Closer Look

MEMORANDUM

Novartis 3Q13 - Galvus up 37% from 3Q12; Lucentis falls 2% but experiences double digit volume growth - October 23, 2013

Executive Highlights

- Sales for the Galvus (vildagliptin) franchise totaled $316 million, up 37% as reported from 3Q12, the highest year-over-year growth figure for the franchise since 1Q12.
- A possible "worst-case" scenario after Germany's G-BA comparative efficacy ruling on Galvus is that the franchise may be withdrawn from the German market.
- Lucentis revenue fell 2% to $581 million, despite double-digit volume growth.

Novartis CEO Joseph Jimenez led the company's 3Q13 financial results call yesterday morning. During 3Q13, Galvus (vildagliptin) and Eucreas (vildagliptin/metformin) revenue totaled $316 million, up 37% as reported (46% in constant currencies) from 3Q12 and up 9% sequentially. Total Galvus franchise sales for the first nine months of 2013 are $872 million. If the franchise maintains this pace, it will reach blockbuster status (annual sales of at least $1 billion) for the first time in its history. In the supplementary materials, Novartis attributed these fairly strong results to new patient gains that resulted from new add-on indications. We wonder if the franchise's growth in 3Q13 may be a bellwether for improved performance of the entire DPP-4 inhibitor class, after the class' disappointing 2Q13 growth (12% from 2Q12). The consensus that currently available data do not support an association between incretin therapies and pancreatic disease could potentially contribute to a rebound in growth. On the negative side, management also discussed the German Federal Joint Committee (G-BA) ruling that Galvus demonstrates "no additional benefit" in terms of glucose-lowering efficacy compared to sulfonylureas, which means that the company cannot negotiate on pricing for the product. The G-BA made the same ruling for Lilly/BI's Trajenta (linagliptin) and BMS/AZ's Onglyza (saxagliptin). However, the body ruled that BMS/AZ's Komboglyze (saxagliptin/metformin), along with Merck's Januvia (sitagliptin) and Janumet (sitagliptin/metformin), showed "hints of an added benefit." The "worst-case" outcome of the G-BA's ruling on Galvus, according to Novartis, is that the franchise may be pulled from the German market. This development highlights how challenging the European reimbursement environment is right now. We imagine it is highly frustrating for companies to receive poor comparative effectiveness rulings (and, as a result, lose the ability to negotiate on pricing) based not on the products' efficacy, but rather on study design choices that are viewed as acceptable elsewhere in Europe and in the US. That said, it certainly shows that companies need to work out ahead of time what various regulatory requirements will be.

Novartis-recognized revenue from anti-VEGF agent Lucentis (intravitreal ranibizumab) for ocular indications including diabetic macular edema (DME) fell 2% year-over-year as reported and fell 1% in constant currencies to $581 million in 3Q13. Management noted that volume growth was actually in the double digits and that revenue suffered from a negative pricing impact due to one-time price reductions needed to secure reimbursement for new indications. The proportion of Lucentis revenue coming from the drug's "new indications" (DME, retinal vein occlusion [RVO] and choroidal neovascularization [CNV] secondary to pathologic myopia) continues to rise - from 16% in 3Q12 to 25% in 3Q13, leading management to comment that the markets for Lucentis are continuing to expand. This is certainly true in diabetes patients.

Development of Novartis' SGLT-1/SGLT-2 dual inhibitor LIK066 appears to be progressing; while a 12-week phase 2 dose-finding study of the agent looks to be a bit behind schedule according to ClinicalTrials.gov, a new phase 2 study testing the candidate's effect on gut glucose absorption has been

registered. We also noticed a new phase 2 trial for an unspecified oral one-daily treatment of type 2 diabetes, LEZ763 (ClinicalTrials.gov Identifier: NCT01619332).

GALVUS FRANCHISE FINANCIALS AND DEVELOPMENT

- **Galvus (vildagliptin) and Eucreas (vildagliptin/metformin) 3Q13 sales totaled $316 million, up 37% from 3Q12 (46% in constant currencies) and up 9% sequentially.** This is the franchise's highest year-over-year reported growth since 1Q12. Total Galvus franchise sales for the first nine months of 2013 are $872 million. If the franchise maintains this pace, it will reach blockbuster status (annual sales of at least $1 billion) for the first time in its history. Both Galvus and Eucreas are available in over 110 countries, though they are not available in the US, prevented by safety issues FDA highlighted that made Novartis drop its submission. The supplementary presentation materials note that growth was strong across multiple markets, including Europe, Japan, Latin America, and Asia Pacific (similar to 2Q13). The franchise's growth was driven by a continued marketing focus on patients who are uncontrolled on metformin, as well as gains obtained through new add-on indications. As an example, earlier in 2013, Galvus received a new add-on indication in Japan for use with any oral antidiabetic agent or insulin. Previously, Galvus could only be prescribed as a monotherapy or in combination with a sulfonylurea.
- **Galvus and Eucreas' results are especially notable given the slowdown in the overall DPP-4 inhibitor market's growth we have seen in 1H13.** In 1Q13 and 2Q13, overall DPP-4 inhibitor growth was just 10% and 12%, respectively, strikingly lower than the 40% growth seen in 2Q12, the 24% growth seen in 3Q12, and the 25% growth seen in 4Q12. For more details on the performance of the DPP-4 inhibitor class in 2Q13, please see our 2Q13 Diabetes Drug and Device Roundup at http://www.closeconcerns.com/knowledgebase/r/735dddcb. We wonder if the Galvus franchise's performance in 3Q13 will be a bellwether of strong 3Q13 performance in the entire DPP-4 inhibitor market.
    - **The upswing in the DPP-4 inhibitor market growth (if it is indeed that) could be due to the reduced concerns over incretin therapies and pancreatic disease.** On July 30, the EMA's CHMP released a statement indicating that its review of currently available evidence on incretins and pancreatitis/pancreatic cancer did not adequately support any new concerns regarding incretin safety (for more information, please see our July 30, 2013 *Closer Look* at http://www.closeconcerns.com/knowledgebase/r/72400858). We have also seen statements by high-profile organizations such as the ADA, EASD, and Endocrine Society supporting this view, and at scientific meetings this summer and fall we have seen a growing consensus to the same effect At this year's ADA, Dr. Vanita Aroda (MedStar Health Research Institute, Hyattsville, MD) provided an overview of the issue and argued that current clinical evidence does not alter the risk/benefit profile of incretin therapies (see page 23 of our ADA 2013 Incretins Report for more information at http://www.closeconcerns.com/knowledgebase/r/6001b62d). More recently, at EASD, Dr. Juris Meier (St. Josef Hospital, Bochum, Germany) delivered a compelling talk in which he explained limitations and weaknesses of the data that raised the initial red flag. Dr. Meier also shared a meta-analysis in which the pooled risk estimate for pancreatitis was neutral - for more details on that presentation, please see page six of EASD Day #5 Report at http://www.closeconcerns.com/knowledgebase/r/a436c2c2.
- **Galvus, like much of the DPP-4 inhibitor class, faces a challenging comparative effectiveness evaluation in Germany.** Earlier this month, the German Federal Joint Committee (G-BA) ruled that Galvus and Eucreas provide "no additional benefit" compared to sulfonylureas, when the goal is to reduce blood glucose to near-normal levels.
    - **The ruling was based on a retrospective comparative benefit assessment of the entire DPP-4 inhibitor class conducted by the German Institute for Quality and Efficiency in Health Care (IQWiG).** The body ruled that the Galvus franchise,

along with Lilly/BI's Trajenta (linagliptin) and BMS/AZ's Onglyza (saxagliptin), demonstrated "no additional benefit." The body's decision on Merck's Januvia (sitagliptin) franchise was split: it ruled that sitagliptin monotherapy showed no additional benefit, but ruled that Janumet (sitagliptin/metformin) showed "hints of an additional benefit" when compared with sulfonylurea. Notably, IQWiG's ruled negatively for most of the products not based on the drugs' efficacy data, but rather were because the drugs' clinical trial programs did not follow the G-BA's strict rules on the choice and administration protocol for comparator therapies.

  - **IQWiG's findings are communicated to the G-BA, which makes the final decision, and is known to have a slightly more flexible viewpoint than IQWiG.** The G-BA deviated from IQWiG's recommendations for BMS/AZ's Onglyza franchise and Merck's Januvia franchise: it said that Januvia has hints of an additional benefit both as metformin and in combination with metformin, and ruled that Kombiglyze (saxagliptin/metformin), but not saxagliptin monotherapy, also had hints of an additional benefit. For more details on the Onglyza and Januvia decisions, please see our BMS 2Q13 report at http://www.closeconcerns.com/knowledgebase/r/db276774 and our Merck 2Q13 report at http://www.closeconcerns.com/knowledgebase/r/8ac8afbc. However, the G-BA stuck with IQWiG's across-the-board negative rulings on Galvus and Trajenta, meaning that the drugs would be subject to reference pricing.
  - **During Q&A, Novartis remarked that a pricing discussion is underway in Germany, and that a possible worst-case scenario is that the franchise will be pulled from the German market.** As background, after receiving a "no additional benefit" ruling from the G-BA, Lilly/BI decided not to launch Trajenta in Germany. We think it is a major danger that the G-BA's decision will restrict German diabetes patients' choices within this remarkably safe drug class. Although we understand the reasons for the increasingly challenging reimbursement environment in Europe, we are disappointed that German patients may lose access to a number of valuable therapies because the drugs' clinical trial designs (which have been accepted by regulatory bodies around the world as valid, including in the US and EU) did not meet the G-BA's rather narrow guidelines. It could be difficult for drug manufacturers to tailor-make their clinical trials to meet the G-BA's guidelines, and we hope that the agency considers re-evaluating its process to ensure that German patients are not deprived of access to other valuable therapies.

- **Another challenge the DPP-4 inhibitor class could face is growth of the SGLT-2 inhibitor class though ultimately we believe companies with access to both will win.** Novartis is not affected by the strong performance of J&J's Invokana (canagliflozin) in the US, as neither Galvus nor Eucreas are available in the US market - as background, J&J recently reported during its 3Q13 update that Invokana has captured a 17% new-to-brand prescription share in the US. However, the SGLT-2 inhibitor class may affect Novartis' sales in markets such as Japan (Merck/Astellas are waiting for a decision on its SGLT-2 inhibitor ipragliflozin, as is Taisho for its luseogliflozin) and Europe, where BMS/AZ's Forxiga (dapagliflozin) is on the market. That said, the availability of dapa didn't seem to affect Galvus too much in 3Q12! Given that SGLT-2 inhibitors share DPP-4 inhibitors' advantage of oral administration, but are thought to have greater A1c-lowering efficacy, as well as at least a slightly less benign side effect profile, we anticipate that the SGLT-2 inhibitor class' growth will dampen prospects for DPP-4 inhibitors in the short to medium term - how large this effect will be remains to be seen. Longer term, we believe that companies with access to developing and commercializing fixed dose combinations will be winners. That said, that assumes formulation and development goes well and isn't too complicated, which is hard to assess at this stage.
- **Additionally, it seems that Galvus may be dragged in to the discussion of the heart failure hospitalization signals seen in recent CVOTs for other DPP-4 inhibitors.** As background, we heard results from SAVOR-TIMI 53 and EXAMINE, the cardiovascular outcomes

trials for BMS/AZ's Onglyza (saxagliptin) and Takeda's Nesina (alogliptin) at ESC's annual scientific meeting this year; see our ESC 2013 Day #1 Report for more details at http://www.closeconcerns.com/knowledgebase/r/2a8925c5. SAVOR's treatment arm had a significant 27% increase in hospitalization for heart failure, while the alogliptin group in EXAMINE had a more modest increase that fell short of statistical significance (this might be due to the smaller size of EXAMINE's patient population). Neither signal was associated with a significant increase in CV mortality. During a very well attended symposium at EASD on the results of these two CVOTs, Dr. Naveed Sattar (University of Glasgow, Glasgow, UK) brought up the possibility that the heart failure signal may be a class-wide effect. Notably, he cited results from the VIVIDD study on Galvus that demonstrated that the drug had a significant impact on left ventricular end-systolic and diastolic volume. We do not think current data is not sufficient to prove such as class effect, but we will certainly be keeping an eye on the results of other CVOTs to see if such an effect emerges. We'll be interested at AHA to hear what the clinical implications are.

- **A phase 4 study (PREFER) comparing patient (and provider) preference for vildagliptin versus Novo Nordisk's Victoza (liraglutide) is now listed as completed on ClinicalTrials.gov.** It is somewhat difficult to interpret the timing of this trial given the information on ClinicalTrials.gov (Identifier: NCT01518101); in July, around the time of Novartis' 2Q13 update, no completion date was listed on the page and the 24-week study was listed as recruiting. However, as of the publication of this report, the page lists the completion date as October 2012. The trial enrolled 62 patients to receive 12 weeks of vildagliptin or liraglutide in a crossover fashion. While vildagliptin is associated with a lower hassle factor (oral administration versus injected), in the past, KOLs have stated that many patients prefer GLP-1 agonists due to the associated weight loss and increased efficacy. We will be interested to see which way the scales tipped (both figuratively and literally) in this study.
- **A phase 4 study sponsored by Novartis is recruiting that will compare vildagliptin vs. sitagliptin as an add-on to insulin.** The basis for this comparison, according to the ClinicalTrials.gov listing, is that vildagliptin and sitagliptin differ in their pharmacokinetic profiles and frequency of dosing. During Novartis' 2Q13 update, the completion date was listed as November 2013, but disappointingly the date has since been moved back to May 2014. The open-label, crossover study will enroll approximately 50 patients, and will assess the two drugs' glycemic efficacy (particularly postprandial blood glucose normalization) as well as their association with hypoglycemia (especially nocturnal hypoglycemia) and heart function (ClinicalTrials.gov Identifier: NCT01686932). We feel that the effect of hypoglycemia on heart function is a worthwhile topic to discuss in type 2 diabetes patients, given that research in type 1 diabetes patients has demonstrated a correlation.
- **ClinicalTrials.gov also lists a phase 4 trial evaluating the effect of vildagliptin on beta cell function and cardiovascular risk markers in type 2 diabetes patients.** While such data would be fantastic to see, the study's webpage has not been updated since March 2012, and the primary completion date is listed as November 2012. The one-year trial is to randomize 44 type 2 diabetes patients on metformin to either vildagliptin or glimepiride. The study's primary endpoint is postprandial increase in intact proinsulin levels (as an indicator for beta cell dysfunction), and secondary endpoints include blood pressure, A1c change, body weight change, and fasting plasma glucose (ClinicalTrials.gov Identifier: NCT01565096).
- **ClinicalTrials.gov continues to list a phase 3 study of vildagliptin for recent onset type 1 diabetes as not yet recruiting** (Identifier: NCT01559025). The trial is expected to randomize 44 people who have had type 1 diabetes for less than six months to either insulin alone or vildagliptin plus insulin for one year. Notably, the primary endpoint will be beta cell function - using an incretin therapy to slow the autoimmune destruction of beta cells is an exciting and certainly ambitious goal. Secondary endpoints include participants' immune and inflammatory profile, secretion of glucagon and GLP-1, and glycemic variability as measured by CGM. Novartis is collaborating on the trial with the Federal University of Säo Paulo (Säo Paulo, Brazil), the study's

sponsor. The trial's schedule still appears uncertain, as the study's original start date was August 2012, its primary estimated completion date is still listed as November 2012, and the posting has not been updated since March 2012. We are hopeful that Novartis still aims to complete this study, given the relative lack of pharmacotherapies (especially oral) for type 1 diabetes patients. On that note, we're hearing of more type 1 patients taking SGLT-2 inhibitors in combination with DPP-4 inhibitors - off label, though some are reimbursed by insurance for both.

- **A phase 3 trial investigating the use of Eucreas in Japanese patients is now recruiting.** Novartis commissioned the study to support the registration of the fixed-dose combination in Japan. The study will evaluate the efficacy and safety of LMF237 (the product code) in patients who are inadequately controlled by vildagliptin monotherapy. Both the 50 mg vildagliptin/250 mg metformin and the 50/500 mg doses will be tested, with A1c change over 14 weeks as the primary endpoint. The planned primary completion date is July 2014 (ClinicalTrials.gov Identifier: NCT01811485).
- **A few other notable trials for vildagliptin are listed on ClinicalTrials.gov.** A phase 4 study sponsored by Rio de Janeiro State University (Rio de Janeiro, Brazil) is investigating whether vildagliptin treatment may have vascular protective effects (ClinicalTrials.gov Identifier: NCT01827280). The trial, currently not yet open for recruitment, will study 40 obese female type 2 diabetes patients using metrics for endothelial function and cardiovascular health (estimated primary completion in February 2014). Another phase 4 study (VERIFY; ClinicalTrials.gov Identifier: NCT01528254) will study the durability of vildagliptin as an add-on to metformin in 2,000 type 2 diabetes patients. Its estimated completion date is in 2019.

OTHER DIABETES PIPELINE UPDATES

- **Novartis' SGLT-1/SGLT-2 dual inhibitor LIK066 was not mentioned during the call; however, ClinicalTrials.gov shows a new phase 2 trial investigating the drug's effect on intestinal glucose absorption.** The four-day trial is to enroll 12 type 2 diabetes patients, and test the rate of appearance of exogenous glucose after a meal (ClinicalTrials.gov Identifier: NCT01915849). Successful inhibition of the SGLT-1 glucose transporter should lead to a reduction of glucose appearance in the blood. The study's primary completion date is slated for December of this year.
    - **In addition, a 12-week phase 2 dose-finding study is registered on ClinicalTrials.gov but is still not open for enrollment** (Identifier: NCT01824264). This represents a significant delay from the planned start date of April 2013 (although the trial could actually be enrolling, as the ClinicalTrials.gov profile has not been updated since April of this year). The stated purpose of the study is to evaluate the efficacy, safety, and tolerability of the drug to inform dose selection for subsequent phase 3 trials. The trial is to enroll 491 drug naïve type 2-diabetes patients and randomize them to either one of seven doses of LIK066 (2.5 mg - 150 mg), sitagliptin, or placebo. The primary outcome is A1c change from baseline to 12 weeks.
    - **Lexicon is also developing an SGLT-1/SGLT-2 dual inhibitor, LX4211, which is expected to begin phase 3 testing later this year.** The company recently announced positive topline proof-of-concept results for the candidate in type 2 diabetes patients with renal impairment, many of who are unable to take selective SGLT-2 inhibitors.
- **Novartis has a phase 2 trial for an unknown candidate for type 2 diabetes (LEZ763) on ClinicalTrials.gov** (Identifier: NCT01619332). The candidate, which (in the trial) is administered orally once daily, is not listed on Novartis' company pipeline. The trial is designed to assess the drug's clinical safety, tolerability and PK/PD profiles. The estimated completion date was in August of this year.

OPHTHALMOLOGY

- **Novartis-recognized Lucentis revenue fell 2% year-over-year as reported and fell 1% in constant currencies to $581 million in 3Q13.** Sequentially, revenue rose 0.9% from 2Q13. As a reminder, Lucentis (intravitreal ranibizumab) is Novartis' injectable anti-VEGF agent for ocular indications (including diabetic macular edema [DME], but primarily wet age-related macular degeneration [wAMD]). Management noted that Lucentis revenue was negatively affected by one-time price reductions needed "to secure reimbursement for new indications." Volume growth was actually in the double digits, which management highlighted as demonstrating an underlying increase in demand. Lucentis' "new indications" (DME [for which it received approval in 2011], retinal vein occlusion [RVO], and myopic CNV) have grown from accounting for 16% of Lucentis sales by value in 3Q12 to 25% in 3Q13, leading management to conclude that these new markets are expanding. As a reminder, Novartis holds rights to Lucentis outside of the US and Roche/Genentech hold rights within the US.
- **The DME competitive landscape continues to be very active and includes several candidates.**
    - **Bayer/Regeneron's Eylea (intravitreal aflibercept, another VEGF-A inhibitor) may be approved for DME in the US mid-2014.** Eylea is already approved for AMD, and it is in three active phase 3 studies for a DME indication.
    - **Alimera Sciences/pSividia's Iluvien is an implantable device that releases fluocinolone acetonide (a corticosteroid) and has received approval for DME in several European countries in 2012 and early 2013.** Friday October 18, the FDA rejected Iluvien for the third time. The FDA's latest complete response letter suggested a new 12-month trial to address safety concerns (concerns were not specified in the company's press release), and indicated that the FDA was open to attempting to identify a patient population for whom the benefits outweigh the risks. We see it as unlikely that Alimera will have the funds to conduct a new trial - in 2Q13, it garnered only $179,000 in revenue from its launch of Iluvien in Germany and the UK, and it ended the quarter with $32 million in cash, cash equivalents, and investments.
    - **Allergan's Ozurdex (dexamethasone intravitreal implant) has been filed for DME and is in ongoingphase 2 and 4 trials for DME.** Dexamethasone is a corticosteroid, like Iluvien, and Ozurdex is already FDA-approved for macular edema following RVO.
    - **Ampio announced earlier in January that the FDA accepted the company's IND for Optina (oral low-dose danazol), and it is currently recruiting for a phase 3 study in DME.**
    - **iCo Therapeutics and JDRF's iCo-007, an antisense inhibitor of C-raf kinase, is currently in phase 2.**
    - **GSK's darapladib (a Lp-PLA2 inhibitor) completed a phase 2 study for DME in February 2013** (ClinicalTrials.gov Identifier: NCT01506895); results have not been released. Darapladib's oral administration would give it an advantage over the anti-VEGF treatments, which require injection.
- **DME drugs in preclinical development** include ActiveSite's plasma kallikrein inhibitor and KalVista's plasma kallikrein inhibitor. It is too early to speculate on the clinical success of these candidates, but they would have the significant advantage of being orally administered.
- For greater detail on all of the above-mentioned candidates, please see our Roche 1Q13 report at http://www.closeconcerns.com/knowledgebase/r/f5191b53.

Questions and Answers

Q: How do you see Lucentis performing in the coming quarters? When should we see volume offsetting the pricing pressure?

A: What I think you're asking is when we will start to reduce the price cuts that we used to negotiate to create market access for the new indications. Most of those price cuts came in the 2Q, some in 3Q, and some in 1Q. So if you project forward, you'd expect to see some of the volume begin to come through largely in the back half of next year. In terms of Europe and loss to healthcare reform, I believe it was about 6% for the quarter.

Q: Regarding Galvus, could you comment on the German G-BA assessment? What are the next steps there, and maybe quantify what sales are at risk in that market?

A: Most of you have probably read in the press that the German Federal Joint Committee, the G-BA, announced that they did a benefit/risk assessment of Galvus as well as a variety of other DPP-4 inhibitors, and they said that our product did not provide an additional benefit relative to sulfonylureas. So, there is now a discussion process that is underway where prices will be discussed. Hopefully we can find a way forward with them, but in the event that they ultimately choose not to be reasonable, then the product could potentially, as a worst-case scenario, go away in Germany. That would be a one-time impact on Galvus, but Galvus still has a lot of growth ahead of it, and we would manage our way through.

--by Manu Venkat, Jessica Dong, Hannah Deming, and Kelly Close