very attractive and promising marketplace.

**Q: Regarding the PCSK9, your competitors don't believe they need outcomes trials to gain FDA approval. Do you feel that you need these outcomes trials for approval, or is this just to broaden your label and for further differentiation?**

A: I think that in this marketplace, our trials are constructed to be able to demonstrate value to society and payers.

A: We believe we've put together a really robust and potentially differentiated program. Clearly we know that LDL-C is a well-established surrogate for cardiovascular risk. But certainly we know from dialogue and discussion with the FDA that it is conceivable that regulators may require demonstration of a beneficial effect on CV events before approving a new class of agents such as PCSK9 inhibitors. At a minimum, robust LDL-C lowering along with a comprehensive long-term safety database will likely be required for initial approval bococizumab and potentially other medicines in the class as well. The bococizumab phase 3 program is designed to address the potential for regulatory authorities to require, in addition to LDL-C lowering, a robust clinical safety database and cardiovascular outcomes data for approval.

A: We have put in a lot of technical capabilities on how to develop antibodies with the most biopharmaceutically appropriate characteristics. When you look at the class, I thin you can see emerging data suggesting that some of the antibodies are very potent, and some are intermediate. We were very encouraged by the potent effect of our antibody in phase 2 and its robust LDL-lowering, tolerability, and low frequency of drug antibodies.

**Q: Could you talk about the timeline for completion of the PCSK9 outcomes trials? Are there opportunities for early stoppage based on interim results? And what is the dosing that is being used in the trial?**

A: The PCSK9 programs are in relatively early stages of their clinical development. We will have to see what will be required for approval, and that is something we will continue to have a dialogue with the agency about. I think it's premature to determine if there is any interim readout of data that would lead to an earlier approval. In terms of dosing, we are using twice-a-month dosing in phase 3. From an analysis of phase 2b data, which we will be presenting early next year, we certainly believe that twice a month dosing actually provides the optimal consistent cholesterol lowering right across the dosage interval to maintain the optimal clinical effect. So we really feel positive about the twice-a-month dosing schedule.

A: It's a really well behaving antibody, and the twice-monthly administration schedule is the logical step. However, we think that a possible lifecycle management strategy could involve exploration of a once-monthly schedule. That may include the use of technology such as the Halozyme technology for which we have exclusive license within the PCSK9 class, which we're now performing early tests on to investigate the suitability of that technology to extend half-life and lower the volume needed. The antibody itself at the higher dose has the potential to be once monthly, but we would rather use a technology like that to make administration more convenient.

*--by Manu Venkat and Kelly Close*