Closer Look

MEMORANDUM

Takeda F4Q13 - Nesina down 22% to ~$90 million; once-weekly trelagliptin halted in US and EU due to high costs of phase 3 development - June 2, 2014

Executive Highlights

- Global Nesina (alogliptin) sales fell 22% year-over-year as reported to JPY 9.4 billion (~$90 million), due to competition and a challenging comparison.
- Takeda will not pursue a regulatory filing for its once-weekly DPP-4 inhibitor trelagliptin (SYR-472) in the US and EU due to the high cost of development, particularly CVOTs.
- The FDA PDUFA date for the partnered obesity drug Contrave (naltrexone/bupropion) is on June 10; management voiced confidence about the drug's approval.

Takeda provided its F4Q13 financial update in a call led by CEO Mr. Yasuchika Hasegawa. The company's cardiometabolic portfolio did not feature very prominently in prepared remarks, but Q&A was rich with commentary and pipeline updates, not all of which were particularly encouraging.

On the financial front, the Nesina (alogliptin) DPP-4 inhibitor franchise struggled in F4Q13, falling 22% year-over-year as reported to JPY 9.4 billion (~$90 million). For FY2013, sales rose 7% to JPY 40 billion (~$400 million), compared to nearly 150% growth in FY2012 (albeit from a much lower base). Nesina's sluggish performance was due to some artificial factors (namely a challenging comparison due to Japanese wholesaler stockpiling in F4Q12) as well as stiff competition in Japan and especially the US - sales were down sequentially in the US in the product's third reported quarter of sales. Actos (pioglitazone), the former blockbuster TZD, continued its downward trend, falling ~50% as reported in F4Q13. Takeda is embroiled in a number of lawsuits in the US over the alleged hiding of safety data on Actos, and could face substantial legal damages.

We were disappointed to hear that the trelagliptin (SYR-472), the company's once-weekly DPP-4 inhibitor that was recently filed in Japan, will not proceed to US/EU phase 3 due to the high costs of that stage of development, especially outcomes trials in the US. However, despite somewhat sluggish sales and the recent pipeline discontinuations, Takeda remains steadfastly committed to diabetes, although management acknowledged today that the greatest potential in diabetes is in emerging markets. We got a glimpse into the company's earlier-stage pipeline during Q&A, which features three early-stage preclinical and clinical candidates (including a GLP-1/GIP co-agonist) that management believes will cause meaningful weight loss in addition to improvements in glycemic control. More broadly, the company believes that weight loss is the key to differentiation in an increasingly crowded diabetes market, and that its partnered obesity drug Contrave (with its PDUFA date right around the corner on June 10) will be key in this regard. Our top five highlights from the call are included below, followed by a selection from Q&A.

TOP FIVE HIGHLIGHTS

1. Global Nesina (alogliptin) franchise sales fell 22% year-over-year as reported in F4Q13 to JPY 9.4 billion (~$90 million), against a challenging comparison (F4Q12 sales rose 126% year-over-year as reported, from a much lower base). Sequentially, sales fell 25% in F4Q13. For the full fiscal year 2013 (FY2013), Nesina franchise sales totaled JPY 40 billion (~$400 million), up 7% as reported compared to 144% growth in FY2012. Nesina sales were hit in both in the US, where the product was launched in June of last year, and in Japan, where it is a slightly more mature product. In the US, sales fell from JPY 1.0

billion (~$10 million) in F3Q13 to JPY 0.9 billion (~$9 million) in F4Q13. In Japan, sales fell 29% year-over-year as reported to JPY 8.5 billion (~$82 million) against a challenging comparison (F4Q12 sales rose 126%).

- **During prepared remarks, management attributed the decline in Japanese sales to "significant stockpiling by wholesalers in Japan" during F4Q12.** Indeed, F4Q13 faced a very challenging comparison from F4Q12: Japanese sales rose from JPY 10.5 billion in F3Q12 to JPY 12.0 billion in F4Q12, before falling to JPY 7.3 billion in F1Q13.
- **Management did also acknowledge that the Nesina franchise is not growing as much as expected, as the DPP-4 inhibitor class is becoming increasingly "commoditized" (especially in the US).** The DPP-4 inhibitor class is in an increasingly crowded marketplace in both the US and Japan, and it increasingly faces competition from SGLT-2 inhibitors, another oral drug class with generally greater efficacy (although a slightly less clean safety profile). Still, we certainly see room for this class to grow, especially as FDC (fixed dose combinations) take hold. Historically, DPP-4 inhibitors have been very especially popular in Japan, perhaps due to their theorized greater efficacy in East Asian populations. Certainly, they have also been popular with providers in the US, especially due to their clean safety profile, helping the class grow to over $8 billion in sales annually (as of the end of 2013). Nesina's post-launch performance in the US is particularly disappointing, as Takeda management has previously characterized the US as a major opportunity area for the product - hopefully F4Q13 represents only a temporary hiccup. Differentiation in the DPP-4 inhibitor class is difficult, but we imagine that a fixed-dose combination with the weight loss medication Contrave (naltrexone/bupropion - see below) could offer Nesina a substantial leg-up.
- **For context, in calendar 1Q14, most members of the DPP-4 inhibitor class experienced sluggish sales performance.** Merck's class-leading Januvia (sitagliptin) fell 3% to $860 billion, and we calculated that AZ's Onglyza (saxagliptin) fell 4% to $194 million. Lilly's share of Tradjenta (linagliptin) revenue grew 81% to $77 million (albeit from a much lower base than most of its competitors). Novartis' Galvus (vildagliptin) was the strong performer of the quarter, growing 15% to $308 million, perhaps because it is only being marketed outside of the US (where the DPP-4 inhibitor class slowdown has been particularly prominent).
- **Takeda forecasts that for FY2014, global Nesina sales will rise to JPY 50 billion.** That would represent growth of 24% from FY2013, indicating that management believes that the franchise can rebound from a challenging past year.

2. Takeda announced that it will not continue development for its once-weekly DPP-4 inhibitor trelagliptin (SYR-472) in the US or EU due to the high development costs necessary for approval in those geographies, particularly outcome studies. We had suspected this decision for some time, as the product appeared to be stalled in US/EU phase 2 since 2008. However, the announcement is still very disappointing, and serves as one of the most explicit examples we have seen of the FDA 2008 CV guidance's impact on drug development and patient access to therapies. During Q&A, management stated that the company is still considering its options, but that the return on investment for SYR-472 simply will not be high enough if the company is required to do an outcomes study.

- **Trelagliptin was filed for regulatory approval in Japan in March of this year (read our report).** Takeda's announcement opens the field for Merck's once-weekly DPP-3 inhibitor MK-3102 (omarigliptin), which is in phase 3 in the US and EU. Zydus Cadilla is also developing a once-weekly DPP-4 inhibitor, ZYDPLA1, which entered phase 1 late last year.
- **How patients will perceive the value of a once-weekly agent as compared to once-daily agents remains to be seen** - certainly it will be an advantage for some, perhaps younger patients or the newly diagnosed and should increase adherence overall. We look forward to seeing dQ&A data on this front (write Richard.wood@d-qa.com for more details). Merck presented the results of a discrete-choice experiment at last year's ADA (read our coverage), demonstrating that only 67% of patients would prefer a once-weekly oral diabetes drug to a daily drug, and that the average patient would only be willing to pay ~$6 more per month for once-weekly convenience.

3. Actos (pioglitazone) continued its downward trend, falling 48% year-over-year as reported and 25% sequentially to JPY 7.1 billion (~$69 million). In Japan, where quarterly sales appeared to hold steady at around JPY 4 billion (~$40 million) through much of calendar year 2013, sales fell to JPY 3.0 billion (~$30 billion) in F4Q13. US sales have been on a continuous sharp downtrend over the past year. The results demonstrate how greatly pioglitazone's genericization, as well as safety fears regarding cancers and bone health, has impacted the former blockbuster drug's performance.

- **For the full fiscal year 2013 (April 2013 - March 2014), Actos sales fell 70% to JPY 37 billion (~$370 million).** The company forecasts sales to total JPY 38 billion (~$380 million) for FY2014, indicating a belief that the franchise's decline will level off. Interestingly, the company's financial data book broke out ex-Japan sales by geography, demonstrating significant differences in geographic performance in FY2013. During RY2013, sales in North America and Latin America fell 93%, while sales in Europe and Russia/CIS fell a more modest 5%. Interestingly, sales in "Asia and Other" (ex-Japan) rose over 50%. The company forecasts that sales in North American and Latin America will rebound, nearly doubling from JPY 6 billion (~$60 billion) in FY2013 to JPY 12 billion (~$120 million) in FY2014. The forecast indicates that the growth seen in "Asia and Other" is not expected to continue into FY2014.
- **Takeda is currently embroiled in a major series of ~7,000 patient lawsuits in the US and elsewhere regarding the alleged hiding of cancer risks associated with Actos.** In April, Takeda and co-defendant Lilly were found liable for a whopping $9 billion in punitive damages in the case of Terrence Allen, et al v. Takeda (read our report). This total will almost certainly be reduced to the neighborhood of <$15 million upon appeal due to a proportionality precedent dictated by the Supreme Court, but that sum is still significant given the number of other lawsuits. Under an agreement between the two companies, Takeda is responsible for indemnifying Lilly for legal expenses and damages related to Actos litigation, but we learned during Lilly's 1Q14 Update that Takeda is challenging this agreement. During Q&A, management noted that the punitive damages will likely be reduced sharply, and that the company intends to appeal the decision. Management did not discuss whether the company might pursue a settlement.

4. During Q&A, management commented on how the partnered obesity medication Contrave (naltrexone/bupriopion) will be a linchpin in Takeda's broader cardiometabolic portfolio. Company Chief Medical and Scientific Officer Dr. Tadataka Yamada noted that the diabetes market is "saturated" with products that are good at controlling blood sugar, and that new drugs will increasingly need to go beyond diabetes and address other components of the metabolic syndrome, especially weight. In line with Orexigen management's guidance from the company's 4Q13 update, Dr. Tadataka suggested that Takeda and Orexigen are pursuing a diabetes indication for Contrave, as well as potential fixed-dose combinations with existing products in the company's portfolio (including Nesina). We have indeed seen a blurring of lines between diabetes and obesity therapy - Arena/Eisai's Belviq (lorcaserin) and Vivus' Qsymia (phentermine/topiramate) have fairly strong glycemic improvement data in hand, and Novo Nordisk has developed a higher dose of its diabetes medication Victoza (liraglutide) for obesity.

- **Takeda believes that US regulatory approval for Contrave is both likely and imminent (PDUFA date of June 10).** During the presentation, management forecast an increase in commercial investments in the US over the course of 2014 in preparation for the drug's launch. Management reiterated that interim results from the drug's CVOT (the Light Study) support CV safety, which was the main reason for the drug's initial FDA Complete Response Letter.

5. During Q&A, management provided a teaser of Takeda's earlier-stage diabetes portfolio, sharing that the company is working on a GLP-1/GIP dual agonist, a compound named TAK-648, and an undisclosed peptidase inhibitor. Unfortunately, the call translation to English may have muddled the exact names of these compounds, and none are listed on the official company pipeline as of yet. The main point management wished to share about these three candidates is that all (at least in animal models) demonstrated profound weight loss in addition to glycemic benefits, a feature that Takeda believes is necessary to effectively compete in the increasingly crowded diabetes drug market. Other GLP-1/GIP dual

agonists in development include Roche/Marcadia's MAR709, currently in phase 1 - preclinical work on the class demonstrates comparable A1c lowering to GLP-1 single agonists without an impact on gastric emptying.

QUESTIONS AND ANSWERS

Q: In the diabetes area, where you have a very strong position and presence, you are now launching a drug that is a once-weekly formulation. In the future, in this area, do you have any plan to develop a new drug with a concept like Actos? What kind of policy do you have for your future in diabetes?

A: We are not exiting the diabetes area. We have considered that many times in the past - it's true that in developed countries it is already a mature market. But on the other hand, in the developing and emerging markets, diabetes is increasing at a very rapid rate. The market is expanding, and it is really the market for new innovative drugs and for generics.

A: In Japan, there is a high unmet medical need in diabetes, but lowering blood sugar is not sufficient. We think that SYR-472 might be able to contribute to patients with milder diabetes and higher CV risk. On Nesina, we believe the product can still contribute to medical therapy and to the company in Japan.

A: From a global standpoint, in diabetes, we believe that the market is saturated with products that are good at controlling blood sugar, but we believe that the market is going to move towards a requirement that molecules not only address diabetes, but more broadly address the metabolic syndrome, and specifically weight loss. The focus of our pipeline has been on diabetes products that can induce weight loss in addition to controlling blood sugar. In this regard, we have Contrave, which we are looking at carefully to assess whether we should progress that towards a diabetes indication, and potentially combinations with existing products that we have in our portfolio. Contrave induces significant weight loss, and interim data from our outcomes trial, the Light Study, shows evidence of cardiovascular safety. On that basis, Contrave is moving towards registration, with a PDUFA date of June 10.

Earlier in our portfolio, we have three assets that are in the clinic or about to enter the clinic very soon. These assets, including TAK-648, a GLP-1/GIP co-agonist, and a peptidase inhibitor, demonstrate a profound ability to cause weight loss in addition to having major effects on controlling blood sugar, at least in animal models. We are looking towards the future and asking what we need to do to compete. We believe that new products will have to address not just diabetes, but also metabolic syndrome, specifically related to weight loss.

Q: Regarding SYR-472, how will it be positioned in the US market?

A: SYR-472 is currently not being developed for the US market. We will explore the possibility. We have had deep discussions in-house, and our conclusion is that the opportunity is not very attractive, and therefore at the moment we are holding the program. As you know, Merck entered into phase 3 for their once-weekly formulation - having that information, we are not sure if we should review this. Unless we have some indication that we will not have to do an outcome study, which you know are very expensive and time-consuming, and given the patent position of SYR-472, it is not clear that we will be able to complete an outcomes study and a full registrational trial to obtain a sufficient return on investment.

A: With both specialists and general physicians in Japan, we have confirmed that there is potential for a once-weekly agent. The potential for DPP-4 inhibitors in Japan is now considered to be greater than was originally expected. It is quite efficacious, and good in terms of hypoglycemia.

Q: For the Actos lawsuit, to avoid the risk of a huge punitive payment, is there any possibility that you might pursue a settlement?

A: Settlement is always one of our options, but at this moment, I cannot answer your question. As for the punitive damages, which are $6 billion to us and $3 billion to Lilly, there is a proportionality rule in the US for the amount of a punitive damage. Generally, the guideline is for punitive damages within ten times the amount of the compensatory damages. What the judge might decide is unknown, but we do not expect that will be the final amount we have to pay.

--by Manu Venkat and Kelly Close