MEMORANDUM

Novartis 4Q14 - Galvus totals $295 million in 4Q14, slowing due to withdrawal from German market; Move into digital medicine with Qualcomm - January 27, 2015

Executive Highlights

- Sales of the DPP-4 inhibitor Galvus (vildagliptin), marketed ex-US only, fell 1% in constant currencies (10% as reported) in 4Q14 to $295 million, continuing to suffer following its withdrawal from the market in Germany due to price negotiations.
- Lucentis (for diabetic macular edema and other ophthalmologic indications) grew 1% in constant currencies and declined 7% as reported in 4Q14 to $588 million.
- Novartis' recently announced joint investment company with Qualcomm Ventures signals a move into the exciting field of digital medicine.
- Recent mentions of the Google smart contact lens partnership continue to focus less on the glucose sensing application relative to other indications.

This morning, Novartis CEO Mr. Joseph Jimenez led the company's 4Q14 financial update. Below are our top five highlights from the presentation, followed by relevant Q&A.

1. The DPP-4 inhibitor franchise Galvus (vildagliptin) declined 1% in constant currencies (10% as reported) to $295 million in 4Q14 due largely to the cessation of sales in Germany; the franchise's FY2014 revenues totaled $1.32 billion, up 2% as reported and 6% in constant currencies.

2. During Q&A, management highlighted Novartis' new joint investment company in digital medicines with Qualcomm Ventures (an investor in wireless technologies and digital health).

3. Management highlighted the collaboration with Google as one of Alcon's (its eye division) "important" moves of the year, emphasizing the accommodating lens project without specific mention of the glucose-sensing contact lens.

4. Novartis' portfolio of diabetes drugs remains largely unchanged, with its SGLT-1/2 dual inhibitor LIK066 remaining in phase 2.

5. The ophthalmologic drug Lucentis (intravitreal ranbizumab) for diabetic macular edema and other indications grew 1% in constant currencies in 4Q14 but declined 7% as reported to $588 million; FY2014 sales grew 2% as reported (5% growth in constant currencies) to $2.44 billion, driven by expanded indications and the new pre-filled syringe.

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TOP FIVE HIGHLIGHTS

1. Global sales of the Galvus (vildagliptin) franchise declined 1% in constant currencies and 10% as reported in 4Q14 to $295 million. Sequentially, sales grew very slightly by ~1% as reported

following an 11% sequential decline in 3Q14. For the full year 2014 the Galvus franchise grew 2% as reported (6% growth in constant currencies) to $1.22 billion, with strong growth earlier in the year compensating for a more disappointing 2H14. As a reminder, Galvus and its metformin fixed-dose combination Eucreas are only marketed outside of the US. The financial supplement mentioned that Novartis' focus with Galvus is patients uncontrolled on metformin monotherapy, with potential to expand usage in elderly and renal-impaired patients.

- **A driver of the sub-par results for Galvus in 4Q14 was the product's withdrawal in Germany as of July 1, 2014.** This depressing news was disclosed in Novartis' 2Q14 call, in which management announced that Galvus will no longer be marketed in Germany following a failure to negotiate an acceptable price with German authorities. The Galvus franchise took a significant hit from this decision as Germany represented ~9% of total Galvus sales ($57 million) in 1H14. The presentation slides also noted that full-year growth for the franchise excluding Germany would have been 15% in constant currencies (9% greater than what was reported with Germany) - another significant indication of how large of an impact this distribution halt had on revenues. On the other hand, while the 4Q14 financial update did not provide specifics on how the franchise is doing in other markets, the financial supplement highlighted that Galvus has "strong growth in many markets around the world" as the product is currently approved in more than 120 countries. Moving into 2015, we wonder if Novartis will thus push for greater uptake in these other markets to compensate for the loss in German revenues; the company did note that it aims to expand Galvus' usage in population segments of elderly and renal-impaired patients with diabetes although no specific marketing or promotion plans were detailed.
    - **As a reminder, this German distribution halt is a consequence of the country's Institute for Quality and Efficiency in Health Care (IQWiG) ruling that Novartis' Galvus showed "no additional benefit" relative to sulfonylureas in 3Q13.** IQWiG and the German Federal Joint Committee (G-BA) have been very harsh in diabetes with most of its negative rulings being frustratingly based upon technicalities of trial design rather than through balanced comparative efficacy assessments. Galvus' decision was part of a class-wide review of DPP-4 inhibitors' cost effectiveness, which resulted in similarly negative rulings for Lilly's Tradjenta (linagliptin) and AZ's Onglyza (saxagliptin) as monotherapy, but notably not for Merck's Januvia (sitagliptin). This "no additional benefit" ruling generally subjects the products to generic-level pricing, which most manufacturers are unwilling to tolerate. The IQWiG vendetta has impacted other drug classes as well, but intriguingly, AZ managed to renegotiate with German regulatory authorities on pricing for Forxiga (dapagliflozin) following the withdrawal of its product, leading to a re-launch - perhaps other companies can replicate that success, although it may involve a degree of concessions on pricing - it is impossible to say what accounts for AZ's success in this realm.
- **As we have noted before, there has been a broader slowdown in the DPP-4 inhibitor class in recent quarters due to a number of factors, including:** (i) the growing pricing pressure payers, driven by increased focus on cost-effectiveness; (ii) the increased price competition due to the entry of more competitors; (iii) the introduction of SGLT-2 inhibitors, which have many of the same benefits but more pronounced for many (greater A1c drop) although also have more pronounced side effects (but that are viewed as manageable); (iv) the slowdown of patient transfers from TZDs to other oral agents (albeit, due in part to the decreasing number of patients still on TZDs); and (v) the reverberations of the incretin-pancreatitis/pancreatic cancer scare peaking in 2013. Keys to reversing this trend will be new longer-acting formulations (such as the excitement surrounding Merck's phase 3 once-weekly omarigliptin that was discussed at EASD), fixed dose combinations, and some good luck on the safety front (it will be a big deal to see whether concerns of heart failure will be disproven by the TECOS CVOT for Januvia, which should be announced at ADA 2015]).

- **We are curious to see how much of DPP-4 inhibitors' 2014 performance will contribute to recent years' trends of significant slowdown.** The DPP-4 inhibitor class brought in a total $8.6 billion in revenues in 2013, up 10% growth from 2012's revenues of $7.8 billion. That said, the market growth of 8% in 4Q13 and 10% in 2013 was,strikingly lower than the whopping 24% growth seen in 4Q12 and 31% growth in full-year 2012 - see our 4Q13 roundup for more details. A year earlier, in 2012, growth was far higher, especially internationally - US growth hit 23% in 2012, compared to international growth of 39%. Novartis is the first DPP-4 inhibitor company to report financial results this earnings season; in all, DPP-4 inhibitors brought in $2.4 billion in 4Q13 and $2.2 billion in 4Q12. In order to assess what the DPP-4 inhibitor class will do as a whole, we look forward to the 4Q14 updates of Lilly, Merck, Takeda, and AZ who will report on January 30, February 4, February 4, and February 5, respectively.

2. Novartis highlighted its new joint investment company with Qualcomm Ventures, with the goal of supporting digital medicines that go "beyond the pill." As background, Qualcomm Ventures is the venture investment group of Qualcomm Incorporated that invests in wireless technologies and digital health. Two weeks ago, Novartis announced that the company established a joint investment company of up to $100 million to support early stage companies with technologies, products, or services in digital medicine. According to the press release, Novartis' management highlighted that digital medicine has the potential to make moves into personalized and precision medicine and that the new era of mobile apps and wearable devices can have significant impacts in the pharmaceutical industry. For diabetes in particular, we could easily envision apps that promote adherence or wearables that provide input on activity levels to guide insulin dosing; the opportunities are essentially endless. This partnership with Qualcomm is notable as various players in healthcare are increasingly moving into digital and mobile health - for example, see our recent coverage of CES to learn more about Walgreens' collaboration with Qualcomm Life.

3. Novartis' references to Google's joint smart contact lens project continue to shift away from the diabetes application towards broader ophthalmologic indications. During the presentation during the earnings call, Mr. Jimenez only referred to the "accommodating lens" project, which (as we understand it) refers to the lens application for presbyopia and myopia. We noticed a similar lack of a specific mention for the diabetes glucose sensing application at Novartis' presentation at JP Morgan. The company has not mentioned any tangible updates on the partnership following its unveiling during Novartis' 2Q14 call - that said, Big Pharma doesn't typically update frequently early stage projects. Indeed, it may be too early to read to far very brief mentions of the Google project, but these recent remarks give us reason to wonder whether the glucose-sensing contact lens project may not be as of higher priority as much as it was formerly expressed. After all, Novartis' established experience is more in general ophthalmologic therapies (via Alcon) than in diabetes technology. However, the shift in focus may also be due to the differences in the timelines of the two different applications (see below).

- **As background, in 2Q14, Novartis presented the Google partnership as one of the company's biggest 2Q14 accomplishments with a greater focus on the development of a glucose-sensing contact lens.** Although the 2Q14 call did not reveal any specific timelines, management had suggested during that call's Q&A session that the glucose-sensing project is more likely to be a few years out rather than a decade out while the autofocus lens technology for presbyopia (where the lens of the eye loses its ability to focus with age, making it difficult to see objects up close) was mentioned as a longer-term project. The presbyopia project was added later onto the partnership as the collaboration experienced a notable broadening of scope since Google[x]'s initial announcement in January 2014, which was completely focused on diabetes and the development of a glucose-sensing contact lens. However, the new in-licensing partnership introduced presbyopia as a new focus area for Novartis, which seems to have been gaining more of the attention recently.

4. No updates were provided on the rest of Novartis' diabetes pipeline, which includes the SGLT-1/SGLT-2 dual inhibitor LIK066 as well as LEZ763, an unspecified phase 2 oral once-daily treatment for type 2 diabetes.

- **The SGLT-1/SGLT-2 dual inhibitor LIK066 remains in phase 2, with a regulatory submission not expected before 2018 (consistent with previous guidance).** The company's clinical pipeline puts the candidate's planned filing under the timeline category of 2019 or later. A 12-week dose-finding study of LIK066 was withdrawn in April of last year prior to enrollment, according to ClinicalTrials.gov (Identifier: NCT01824264), while a study testing the candidate's effect on glucose absorption was completed in January of last year (ClinicalTrials.gov Identifier: NCT01915849). Both LIK066 and its main SGLT-1/2 dual inhibitor competitor, Lexicon's LX4211, have had some trouble moving into phase 3 for type 2 diabetes, although LX4211 will soon be moving into phase 3 for type 1 diabetes.
- **In September, Novartis completed a phase 2 trial of LEZ763, an unspecified oral once-daily treatment for type 2 diabetes (ClinicalTrials.gov Identifier: NCT01619332).** The status of this trial has not changed since 4Q13. This candidate has flown under the radar for quite a ways, as (to our knowledge) we have not heard any mention of this compound from management and it continues to not appear on the company pipeline.

5. The ophthalmologic drug Lucentis (intravitreal ranbizumab) for diabetic macular edema and other indications grew 1% in constant currencies and declined 7% as reported to $588 million in 4Q14. Sequentially sales declined 4% as reported from 3Q14, following a ~1% decline in 3Q14. Lucentis' full-year 2014 sales experienced YOY growth of 2% as reported (5% growth in constant currencies) to $2.44 billion. During the presentation, management credited the franchise's performance in the face of new competitors to market expansion from new indications and the continued rollout of the new pre-filled syringe. However, weak results for Lucentis vs. Regeneron's Eylea (aflibercept) in a recent NIH study (see item #3 in our Novartis 3Q14 Report) may stiffen the competition in coming quarters.

- **According to management, the new indications contributed to 41% of sales in 2014 (up from 27% in 2013), reaching $1 billion in revenues for the full year;** in 4Q14, these indications contributed 43% of sales. These additional non-age-related macular degeneration (non-AMD) indications also helped offset the impact of competition in the wet AMD indication.
- **Management also highlighted that the pre-filled syringe form was successfully launched in key markets** including France, Italy, Spain, UK, Japan, and Australia. Specifically, this form was successfully launched in Belgium, Denmark, Spain, Netherlands, and Australia in 3Q14.
- **As a reminder, Novartis markets Lucentis ex-US only.** Roche/Genentech market the drug within the US, and received FDA Priority Review status for a diabetic retinopathy indication in October - a very exciting development for the product, although not one that Novartis will benefit from directly.
- **Novartis' press release noted that Alcon has initiated a phase 3 trial of the wet age-related macular degeneration (AMD) candidate RTH258 (formerly ESBA 1008), after positive phase 2 results.** This candidate is a novel single chain antibody fragment that management expressed excitement about as a "follow on next-generation product in the space." The phase 3 trial (ClinicalTrials.gov Identifier: NCT02307682) looks at the efficacy and safety of RTH258 vs. Eylea (aflibercept) and began dosing in the first patient this past December. Management noted that the trials aim to enroll about 1,700 patients. During Q&A, we learned that two phase 2 trials took place, investigating the efficacy of the candidate vs. both Lucentis and Eylea. Management mentioned that these results have been positive and that some of these results will be presented at the 38th Annual Macula Society Meeting in February, where the company will share further details about the product's profile, dosing, and duration. As wet AMD stands as a complication of diabetes, we are curious to see how this new candidate measures up to existing products for similar indications such as Lucentis.

QUESTIONS AND ANSWERS

Q: Regarding the RTH258 candidate in the pipeline, I see it moved to phase 3. The press release mentions positive phase 2 data vs. both Lucentis and Eylea. Can you just give us some more information there? Did it show superiority to Eylea in the Phase 2 study and when can we expect to see that data?

A: This compound, formally known as ESBA 1008, is the novel single-chain antibody fragment that we're really excited about in the treatment of wet AMD as a follow on next generation product in the space. So in December, we did initiate phase 3 clinical trials to evaluate the safety and efficacy of RTH vs. Eylea. There are two studies in our phase 3 clinical program. We had our first patient, first dose in mid-December, and we aim to enroll about 1,700 patients. We had two pivotal phase 2 studies, one vs. Lucentis, one vs. Eylea. The data that we haven't released yet will be presented at the 38th Annual Macula Society Meeting next month, where we'll be able to share a bit more regarding the profile of the product, its dosing frequency advantage, and the longer duration of action that we're seeing with that product.

Q: Could you just comment on what the business development priorities are within pharma?

A: There are three components to the approach. One is to build more depth into the key franchises, just as we did with the GSK deal. Second is to go up to other game-changing therapies; as you saw, we signed the University of Pennsylvania deal around cell and gene therapy. Last but not least, we are starting some efforts into digital medicine; you saw that we signed and created a new joint venture company with Qualcomm last week, which will bring to us the digital technologies. We believe we need to surround our medicines within this space in order to improve patient outcomes.

-- by Melissa An, Manu Venkat, and Kelly Close