Closer Look

MEMORANDUM

Sanofi 2Q14 - Diabetes Division up 10%; US Lantus sales exceed €1 billion for the first time - July 31, 2014

Executive Highlights

- Global Diabetes Division sales grew 10% in 2Q14 as reported (16% in constant currencies) and rebounded 8% sequentially to €1.8 billion (~$2.5 billion).
- Global Lantus sales reached €1.6 billion (~$2.1 billion), up 11% as reported (16% in constant currencies), driven largely by 15% US growth.
- Toujeo (insulin glargine U300), currently under review in the US and EU, stands to be the first next-generation glargine to reach the market.

Sanofi provided its 2Q14 financial update this morning in a call led by CEO Mr. Chris Viehbacher. Below, we include our top ten highlights from the presentation, followed by selections from Q&A.

1. Global Diabetes Division sales grew 10% year-over-year (16% in constant currencies) and 8% sequentially to €1.8 billion (~$2.5 billion) in 2Q14, driven unsurprisingly by Lantus.

2. Lantus sales reached €1.6 billion (~$2.1 billion), up 11% YOY as reported (16% in constant currencies); US sales grew 15% to €1 billion (~$2.1 billion), largely due to price increases.

3. Management shared that a pre-trial "Markman hearing" for its lawsuit over Lilly's insulin glargine formulation will take place this fall; the actual trial will take place in September 2015 (this was the first time we'd heard a date set).

4. During Q&A, management spoke enthusiastically about Sanofi's next-gen basal insulin Toujeo (U300 insulin glargine), suggesting that the company will focus very heavily on Toujeo's hypoglycemia benefit over Lantus in positioning the drug.

5. Sanofi's biosimilar insulin lispro SAR342434 remains on track to enter phase 3 in 2H14; the candidate was not discussed in much depth during the call.

6. Lyxumia (lixisenatide) sales grew modestly to €6 million (~$8 million); Sanofi plans to take legal action against the reimbursement level set by a German arbitration board that drove Sanofi to withdraw the product earlier this year.

7. LixiLan (a combination of Lyxumia and Lantus) is on track for a submission as early as the end of 2015; proof-of-concept data on the candidate was presented at ADA suggesting similar A1c-lowering efficacy to Lantus with more favorable post-prandial control and weight changes.

8. Management highlighted Sanofi Diabetes' newly minted strategic alliance with Medtronic, which focuses in drug/device combinations and integration of care.

9. Sales of Apidra (insulin glulisine), Insuman (human insulin), and Sanofi's BGM products (BGStar and iBGStar) rose modestly, while Amaryl (glimepiride) sales fell slightly.

10. In quite the unconventional move, Sanofi purchased an FDA Priority Review Voucher from another company to potentially cut the FDA review time for its PCSK9 inhibitor alirocumab - this could put Sanofi ahead of Amgen to be first in line to launch a PCSK9 inhibitor.

Table 1: Diabetes Division 2Q14 Sales by Product

	2Q14 Sales (millions)	Reported (Operational) YOY Growth	Reported Sequential Growth
Total Diabetes Division	€1,788 ($2,450)	10% (16%)	8%
Lantus	€1,557 ($2,133)	11% (16%)	8%
Lyxumia	€6 ($8)	500% (500%)	20%
Apidra	€77 ($105)	13% (19%)	3%
Insuman	€33 ($45)	3% (6%)	3%
Amaryl	€96 ($132)	-3% (4%)	12%

*Calculations assume an average 2Q14 €/$ exchange rate of 1.37

Table of Contents

Top Ten Highlights

1. Sanofi's Diabetes Division achieved total sales of €1.8 billion (~$2.5 billion) worldwide in 2Q14, up 10% year over year (YOY) as reported (16% in constant currencies) and 8% sequentially as reported. The YOY results were fairly consistent with the previous quarter (the portfolio grew 8% YOY in 1Q14), though growth has been slightly slower in 2014 compared to 2013 (ranging from 8% to 13% in the four quarters of that year), which is understandable considering the ever-increasing base. Keeping with previous quarters, foreign exchange had a sizeable negative impact (~6%) on the portfolio's performance. Growth was driven by Lantus (insulin glargine), which continues to be, by far, the company's best-selling diabetes product (and is, in fact, the best selling diabetes drug in the world, with full-year 2013 sales of €6.5 billion [~$8.7 billion]).

- **Management commented during Q&A that the overall diabetes market has grown slightly faster in 2014 than in 2013.** Sanofi believes that this may be due to a small degree to the Affordable Care Act, which is expanding coverage for a broader patient population in the US. While most individuals that are signing up for the insurance exchanges previously had insurance, around 20-30% (according to management) represent newly covered individuals. This expansion of coverage does not guarantee increased sales volume, however, as many patients that switch to those new plans face greater copays.

2. Global sales of Lantus (insulin glargine) reached €1.6 billion (~$2.1 billion), up 11% YOY as reported (16% in constant currencies). As with the Diabetes Division as a whole, the Lantus YOY results were generally comparable to previous quarters, with the 8-11% YOY growth this year falling slightly short of the 13-20% seen in 2013. Sequentially, global Lantus sales grew 8% against a fairly easy comparison, as sales in 1Q14 fell 4% sequentially from 4Q13. Table 2 provides a breakdown of Lantus sales by region.

Table 2: Lantus Revenue by Region

Region	2Q14 Sales (millions)	Reported (Operational) YOY Growth	Reported Sequential Growth

Worldwide	€1,557 ($2,133)	11% (16%)	8%
US	€1,035 ($1,418)	15% (20%)	9%
Western Europe	€213 ($292)	5% (4%)	2%
Emerging Markets	€243 ($333)	6% (16%)	8%
Rest of World	€66 ($90)	-10% (0%)	3%

*Calculations assume an average 2Q14 *€/$* exchange rate of 1.37

- **Lantus sales in the US rose 15% YOY as reported (20% in constant currencies) and 9% sequentially to €1 billion (~$2.1 billion).** This is the first quarter that Lantus has posted sales of over €1 billion in the US market, which is responsible for approximately two-thirds of total Lantus sales. Sales of the Lantus SoloSTAR pen continue to account for an increasing proportion of Lantus sales, representing 61% of total US revenue compared to 56% in 2Q13. During Q&A, management shared that total script growth was approximately 4.5% - the rest of the growth was presumably due to pricing. CEO Mr. Chris Viehbacher framed the pricing increase during Q&A as a realignment of Lantus' pricing with its therapeutic value, suggesting that Lantus had previously been undervalued relative to GLP-1 agonists and DPP-4 inhibitors (a gap that the company is now closing). This upward trend in pricing may be only temporary, however, given the approach of Lantus' patent expiration and new "biosimilar" glargine products on the horizon (see below).
    - **During Q&A, management acknowledged that Novo Nordisk's Levemir (insulin detemir) has been growing faster than Lantus in recent quarters.** However, management attributed this largely to the imbalance in the two companies' basal insulin market share (Lantus holds a ~80% share while Levemir holds a ~20% share). Occasionally sales force energy can sag when a product approaches market saturation, and Sanofi emphasized its investments in sales force excellence, which it believes should help it retain the lion's share of the US basal insulin market against products like Levemir.
- **Lantus sales reached €243 million (~$330 million) in emerging markets, rising 6% YOY (16% operationally) and 8% sequentially.** Management remarked that performance was particularly strong in China, Turkey, the Middle East, and some Latin American countries - growth in these areas was counteracted by the broad impact of foreign exchange.

3. Management offered some insight into the timeline of its intellectual property lawsuit against Lilly. According to management, a pre-trial "Markman" hearing is scheduled for this fall. A Markman hearing is a meeting in which a judge determines the meaning of words in patent claims that are under dispute, which is an important preparatory step for the actual trial in which a jury will interpret the patent claims to determine whether the patent has been infringed upon. The actual trial is scheduled to take place in September 2015 (this is the first time we have heard a specific date), and barring a "summary judgment" (when a judge issues a ruling without a full trial), a ruling will likely only occur in 2016. As a reminder, Lilly/BI submitted a 505(b)(2) New Drug Application (NDA) to the FDA in December 2013 for their new insulin glargine formulation; we learned in January that Sanofi filed a lawsuit against Lilly alleging infringement of Lantus' patent, which expires in 2015. The lawsuit triggered a hold on possible US approval for 30 months or until the case is ruled in Lilly's favor. The candidate recently received a positive CHMP opinion from the EMA, suggesting that EU approval could come within the next few months. Phase 3 data presented at ADA suggested that LY2963016 has a fairly identical safety and efficacy profile to Lantus (see our coverage of the ELEMENT 1 and ELEMENT 2 trials).

- **Other companies with biosimilar insulin glargine formulations include Merck/ Samsung Bioepis and Biocon.** Merck announced in February that it would collaborate with Korean biopharmaceutical and biosimilar manufacturer Samsung Bioepis to develop a biosimilar insulin glargine formulation (MK-1293). According to ClinicalTrials.gov, two phase 3 trials for

MK-1293 are currently recruiting: one in type 1 diabetes patients expected to complete in October 2015 (Identifier: NCT02059161), and a second in type 2 diabetes patients expected to complete in January 2015 (Identifier: NCT02059187). Biocon has a biosimilar insulin glargine on the market in over ten countries (mostly in the developing world) and is "on track" to begin a global phase 3 program in partnership with Mylan (see our Biocon F4Q14 report).

- **During Q&A, management attempted to assuage investor concerns about the anticipated decline in Lantus revenue post-patent expiration.** Management pointed to several positive developments for Lantus in 2Q14, namely an increase in total script share (TRx) and new-to-brand (NBRx) share in the US as well as a slight increase in volume due to the larger population of newly insured patients following implementation of the Affordable Care Act.
    - **The price of Lantus in the US has increased significantly in the past few years.** In response to a question about whether there was room for further increases in the coming quarters, management said that the increases had brought the current price (daily treatment cost of ~$8) more in line with the product's therapeutic value, using the even more expensive GLP-1 agonist and DPP-4 inhibitor classes as benchmarks.
    - **Dr. Irl Hirsch (University of Washington, Seattle, WA) recently delivered a provocative presentation on the skyrocketing cost of Lantus and other insulin analogs at this month's Keystone conference.** The message was well received among the room of providers and educators. Dr. Hirsch predicted that if insulin remains unaffordable to the current extent, it is "only a matter of time" before government will intervene.
    - **While achieving better price parity relative to other diabetes therapies is one of Sanofi's shorter-term goals, CEO Mr. Chris Viehbacher also stressed the need to work with payers to achieve the ultimate goal of "better outcomes at a lower cost."** This mentality feeds into Sanofi's mission to explore partnerships and to "move beyond the pill" towards integrated care (read our highlight on the company's new Medtronic partnership below). Broadly, with the US healthcare system moving towards a more comprehensive approach that emphasizes quality, we see Sanofi's efforts to expand beyond a specialized pharma role and instead pursue integrated care solutions that tie together drug therapies, devices, and education as a step in the right direction.

4. The imminent launch of Toujeo, Sanofi's U-300 insulin glargine formulation, was a major focus of the call; management unequivocally characterized it as a "better product" than Lantus. Management explicitly stated during Q&A that Sanofi will "deprioritize" Lantus once Toujeo arrives on the market (this of course is not surprising). One analyst on the call, however, was not convinced that Toujeo is definitively better than Lantus, and we would agree that the hypoglycemia benefit is not necessarily as clear-cut as management has made it out to be (see our coverage of Sanofi's analyst call at ADA to discuss Toujeo data). The FDA accepted the NDA for Toujeo on July 8 and is expected to announce a decision in the first half of 2015; the EMA accepted the marketing authorization dossier for Toujeo on May 27, suggesting potential European approval in 1H15 as well. Although there is some ongoing discussion about Toujeo's clinical profile and how it stacks up against Lantus' profile, the product is Sanofi's best candidate to serve as a successor to its mega-blockbuster - if and when it reaches the market, we expect nothing less than a full-court press.

- **The NDA for Toujeo is based on results from the global phase 3 EDITION program, which demonstrated equal A1c reductions with Toujeo compared to Lantus.** The finding of non-inferiority in A1c reduction with Toujeo was consistent in all three global trials: EDITION I (~800 type 2 diabetes patients already on basal/bolus therapy), EDITION II (~800 type 2 patients on basal insulin plus oral agent[s]), and EDITION III (~800 insulin-naïve type 2 patients). In a meta-analysis of the three studies presented at Sanofi's ADA Investor Call, the average A1c reduction after six months was ~1.1% with both Toujeo and Lantus (from a baseline A1c of 8.3% in both arms).

- **Sanofi considers hypoglycemia benefits to be one of the major factors differentiating Toujeo from Lantus, but the EDITION results are not entirely conclusive.** The EDITION meta-analysis concluded that patients treated with Toujeo had lower rates of nocturnal and overall hypoglycemia than those treated with Lantus (31% and 14% relative rate reduction, respectively). The percentage of people experiencing at least one hypoglycemic event (confirmed ≤70 mg/dl or severe) was significantly lower with Toujeo (9% relative rate reduction for anytime hypoglycemia and 25% relative rate reduction for nocturnal hypoglycemia). However, it remains unclear whether the EDITION results will be robust enough to convince clinicians and regulators that Toujeo offers a clinically meaningful hypoglycemia benefit. Many of the individual EDITION trials failed to demonstrate a statistically significant reduction in hypoglycemia in all time periods that were analyzed; during the company's ADA investor call, several analysts questioned the validity of Sanofi's "slicing and dicing" of timing used for the hypoglycemia calculations, particularly when the time periods used were not part of the prespecified hypoglycemia endpoint. Given the FDA's conservative approach when it evaluated Novo Nordisk's hypoglycemia claims for Tresiba (insulin degludec), there is likely a legitimate cause for concern about how regulators will respond to similar claims for Toujeo. See table 3 below for a breakdown of hypoglycemia results in the individual EDITION trials.
    - **During Q&A, when asked whether Toujeo's hypoglycemia benefit will be perceived as sufficiently robust by clinicians, management pointed out that financial analysts asked the same question about Lantus before its launch.** It is lucky, as management said, that it is ultimately up to clinicians (rather than financial experts) to assess drugs' clinical profiles.

Table 3: Hypoglycemia endpoints and reported six-month results from EDITION program

Trial	Prespecified hypoglycemia outcomes (according to ClinicalTrials.gov)	Selected reported hypoglycemia outcomes (all vs. Lantus)
EDITION I	% of patients with ≥1 nocturnal hypoglycemia event from week 9 to endpoint, defined as severe and/or confirmed by plasma glucose ≤70 mg/dl between 0:00 and 5:59 hours	Statistically significantly fewer people on Toujeo had ≥1 severe or confirmed nocturnal hypoglycemia during month three to month six (21% relative rate reduction). Occurrence of anytime hypoglycemic events was numerically lower in the Toujeo arm but did not reach statistical significance.
EDITION II	"	Statistically significantly fewer people on Toujeo had ≥1 severe or confirmed nocturnal hypoglycemia during month three to month six (23% relative rate reduction). Over the entire six-month treatment period, 27% fewer patients on Toujeo experienced a nocturnal hypoglycemia event, and 10% fewer experienced a daytime hypoglycemia event (both differences were statistically significant).
EDITION III	"	No significant reduction in % of patients with ≥1 severe or confirmed nocturnal hypoglycemic event (≤70 mg/dl) from nine weeks to six months. However, this difference became significant when the analysis was extended to

		include the full six-month study period, showing a 24% relative rate reduction. Percentage of patients with ≤1 severe or confirmed hypoglycemic event any time of day (not just nocturnal) was additionally significant the full six-month study period (25% relative rate reduction).
EDITION IV	Number of patients with various types of hypoglycemia events over 12 months.	No significant reduction in rates of anytime confirmed (≤70 mg/dl) or severe hypoglycemia during full six-month duration of trial, although Toujeo users had statistically significantly reduced nocturnal hypoglycemia in the first eight weeks of treatment (31% relative rate reduction).
EDITION JP I	Number of patients with various types of hypoglycemia events over 6 months.	% of patients reporting ≥1 confirmed (≤70 mg/dl) or severe hypoglycemia event was statistically significantly lower from baseline to week eight for both anytime and nocturnal hypoglycemia (16% and 29% relative rate reductions, respectively). For the time period of week nine to six months, statistical significance was not reached. For baseline to six months, statistically significance was reached for nocturnal hypoglycemia (15% relative rate reduction) but not anytime hypoglycemia. % of patients reporting ≥1 confirmed (≤54 mg/dl) or severe hypoglycemia event was statistically significantly lower from baseline to week eight, from week nine to six months, and from baseline to six months for both nocturnal and anytime hypoglycemia. Over the full six months, the relative rate reductions were 31% and 23% for nocturnal and anytime, respectively.
EDITION JP II	"	% of patients reporting ≥1 confirmed (≤70 mg/dl) or severe hypoglycemic event was statistically significantly reduced for nocturnal hypoglycemia from baseline to six months (38% relative rate reduction) and week nine to six months (42% relative rate reduction), but not from baseline to week eight. For anytime hypoglycemia, there was a statistically significant 31% relative rate reduction from baseline to week eight, but no statistical significance achieved from baseline to six months.

5. Sanofi's biosimilar insulin lispro candidate (SAR342434) remains on track to enter phase 3 trials in 2H14; management did not speak in depth on this candidate during the call. During Sanofi's ADA Investor Call, management said that SAR342434 has completed phase 1 trials in which it demonstrated similar activity and exposure to Lilly's Humalog (no trials are currently listed on ClinicalTrials.gov). The phase 3 program will recruit ~1,000 patients and consist of one trial in type 1 diabetes and one in type 2 diabetes, both using Humalog as the direct comparator. Humalog's patent expired in 2013. Previously, Sanofi has suggested that it had two insulin biosimilars in development, the other likely being a

biosimilar of Novo Nordisk's NovoLog (insulin aspart) - the patent for NovoLog extends until 2017. However, currently only the lispro candidate shows up in Sanofi's pipeline.

6. Lyxumia (lixisenatide), Sanofi's short-acting once-daily GLP-1 agonist, achieved €6 million (~$8 million) in sales in 2Q14. This continues the product's modest early growth trajectory since its launch: sales totaled €5 million (~$7 million) in both 4Q13 and 1Q14. Lyxumia is now available in Japan, the UK, Italy, Spain, and Mexico, and management said additional launches are expected in 2014.

- **Sanofi's press release notes that in Germany, Lyxumia received a new reimbursement decision in June 2014, but it appears not to have been satisfactory, as Sanofi decided not to resume sales of Lyxumia in Germany and to file legal action against the adjudication.** For background, the company pulled Lyxumia from the German market on April 1 because Lyxumia had been ruled to have "no additional benefit" over generics, meaning that it would be subject to generic-level pricing. Sanofi then entered into negotiations with German authorities for months, and the June 2014 decision was the outcome of those negotiations.
    - **A number of diabetes drug manufacturers have expressed frustration about the rigid reimbursement environment in Germany** - see our report on BMS/AZ's withdrawal of Forxiga (dapagliflozin) from Germany late last year for a more in-depth analysis of the German comparative efficacy review process.
- **Management did not provide an update on ELIXA, the ongoing cardiovascular outcomes trial (CVOT) for Lyxumia.** As a reminder, Sanofi withdrew its US FDA submission for Lyxumia in September 2013 due to the fear that interim disclosure of ELIXA results could compromise the integrity of the study. Full results from ELIXA are expected in 1H15, and a US re-submission should follow soon thereafter. In an analyst breakfast at ADA, Zealand management suggested that non-inferiority is the most likely outcome of the trial - there has been some hope that GLP-1 agonists could potentially be cardioprotective due to the combined effect on glucose and body weight, but longer trials may well be needed to uncover any protective effect. Due to their enormous cost, most CVOTs are designed to accrue only the minimum number of events needed to demonstrate non-inferiority.
    - **The FDA is holding a public hearing on August 11 to discuss the issue of interim data disclosure in CVOTs.** This meeting could presage a broader discussion on the ripple effects of the Agency's 2008 CVOT guidance, which has contributed an enormous amount of uncertainty and unpredictability to the diabetes drug development process.

7. The call did not feature much discussion on LixiLan, a fixed-ratio combination of Lantus and Lyxumia. Two phase 3 trials, LixiLan-O (ClinicalTrials.gov Identifier: NCT02058147) and LixiLan-L (ClinicalTrials.gov Identifier: NCT02058160) are currently recruiting; both studies have completion dates in August 2015. This timeline is consistent with previous predictions of a submission in late 2015 and places LixiLan on track to be the first basal insulin/GLP-1 agonist combination on the US market, as Novo Nordisk's Xultophy (IDegLira; insulin degludec/liraglutide) combination pushed back until at least late 2015 due to the FDA CRL for insulin degludec. Xultophy will almost certainly be the first to the European market, as it received a positive CHMP opinion from the EMA on July 25 and is likely to be approved within the next two to three months.

- **We saw the first proof-of-concept data on LixiLan at ADA:** the results were impressive, though the comparison between LixiLan and Lantus monotherapy may have been affected by a very strong showing from the Lantus arm. Both groups achieved similar and striking A1c reductions (1.8% reduction with LixiLan compared to 1.6% with Lantus from 8% baseline), and LixiLan blunted postprandial glucose excursions substantially more than Lantus (reductions of 70 mg/dl and 12 mg/dl, respectively; $p<0.001$) while also offering a weight benefit.

8. Sanofi highlighted its newly minted "strategic alliance" with Medtronic focused on improving type 2 diabetes management. The alliance will pair Sanofi's insulin portfolio and drug

development expertise with Medtronic's background in insulin pumps and CGM; key priorities include developing new drug-device combinations and devising methods to "improve adherence, simplify insulin treatment, and help people with diabetes better manage their condition." Specific drug-device options being explored include pre-filled insulin cartridges for Medtronic pumps and type 2 diabetes-specific drug delivery patches. The alliance will also build upon Medtronic and Sanofi's current work on the MiniMed Implantable Pump, which is used by a subset of patients in Europe that cannot achieve glucose control with subcutaneous insulin delivery.

- **We first heard about this partnership during Medtronic's Analyst Day in June, and Sanofi management highlighted it during its ADA Investor Call as an example of how the company is leading the way toward integrating care for patients.** We agree that this initiative is an excellent step toward management's stated goal of moving "beyond a pill" and focusing on outcomes, and we could imagine multiple products coming out of the alliance, especially prefilled patch pen-like wearable devices or simplified prefilled insulin pumps. We also wonder if there is potential for a concentrated insulin partnership, similar to the approach Insulet and Lilly are taking. As a reminder, Sanofi and Medtronic have an existing agreement serving specific type 1 patients in Europe with implantable pumps.

9. The press release also featured financial updates on Sanofi's other diabetes product lines:

- **Sanofi's rapid-acting insulin analog Apidra (insulin glulisine) rose 13% YOY as reported (19% in constant currencies) and 3% sequentially to €77 million (~$105 million).** Apidra's growth has been generally strong in recent quarters (albeit from a much smaller base than Lantus or other companies' rapid-acting analogs), ranging from 14% in 1Q14 to 28% in 3Q13. Total sales for the product peaked in 4Q13 (€81 million [~$110 million]) and have remained in the mid-70-million Euro range so far in 2014. Apidra was not mentioned during the call.
- **Sanofi's human insulin Insuman rose 3% YOY as reported (6% in constant currencies) and 3% sequentially to €33 million (~$45 million).** This is the first quarter of positive YOY growth for Insuman in the recent past following four quarters of flat or declining sales. Growth in emerging markets counteracted a slight decline in Western Europe.
- **Amaryl (glimepiride) sales fell 3% YOY as reported but rose 4% in constant currencies and 12% sequentially as reported to €96 million (~$132 million).** The 3% decline was a relatively strong performance for Amaryl, which has been sputtering for some time (full-year 2013 sales fell 11%).
- **Revenue from the BGStar and iBGStar blood glucose meters was €16 million (~$22 million), up 33% YOY in constant currencies.** We previously estimated that sales totaled ~€12 million (~$16 million) in 2Q13.

10. Outside of diabetes, Sanofi's phase 3 PCSK9 inhibitor alirocumab (for hypercholesterolemia and other associated indications) was the single largest focus of the call, due to some unconventional news that Sanofi had shared the previous day. Sanofi and co-developer Regeneron Pharmaceuticals announced that they had bought an FDA Priority Review "Voucher" from BioMarin Pharmaceuticals to potentially accelerate the approval process for alirocumab in the US. BioMarin had received the voucher through the FDA's Rare Pediatric Disease Priority Review Voucher program (the FDA initially distributes vouchers to companies working on therapies for rare pediatric diseases, but they can be used in other disease areas if the original recipients choose to sell them - a bizarre system we have not seen used much in diabetes). If the FDA accepts the PRV for alirocumab's BLA, it would allow for an expedited review cycle of six months after the filing date rather than the standard 12 months.

- **This news adds a new twist to the race between Sanofi and Amgen to market the first PCSK9 inhibitor.** Sanofi was the first of the two to report topline phase 3 data in late 2013, but at this point it seems that Amgen is more likely to submit its candidate (evolocumab) first (in 3Q14, according to the company's recent 2Q14 presentation). Sanofi plans to submit alirocumab in the US

and the EU by the end of 2014. Now, with its PRV, Sanofi might get to market first even if Amgen is the first to submit its compound.

- At the same time, Sanofi and Regeneron also announced that all nine phase 3 trials (the ODYSSEY program) of alirocumab in people with hypercholesterolemia had met their primary endpoint of greater LDL cholesterol reduction at 24 weeks compared to control. The press release did not provide specific numbers but said efficacy results were consistent with previous trials - phase 3 results presented earlier this year showed a mean LDL reduction of 47% with alirocumab as monotherapy. Notably, one of the nine trials, ODYSSEY ALTERNATIVE, showed positive efficacy results and a benign safety profile in statin-intolerant patients, a population we believe could derive a particularly high benefit from PCSK9 inhibitors.
- **Other PCSK9 inhibitor candidates in development besides Sanofi/Regeneron and Amgen's candidates include:** Pfizer's bococizumab (phase 3), Lilly's phase 2 LY3015014 (which might be dosed less frequently than evolocumab), and Catabasis' CAT-2003 (in phase 2) and CAT-2054 (preclinical). BMS had previously listed a PCSK9 adnectin as of June 2013, but it no longer appears in the company's pipeline - this is unsurprising since it left diabetes and presumably related areas in late 2013. Similarly, Roche's phase 2 RG7652 was recently discontinued.

Honorable Mentions

- **Sanofi has advanced a GLP-1/glucagon receptor co-agonist (SAR425899) into phase 1 for diabetes.** This is the first we have heard of this compound, and no trials are listed yet on ClinicalTrials.gov. Other companies developing GLP-1/glucagon dual agonists include Lilly (TT401 in phase 2 and an oxyntomodulin in phase 1), Prolor/OKPO (preclinical long-acting oxyntomodulin), Zealand Pharma/BI (Zealand now in sole control of phase 1 ZP2929; new lead candidate being selected for BI partnership), and Xenetic Biosciences (PSA-Oxyntomodulin in phase 1).
- **Sanofi was named as the chief coordinator (along with co-coordinator JDRF) of the type 1 diabetes program in the recently launched second phase of Europe's Innovative Medicines Initiative (IMI2).** The €3.3 billion (~$4.5 billion) public-private partnership released its first call for proposals on July 9; excitingly, the call included a €35 million (~$47 million) program devoted to type 1 diabetes research. Other key players involved in the program include the JDRF (named as a co-coordinator), the Helmsley Charitable Trust, GSK, Novo Nordisk, and Lilly.

Questions and Answers

Q: There's a lot of discussion around pricing above GLP-1 levels for these [alirocumab] agents, possibly more towards the TNF agents. But some commercial players think that GLP-1's growth has been hampered by premium price levels to let's say, Lantus, as an example. So could you just talk us through any rationale as to why these agents could be priced above GLP-1 agonists?

A: I don't want to get into this pricing today, but I will say that I do not consider, and certainly all our market research, does not consider the GLP-1 market as a relevant comparator or an analog. You're looking at many different levels of efficacy and a very different type of market, and a very different set of treatment alternatives, as well as a very different set of outcomes. So I personally don't really pay much attention to GLP-1 when it comes to alirocumab. But, our teams have done market research now. We obviously know more about this product today than we did even a week ago, and the robustness of the results is something that we'll be exploring with physicians and patients, and you'll have a first look in Barcelona and then we'll try to bring all of that together in November.

Q: Is it fair to assume a marked deceleration of Lantus in 2015, because of the flattening price in the US and the growing rebates? And assuming that what's happening is an industry event.

A: There are a number of factors that are going on obviously in 2015. First is the question of whether or not a biosimilar will arrive. As you know, there's a Markman hearing that's been scheduled for this fall and there is

a court hearing. The trial is scheduled currently to take place in September of 2015. Unless there's a summary judgment, one wouldn't expect a biosimilar until the decision on patent infringement has been taken, which would probably take you out into 2016. Then of course, obviously with the launch of Toujeo, we are going to considerably deprioritize Lantus because we believe Toujeo is a much better product. So in any case, you are going to see a decline in Lantus as we ramp up effort behind Toujeo.

It's difficult to predict on the rest in the market. The whole diabetes space is clearly a very competitive space. Equally, I think we have put a lot more focus in our US business on sales force execution. And we have actually seen NRx share gain now over the last seven or eight weeks, and actually TRx share gain again.

The other effect, although very modest at the moment, is that there does appear to be some benefit from the ACA. We are seeing the overall diabetes market grow a little faster in 2014 than it did in 2013. Now we all know that those who are enrolling in the exchanges, to a great degree, are people who previously had health care insurance and are just switching. But there is probably 20% to 30% of new patients coming in that didn't have healthcare insurance before. There is also some evidence that some smaller employers are starting to get insurance.

Now, the offset to that, of course, is that the new insurance often comes with much higher co-pays and co-insurance. So that's why I think we have to be extremely prudent about actually seeing any real benefit in volume, but there appears to be some. What we can also say for our diabetes business is that, we have just hired a new head of our diabetes business unit and that person formerly used to work for Novo Nordisk. So we're looking for some new energy in that part of our business in the US.

Q: Regarding Toujeo and about de-prioritizing Lantus, when we talk to investors, the feedback from many in the market is that they're not convinced that Toujeo is a better product. But financial commentators don't determine prescribing. What is your market research, which is coming from actual prescribing physicians, on Toujeo vs. Lantus?

A: I think we'll come back on November 20 with that answer. The one thing I will say is that there are still a number of people in the company who launched Lantus. And it seems that the financial community didn't really think much of the prospects of Lantus either. So I think, as you say, it's probably a pretty good thing that it's physicians prescribing these products.

Q: Given the payer pressure in the US, given that you're effectively in a duopoly with Lantus, do you still believe that you have scope for price increases there?

A: So on payers, there are two types of price increases, obviously. There's the WAC price, the list price changes, and then there's the net price changes. Largely, the list price changes are a function of competitor activity. To a great extent, I think Lantus was seen as being lower priced compared to its therapeutic value, if you compared it to, for instance GLP-1s or to even DPP-4s. And I think we've got better price alignment with that. Today, Lantus has a daily treatment cost of around $8, so still less than the GLP-1s, but more in line with the DPP-4s. Then the question is how much of that price increase can you translate to the bottom line? And I think that's where there's increasing pressure. So we need to keep volume moving.

We need to also continue to work with payers to really show how do we get to better outcomes? Because the real target is not lower prices of medicines, but it's better outcomes for patients at a lower cost. And I think actually doing a better job with partnering with some of our payers could actually help us on that. And that's largely why we've moved on this path of integrated care and moving beyond the pill. I think outcomes are going to be much more important in the payer environment, and I don't think as a company, you can really just continue to supply a medicine.

I think you have to try to think about what can you combine this with, with devices, with education, with programs, with information to actually help patients cope with their disease. Because, you know, type 2 diabetes is probably one of the number one cost drivers for the whole healthcare system. We know if you take a more proactive intervention, you can actually reduce the cost of patients while giving them better health. So I think there's a big prize to be had, actually, in diabetes. And we probably need better collaboration within that.

Q: You said on Lantus you're not going to yield share to anybody yet. In H1 at least, you have been not growing as fast as the market in the long-acting insulin analogs. I think you grew 4% TRx while the market grew 7%. Why is that? Is that due to disciplined contracting?

A: On Lantus, TRx growth was 4.5% for the last two quarters. In Q1, it was 4.6%. We compare that to a select insulin market that grew at 4.1% and 4.1%, so we've been outgrowing that. Now Detimir has outperformed Lantus a little bit in some of that period but they've got a 20% market share to our 80% market share. So it's kind of hard given the amplitude of the two numbers. Largely, what we have been focusing on is field force excellence. I think when you've got 80% market share, there's always a risk of not being as energized as one could be. And I think a lot of effort has gone into that by our US team. We don't see anything really in terms of outperformance in the marketplace.

In terms of pricing, this is something that's affecting everybody. But again, I think there is an element here of not necessarily getting into price wars and getting into battles with payers, but really saying this is the most expensive part of healthcare. We can give people all the great medicines that you can, but if they don't really have a change in diet or exercise or other lifestyle elements, you're not necessarily going to get to better outcomes. And that's really, again, coming back to why we want to get into integrated care - it is to really try to have some influence on the overall patient treatment experience.

Q: Can we expect Sanofi to push into new areas like medical devices or diagnostics?

A: We're happy with our perimeter - there is a balance to be struck between diversification and management bandwidth, quite honestly. I think we have our hands full on this, so I would expect us to be building out versus expanding. I have to say, I really don't know anything about medical devices, except for where we want to be in devices, which is why we decided to get together with Medtronic, for example. We recognize that we have some competencies and products that can be useful to Medtronic. But Medtronic knows a lot of things that we don't know about, and so where we need to be in a broader area we will do that through partnership.

Q: On the alirocumab priority review voucher, you used some conditionality in your statement of intent to use that, so phrases like "potentially use" or "plan to use." So is there any risk at all that you might not be able to use it? And to what extent was that voucher purchase the result of any broader discussion of BioMarin?

A: At the end of the day until you see ink drying on the NDA, I think anything is possible. But generally, you have to give the agency three months' notice. They know there are two types of vouchers. One is related to rare pediatric disease, the other is to tropical diseases. The tropical disease one actually requires a longer notice period, and that's why the pediatric voucher - the rare disease voucher - is considered more valuable.

This is a request to have an accelerated review. Obviously, you're back into the normal review cycle then. You can be awarded an accelerated review for any type of product, even without a voucher, but that doesn't always mean you're going to get it. But at this stage, all we can do is say we've acquired the voucher and at this stage, our intention would be to try to use it for that.

Q: With Toujeo and PCSK9 next year, that's two pretty big potential launches. If we then go and assume that you do get a broad label for PCSK9, how should we be thinking about the incremental commercialization efforts of both assets? If we were just to simply assume that there is a significant expansion in both the diabetes and the primary care sales force, is that the right way of thinking about it? Or can you help us think about it a bit more intelligently?

A: I can tell you inside the company, things are pretty busy. In pretty much every business, we've got new product launches either underway or about to get underway. Genzyme with Cerdelga and Lemtrada. We already talked about the others. Here we've got Toujeo. We're still rolling out LixiLan and now, PCSK9.

The interesting thing I think is that, clearly Sanofi, when we talk about this gang of four, you hear that diabetes is one of the four risk factors. You know, obviously, we are exploring what kinds of synergies we might get between these two. I think next year, we are already putting more money into the business. Last year, we had a big investment building up our MS platform. This year, we had significant net increase. So you

don't necessarily see it in the numbers because we are busy driving savings out of the rest of the business. But we've put well over €700 million of new investment into the business just because of this burgeoning pipeline.

Next year, I think we've got both continued pipeline investment and commercialization costs. I think it's too early to tell what impact that will be. You know, I don't think we're looking at PCSK9 initially as a primary care product, however. I think we're going to be focused probably more on specialty audiences.

Q: Can you help us create an expectation for the rollouts of Toujeo and alirocumab in 2015? The company clearly is excited and optimistic, and your experts apparently are as well. Should we conclude that payer adoption will be brisk and the rollouts will be very strong? Or would you urge us to lean more cautiously on the rollouts?

A: Particularly on alirocumab, we're talking about a paradigm shift in treatment here just because of the extraordinary level of efficacy. When you're talking to key opinion leaders, nobody really knows what happens when your LDL goes below 70 mg/dl. And the fact that we've just had these phase 3 results as well as the long-term study, we're going back and updating our market research on this.

Then there are also a whole lot of other questions because there are, for instance, two doses here. You've got a 75 mg and a 150 mg, which actually Amgen does not have. And you're going to have two schools of thought here about "lower is better and faster" vs. "this is a new class of drugs, so let's do what cardiologists have tended to do, which is to titrate up." So there are a lot of moving parts in how this is going to take place. So we're actually doing a lot of work on that and I'd really rather give you a more detailed answer on November 20 because it's pretty rich.

Now, I think Toujeo is a lot simpler. We do think this is a better medicine. We are going to be driving to get a maximum rollout. We will be on alirocumab too. It's just early days to give you some sense of that. But regarding Toujeo, we want to actually really get behind this next generation insulin.

Q: You've mentioned in the press release the increased payer pressure. I just wondered whether you could add more color why that is specifically mentioned now and where you see that pressure within your business particularly.

A: I think the increased payer pressure is an industry phenomenon. I've certainly seen notes out from various companies who've held panels on this. You know this is partly due to the pressure from some new medicines. It's partly due to some of the pressure that some companies are facing from the ACA, and partly, quite honestly, just due to our own competitors. You've got a number of people out there who are being much more aggressive in contracting to try to gain market share.

You know clearly Sanofi's not about to yield share to anybody. But I think that's normal. I think you've seen it with other companies. And it's just sort of something to keep an eye on. Nonetheless, this comes back to the diversity of the company that yes, it's there, but even though we know it's there, we can still maintain and perhaps even slightly increase the outlook for the rest of the year.

Q: On the ODYSSEY trial, you put that test in the press release yesterday as well as a long-term trial and a post-hoc analysis. I was wondering if you could talk about how those patients looked at baseline, maybe their baseline LDL level, what those CV event rates were post hoc, and whether there's any comment on the different time points where those events occurred? Say one year vs. 24 weeks and 18 months, or any color you could add overall?

A: So the long-term safety study is a study of about 2,341 patients. In terms of the baseline levels, we started every patient on statins so all of them are on statins and their baseline levels are no different than the populations that would be selected upon this criteria. I can't be specific about levels because I don't want to jeopardize publication rights and presentation at the ESE.

In the pre-specified analysis, we were looking at the MACE criteria, which are the exact same criteria that you would look at in the cardiovascular outcome study, which is the study that ODYSSEY is continuing on 18,000 patients. The time points were pre-specified analyses; we would say the first analysis would be at 50% of patients having been exposed more than 12 months and 25% at 18 months. So the analysis that we're reporting in favor of alirocumab is based on this planned interim analysis.

Q: On additional data that we could look at, are there any DSMB interim looks on the cardiovascular outcomes trial?

A: As you know, the long-term cardiovascular outcome study called the ODYSSEY outcome, is an event-driven design. In other words, we are basically dependent upon the event rate; the number of events observed that are adjudicated amongst the patients who are treated. In terms of those studies, there always are planned interim analyses that are performed during the conduct of the trial, by the DSMB, and to which we're blinded.

During those times, the DSMB has total discretion to assess the risk benefit on both sides of the equation. They're looking to see if there are fewer events, or more events in one arm vs. another. So we do have planned interim analyses at a certain number of events as agreed upon with the agency, at which point the DSMB has discretion to continue or terminate the trial depending on what is observed.

Q: How many of these events are possible? Can you give us any kind of feel for when they would be?

A: In terms of timelines, 2017/2018 is our timeline. You know plus or minus six months is possible on those dates. So I can't really predict more than that at this point. It's recruiting at the rate that we expect it to recruit. And the event rate is what we expect. So I would say that we should hold ourselves to those timelines at this point.

Q: Should we expect any pharmacoeconomic data at upcoming cardiology meetings?

A: There are two fundamental questions that affect this field. One is, are PCSK9 inhibitors capable of increasing the better outcomes that we see with statins? And there is a central question, which is that statins per se have a salutary effect that other drugs have not proven. I think the results that we reported yesterday in a long-term study with the 2,341 long-term patient cohort are the first evidence, in my view, that in fact that notion is not correct. These results show that in fact lowering the LDL-C is having an additional impact on top of optimal statin therapy.

So because of that, that will change the pharmacoeconomics to a large extent, given that it is confirmed by the ODYSSEY long-term study in terms of the ability for us to lower the morbidity/mortality of this disease beyond that of maximum statin treatment. In pharmacoeconomics terms, now you can see a baseline, an upside that is essentially trending toward the up side given the recent results.

In terms of the other parts of pharmacoeconomics, I would say that it's still evolving. We absolutely believe that there will be a need for addressing unmet high-risk cardiovascular patient needs after the launch of this product, even before the full cardiovascular outcome study is published because I don't think the risk/benefit is something that you would want to weight towards the risk in these patients. You would probably want to err on the side of giving the benefit of the doubt to the patient, given what we know today.

A: I agree with all of that and I think we need to spend some time with what we have learned. I think there is an assumption out there that there's statins and everybody is well controlled and the problem is solved but in actual fact, it's pretty astounding when you look at the number of people who despite statin use are nowhere near goal. And I think when you couple that with patients who have other risk factors as one cardio KOL described them as the gang of four, between smoking, high cholesterol, hypertension, and diabetes.

When you have those four conditions, which are four controllable elements of cardiovascular disease, this is really why cardiovascular death is still one of the leading causes of death. So that's why I would say that we don't really look at the GLP-1, which is looking at a broad spectrum of patients and a broad spectrum of treatment. LDL cholesterol is a factor in itself, but it is also effectively a biomarker for identifying patient options.

And I think you're going to see a much more targeted approach, and we don't really do that in the GLP-1 segment. But again, this is something where you actually have to spend a fair amount of time. One needs a fairly granular analysis, but I think you'd probably be surprised at the numbers also involved. But we'll talk more about that at another time.

Q: Regarding alirocumab and the post hoc analysis of the ODYSSEY long-term trial, can you please tell us if you think the results of that study can be part of the product label and then will give you an advantage before the publication of the ODYSSEY outcomes trial?

A: In terms of the long-term study, which involves 2,341 patients, one thing I'd like to stress is that, we've been extremely careful to design quality over speed in our trials. We have 5,000 patients. We didn't go to 12 weeks. We went to 24 weeks. We didn't go to 12 months follow-up, but to 18 months follow-up. We have 75 mg, and 150 mg and 300 mg doses, so the quality of the program allows us, in fact, to submit the data at the time of submission.

Will it be in the label? Obviously, we need the cardiovascular outcomes study, the 18,000 patient study to make it on the label, but it will certainly, I hope, be in the clinical section. The impact, obviously, is that this is the first, solid quality evidence of a differential effect on cardiovascular outcomes of alirocumab on top of statins. So I'm pretty confident and hopeful that it will make it to the clinical section, but not in the label itself from the first try as it needs to be confirmed by the larger study.

Is there going to be an advantage? I think in generic terms there will be a significant advantage in having shown some definitive or strong early evidence of better outcomes with PCSK9. In particular, one of the things that we have been very careful in our design is to focus on high-risk cardiovascular populations, the ones most in need for intervention.

I'm obviously intending to put these data in our submission for inclusion in the clinical section. From the scientific and medical standpoint, there is clearly an advantage in having demonstrated through this very careful, more long-term program that we have done, where we have, really, explicitly favored quality over speed. I think this would make a significant difference in my opinion, and I hope so.

A: I would just add that I think one particular area where we might have some benefit is actually in Europe because obviously economic hurdles for new drugs are much higher in Europe. And we might've anticipated some payers saying, well that's great you reduce LDL but we want to see outcomes. I think it might be interesting to see while this wasn't the primary endpoint by any means, we do need to be prudent about how we look at this. Nonetheless, I think it is an important signal and just from a medical ethics point of view, I think we'll certainly get some European payers to potentially look at this differently than they might have otherwise done.

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