CLOSER LOOK

MEMORANDUM

Sanofi 4Q17 - Sanofi's diabetes portfolio falls 11% in 2017 driven by continued Lantus decline (-18%); GLP-1 category grows 32% YOY to $6.5B in 2017 from high base; Modest growth for rapid-acting insulin class/modest decline for basal insulin class in 2017 - February 7, 2018

Executive Highlights

- **We begin this report with five pooled market highlights. In rapid-fire fashion:** (i) GLP-1 agonists grew an encouraging 32% YOY to $6.5 billion in 2017 (from $4.9 billion in 2016). (ii) The basal insulin market fell 3% YOY to $9.9 billion in 2017 (from $10.2 billion in 2016). (iii) Next-generation basals - Sanofi's Toujeo and Novo Nordisk's Tresiba - represent bright spots in the broader market. Combined next-gen sales grew 57% YOY to $2.1 billion in 2017 (from $1.3 billion in 2016). (iv) The rapid-acting insulin class grew a modest 4% YOY to $6.4 billion in 2017 (from $6.1 billion in 2016), against an easy comparison of 4% YOY decline in 2016. Insulin overall was flat between 2016 and 2017 at $16.3 billion. (v) In another disappointing quarter, basal/insulin GLP-1 pooled sales rose only 45% sequentially to $54 million in 4Q17 (from $37 million in 3Q17) - this is shameful for our field, that such effective new medicine is doing so poorly commercially.
- **In sum, the market for branded diabetes drugs grew 7% YOY by our calculations, to just over $36 billion in 2017 revenue vs. just under $34 billion in 2016.**
- **Turning back to Sanofi, the company's overall diabetes portfolio experienced another challenging quarter and disappointing year compared to 2016.** In 4Q17, total diabetes sales declined 16% YOY and 1% sequentially to $1.8 billion. In 2017, the portfolio fell 11% YOY to $7.2 billion. While this is still a massive (and influential) business, it's undoubtedly encountering headwinds. In the US, whole portfolio sales dropped 23% YOY to $3.5 billion in 2017, also falling 30% YOY to $875 million in 4Q17. Lantus was the no. 1 cause of decline for Sanofi Diabetes overall. Sales of the flagship product fell 18% on the year (to $5.2 billion) and dropped 21% YOY and 4% sequentially in 4Q17 (to $1.3 billion). We expect it to continue to fall and though it was positive to see Toujeo hit nearly $1.0 billion in sales, we were surprised it did not grow faster. There are so many patients who deserve next-gen basal insulin, and we hope to see awareness and coverage improve.
- **Indeed, Toujeo was the sole bright spot for Sanofi Diabetes in 2017,** and sales of the next-gen basal climbed 27% YOY to $926 million. That said, Toujeo's 4Q17 performance was relatively weaker, down 4% YOY (but up 9% sequentially) to $259 million.
- **There was notable and exciting movement in Sanofi's diabetes pipeline in 4Q17.** The company started a phase 3 study of once-weekly GLP-1 agonist efpeglenatide, and announced that an autoinjector has been developed already. Admelog (biosimilar insulin lispro) was FDA-approved, and will launch in the US sometime this year, likely 1H18. Excitingly, Sanofi is targeting 1Q18 to file an NDA for Lexicon-partnered SGLT-1/2 dual inhibitor sotagliflozin for type 1 diabetes. The company also plans to launch a phase 3 program for its GLP-1/glucagon dual agonist in obesity in 2018.

Sanofi provided its 4Q17 update in a Wednesday morning call led by CEO Mr. Pascal Soriot. See the presentation, clinical trials appendix, and press release. It was another tough year for the company's diabetes business, but we see great potential with next-gen basal Toujeo, the SGLT business coming, and the GLP-1/basal combo Soliqua.

We start this full report with pooled analyses of GLP-1 agonists, basal insulins, rapid-acting insulins, and basal insulin/GLP-1 combos. Below that, you'll find financial highlights covering Sanofi's major diabetes products, pipeline highlights related to diabetes/obesity, and select Q&A from the call.

Table 1. Pooled Markets Summary for 2017

Therapy Class	Pooled Sales in 2017	YOY Growth	Pooled Sales in 2016
GLP-1 Agonists	$6.5 billion	+32%	$4.9 billion
SGLT-2 Inhibitors	$3.5 billion	+24%	$2.9 billion
Basal Insulin	$9.9 billion	-3%	$10.2 billion
Next-Generation Basal Insulins	$2.1 billion	+57%	$1.3 billion
Rapid-acting Insulin	$6.4 billion	+4%	$6.1 billion
Basal insulin/GLP-1 Combos	$144 million	--	--
DPP-4 Inhibitors	$9.7 billion	0%	$9.7 billion
Sum of Branded Diabetes Drugs	$36.1 billion	7%	$33.8 billion

Table 2. 2017 Financial Results for Sanofi's Major Diabetes Products

	2017 Revenue (millions)	YOY Growth (reported / CER)
Total Diabetes	€6,373 / $7,231	-13% / -11%
Lantus	€4,622 / $5,244	-19% / -18%
Amaryl	€337 / $382	-7% / -1%
Apidra	€377 / $428	3% / 5%
Insuman	€107/ $121	-17% / -16%
Blood Glucose Monitoring (BGM)	€62 / $70	-6% / -6%
Adlyxin	€26 / $30	-21% / -18%
Toujeo	€816 / $926	26% / 27%
Soliqua	€26 / $29	-
Praluent (not included in Total Diabetes)	€171 / $194	63% / 67%

Table 3. 4Q17 Financial Results for Sanofi's Major Diabetes Products

	4Q17 Revenue (millions)	YOY Growth (reported / CER)	Sequential Growth (reported)
Total Diabetes	€1,525 / $1,827	-21% / -16%	-1%
Lantus	€1,076 / $1,289	-27% / -21%	-4%
Amaryl	€81 / $97	-9% / -2%	-1%
Apidra	€97 / $116	2% / 8%	9%
Insuman	€26/ $31	-16% / -13%	0%
Blood Glucose Monitoring (BGM)	€15 / $18	-6% / -6%	7%
Adlyxin	€5 / $6	-22% / -22%	-29%
Toujeo	€216 / $259	-9% / -4%	9%
Soliqua	€9 / $11	-	13%
Praluent (not included in Total Diabetes)	€53 / $63	43% / 54%	26%

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Pooled Market Highlights

1. GLP-1 Agonists Growing Fast from a High Base: Sales Rise 32% YOY to $6.5 Billion in 2017; Victoza Steady at 54% Market Share by Value, Followed by Trulicity with 34%

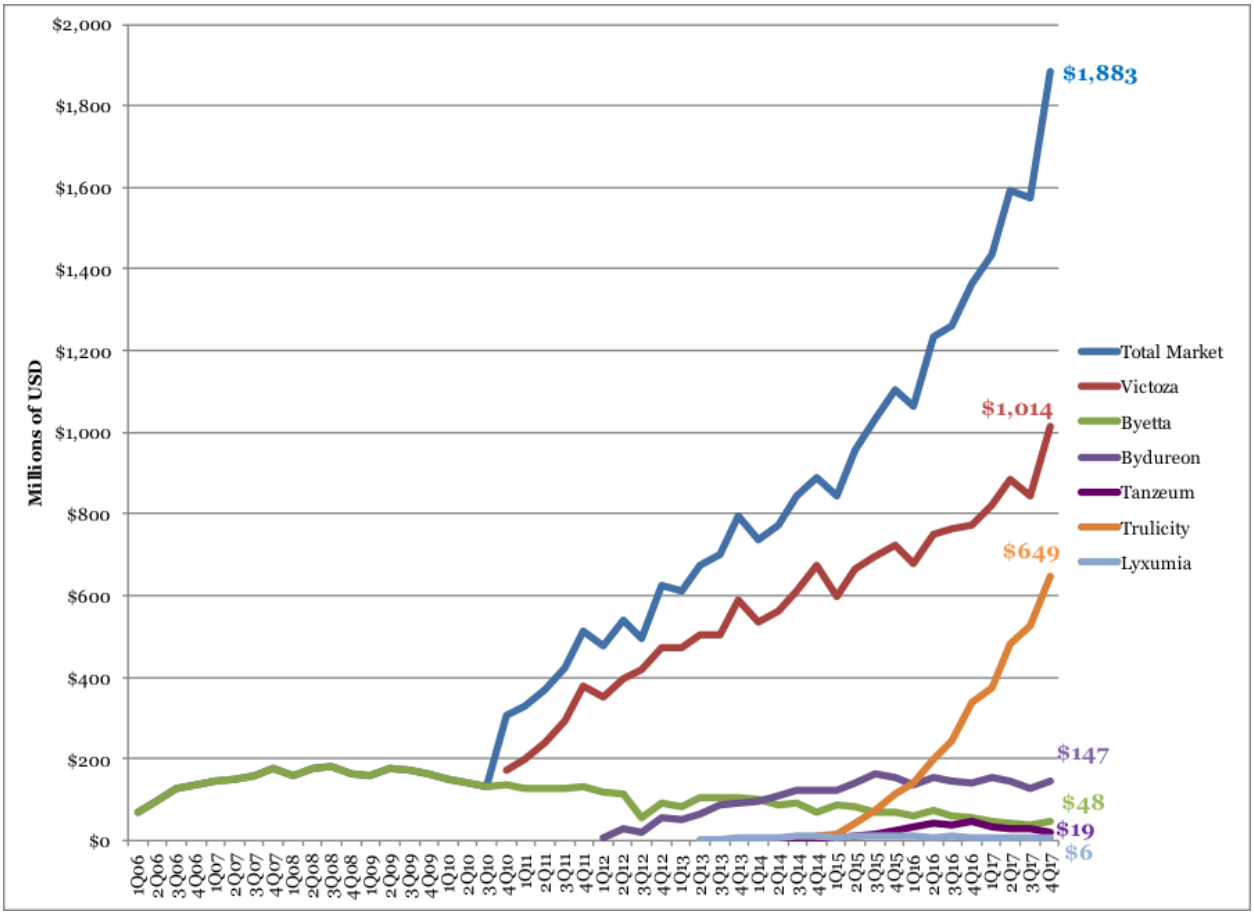
On a pooled basis, the GLP-1 agonist class grew an encouraging 38% YOY in 4Q17 for $1.9 billion in quarterly sales (vs. $1.4 billion in 4Q16), also rising 19% sequentially from $1.6 billion in 3Q17. This is the highest YOY jump for the class since 3Q13, and it builds on a very strong year of 35% YOY growth in 1Q17, 29% in 2Q17, and 25% in 3Q17. Total sales for 2017 were just below $6.5 billion, climbing 32% YOY from $4.9 billion in 2016. The GLP-1 market is growing faster from a higher base than the SGLT-2 market, which we think is quite notable (SGLT-2 inhibitors are a more recent addition to the diabetes treatment toolkit) - this speaks to ongoing innovation in GLP-1 therapy, and to accumulating evidence for strong efficacy as well as safety/tolerability (whereas SGLT-2s have been hit with some safety concerns surrounding amputations and bone fractures). Novo Nordisk's Victoza (liraglutide) continues to lead the GLP-1 agonist market by value, with $1 billion sales reflecting a 54% market share in 4Q17. In second place, Lilly's Trulicity (dulaglutide) posted $649 million in 4Q17 and captured 34% of pooled sales. AZ's Bydureon (exenatide once-weekly) posted $147 million and held 8% of pooled sales. (These are the exact same value shares, by our calculations, as in 3Q17, reflecting strong underlying class growth.) AZ's Byetta (exenatide twice-daily) posted $48 million in 4Q17, claiming 3% of the market by value, followed by GSK's Tanzeum (albiglutide) with $19 million and 1%, and Sanofi's Lyxumia (lixisenatide) with $6 million and <1%. Market share by volume tells a slightly different story, at least in the US: The latest numbers from November 2017 indicate that Victoza held 44% of US GLP-1 agonist prescriptions (TRx), followed by Trulicity at 37%. According to Lilly management, Trulicity very recently passed 40% market share (though it was unclear whether this reflected volume or value). Overall, we're extremely optimistic about the growth prospects for this class, led by the strong upward trajectory of Victoza and Trulicity, not to mention the recent launch of Novo Nordisk's second-gen Ozempic (semaglutide). So many more patients could be benefitting from GLP-1 agonists than are currently on them, implying abundant head room for whole market growth - according to a recent Diabetes Care article, only 7% of second-line diabetes prescriptions in the US go to a GLP-1 product, and Lilly management recently shared that GLP-1 prescriptions reflect a mere 30% of total basal insulin prescriptions worldwide.

- **With a combined 88% of pooled sales, Victoza and Trulicity have become the face of the GLP-1 agonist class - but with Novo Nordisk's Ozempic launching in the US this week, we expect ripples in this dynamic market.** Trulicity skyrocketed in 2017, more than doubling YOY for >$2 billion in sales. Victoza also rose 16% YOY from a much higher base, hitting

$3.6 billion in 2017 revenue. To be sure, both businesses are driven by underlying class growth, mainly due to PCP adoption. Novo Nordisk also emphasized higher than expected realized prices and Victoza's relaunch with a new CV indication on the company's recent 4Q17 earnings call, while Lilly believes the patient experience with Trulicity (the product comes in a patient-friendly autoinjector) will allow the product to compete with Ozempic despite unfavorable SUSTAIN 7 results (semaglutide showed superiority to dulaglutide head-to-head). On a similar note, we're watching closely to see how the impending launch of the Bydureon BCise autoinjector might impact AZ's exenatide business. Indeed, we feel strongly that Ozempic should help drive overall class growth more than anything, but Novo Nordisk also expects the new once-weekly GLP-1 agonist to claim some of Victoza's market share as liraglutide approaches patent expiry. We're looking forward to another highly positive and interesting year for the GLP-1 agonist class in 2018!

- **Moreover, 2017 reinforced just how important CVOT results are becoming for GLP-1 agonists (and diabetes drugs in general):** While Victoza hit an inflection point following approval of a new CV indication, Bydureon sales were relatively flat in 4Q17 ($147 million) and 2017 ($574 million), despite overall class growth, following release of neutral EXSCEL results. With Trulicity's REWIND CVOT completing in July 2018, we're eager to see the promised topline results by year-end. While some have speculated that results may be neutral due to a lower-risk population at baseline, Lilly management has been consistently confident about the trial. With Ozempic already having shown CV benefit in SUSTAIN 6, and with Novo Nordisk launching the post-market SOUL CVOT of semaglutide in type 2 diabetes by mid-2018, the stakes are high. However, we also note that both Victoza and Trulicity have seen huge commercial success before and without a CV indication (though this is changing as the bar rises for new diabetes drugs/beyond-A1c benefits). Perhaps most of all, we're hopeful that REWIND results will add clarify to the issue of a GLP-1 agonist CV class effect - stay tuned…
- **On the strength of GLP-1, the market for branded diabetes drugs grew 7% YOY by our calculations.** Total sales of basal insulins, rapid-acting insulins, GLP-1 agonists, SGLT-2 inhibitors, DPP-4 inhibitors, and basal/GLP-1 combos rose from $33.8 billion in 2016 to $36.1 billion in 2017.

Figure 1. Pooled GLP-1 Agonist Sales (1Q06-4Q17)



2. Basal Insulins Fall 3% YOY in 2017 to $9.9 Billion, Driven by Lantus and to a Lesser Extent Levemir; Shifts in Medicare Part D Coverage for 2018 Favor Tresiba and Basaglar Over Lantus and Toujeo

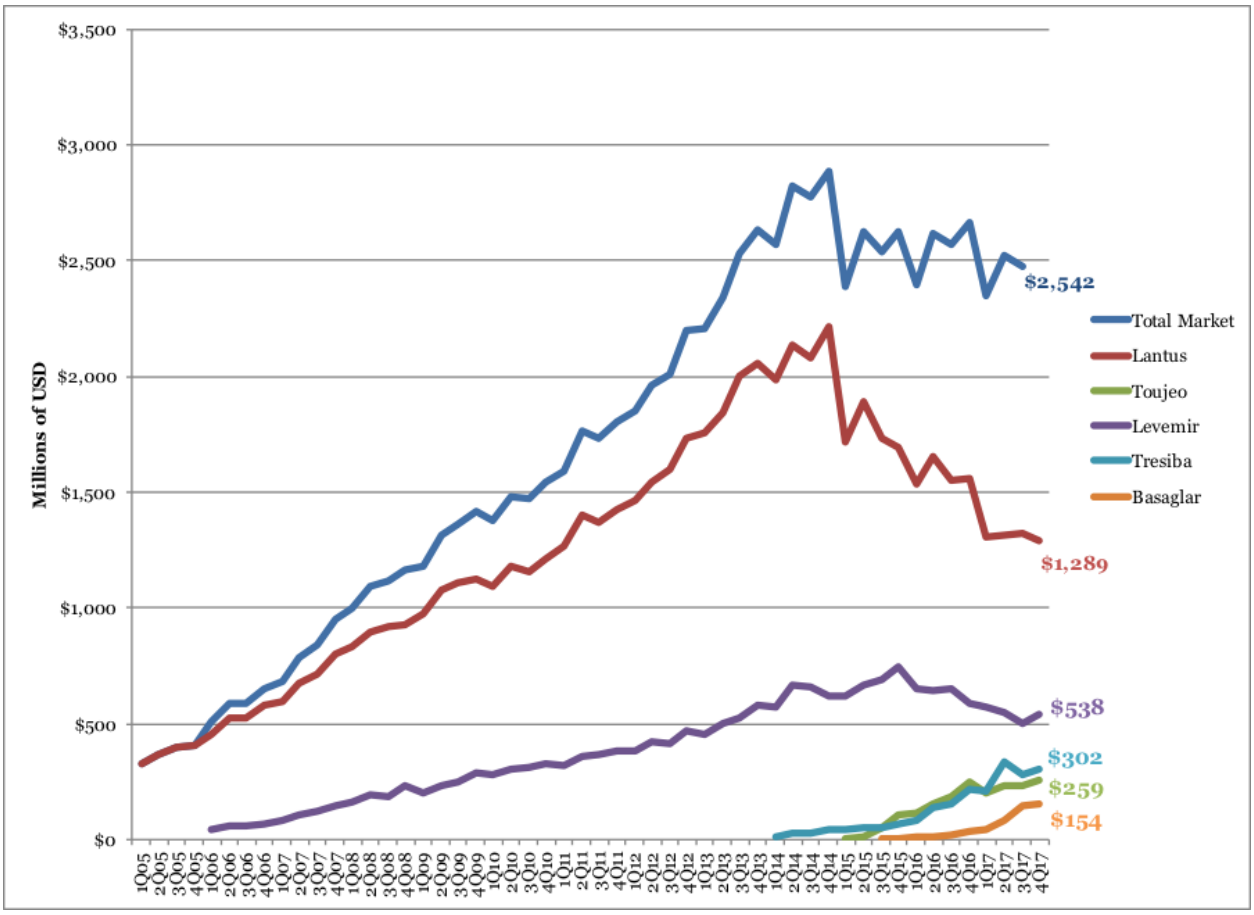
The basal insulin market fell 3% YOY in 2017 to $9.9 billion, down from $10.2 billion in 2016. Pooled sales also declined 5% YOY in 4Q17 to $2.5 billion, down from $2.7 billion in 4Q16. Sequentially, pooled revenue from all major basal insulin products rose 3% from ~$2.5 billion in 3Q17. This class as a whole has experienced single-digit declines throughout 2017 (-2% YOY in 1Q, -3% YOY in 2Q, -4% YOY in 3Q, before -5% YOY in 4Q), driven primarily by a struggling Lantus franchise. Revenue from Sanofi's flagship product has fallen consistently since 3Q15, but this was accelerated in the past year (down 21% YOY and 4% sequentially in 4Q17 to $1.3 billion) as Lilly/BI's biosimilar Basaglar launched in the US and won preferred status over Lantus on the CVS Health and UnitedHealthcare formularies. These formulary exclusions for Lantus carry over into 2018. Lantus and Toujeo have also been shifted to a higher tier on the Medicare Part D formulary for 2018, with less coverage/higher out-of-pocket cost, which will likely be another headwind. Notably, Sanofi does not expect Lantus to grow or even to stabilize at this point (as EVP of Diabetes & Cardiovascular Mr. Stefan Oelrich put it, "we're in line with what was expected for Lantus, and I don't see that going to change") - this is baked into the company's financial guidance, but it also means that the basal insulin market may continue to show sluggish sales (next-generation basal insulins are offsetting some of the decline, but Lantus still has a powerful impact given its high base). Novo Nordisk's first-gen Levemir also had a challenging 2017, with revenue dropping 15% on the year to $2.2 billion (vs. -18% YOY to $5.2 billion for Lantus) - the fact that it dropped nearly as much in revenue from a lower base was certainly a negative sign, though the lion's share of the ~$800 increase in next-gen basal insulins reflected Tresiba growth. Indeed, for both Novo Nordisk and Sanofi, their next-generation basals (Tresiba and Toujeo, respectively) are becoming more important products in terms of driving portfolio growth - more on this

below. By our calculations, Lantus (insulin glargine) captured 51% of total basal insulin sales in 4Q17 (posting $1.3 billion in revenue) - the product continues to lead the class by a long shot, though its market share by value is dropping steadily (53% in 3Q17, 59% in 4Q16). Levemir (insulin detemir) posted $538 million and held 21% market share by value in 4Q17 (this was surprising). Tresiba (insulin degludec) grew 31% YOY to $302 million and held 12%, while Toujeo (insulin glargine U300) fell 4% YOY to $259 million and held 10%. With $154 million in 4Q17 sales (more than tripling YOY, albeit from a much lower base), Basaglar came in with a 6% market share by value, and this is notably climbing (just under 6% in 3Q17, <2% in 4Q16).

- **By volume,** Lantus accounted for 45% of total basal insulin prescriptions in the US (TRx) as of January 2018, according to Novo Nordisk's 4Q17 earnings presentation (slide 9). Levemir held 23% US TRx in January 2018, followed by Tresiba with 11%, Toujeo with 8%, and Basaglar with 6%. Based on these figures, Novo Nordisk's total share of the basal insulin market by volume is 34% (Tresiba + Levemir), Sanofi's is 52% (Lantus + Toujeo), and Lilly/BI's is 6% (Basaglar) - we suspect the remaining 8% goes to non-branded/human basal insulins. Lantus' TRx fell 4% from 49% as of October 2017, and in the same three months, Tresiba's TRx climbed 2% from 9%, while Basaglar's TRx climbed 2% from 4%. This suggests that more basal insulin prescriptions (whether new patient starts or patient switches) are going to the next-generation product and to the biosimilar over first-generation Lantus and Levemir. Indeed, we view Tresiba, Toujeo, and Basaglar as the bright spots within this class.
- **Basaglar had an outstanding year, and Lilly management forecast a strong 2018 for the biosimilar as well, due to increasing familiarity among HCPs and improved formulary positioning within Medicare Part D.** Indeed, Novo Nordisk CEO Mr. Lars Jørgensen has suggested that Basaglar will become a greater competitive threat to other basal insulins as the diabetes community grows accustomed to the concept of biosimilar insulin. We do think it's reasonable that it's taken some time for providers to feel comfortable with the equivalent safety/efficacy to standard of care Lantus, but we're also glad to see Basaglar quickly becoming a more established product on the market - listed at a 15% discount vs. Lantus, this drug could be cost-saving for patients, payers, and health systems.
    - **Two more biosimilar basal insulins are coming soon:** (i) Merck's Lusduna Nexvue (biosimilar glargine) received tentative FDA approval in July 2017, while (ii) Mylan/Biocon submitted an NDA for Semglee (also a biosimilar version of glargine) in 3Q17. Both products are currently facing patent infringement lawsuits from Sanofi over Lantus, which need to be resolved prior to full approval/US launch. That said, Lilly/BI faced a similar lawsuit from Sanofi and settled this with a royalty deal and agreement to delay Basaglar's US launch. All things considered, it seems like we could be looking at a basal insulin market with three biosimilars by 2019/2020. Lusduna Nexvue and Semglee could also benefit from Basaglar paving the way and cultivating familiarity with the concept of a biosimilar, though we imagine Mylan/Biocon may encounter some quality assurance issues, as neither company has extensive experience in insulin manufacturing.
- **Changes to the Medicare Part D formulary for basal insulin have been a talking point on several 4Q17 earnings calls.** In 2018, Medicare Part D has excluded Lantus and Toujeo, favoring Tresiba and Basaglar as tier 2 drugs (where a higher tier suggests lower coverage/higher out-of-pocket costs for the patient). Management from Novo Nordisk and Lilly called attention to this revision as an upcoming tailwind, and Lilly's Head of Diabetes and SVP Mr. Enrique Conterno shared that Basaglar uptake has been particularly strong since the new formulary went into effect on January 1. On the flip side, Sanofi management pointed to expected loss in the Medicare Part D channel in the year ahead. This is the latest formulary exclusion for Lantus (after CVS Health and UnitedHealthcare), and it could be a blow to the Toujeo business in 2018 as well. These are our early speculations; we'll learn more about Part D basal insulin dynamics during 1Q18 earnings season. Big picture, this latest formulary story underscores persistent US pricing pressure around diabetes drugs - and above all, around insulin - as private and public payer contracts become more exclusive. As the ADA highlighted in a statement issued last Summer, this practice from PBMs can be quite

damaging for patients, as it restricts therapy choice and often interrupts continuity of care for an individual with diabetes.

Figure 2. Basal Insulin Market (1Q06-4Q17)



3. Next-Generation Basal Insulins Climb 57% YOY to $2.1 Billion in 2017; Tresiba Awaiting FDA Ruling on Hypo Claim in 1Q18; Novo Nordisk and Sanofi Forge Ahead with Head-to-Head Trials of Tresiba vs. Toujeo

Combined full year sales of Novo Nordisk's Tresiba (insulin degludec) and Sanofi's Toujeo (insulin glargine U300) grew a remarkable 57% YOY to $2.1 billion (from a base of $1.3 billion in 2016). This jump is all the more impressive against the backdrop of 3% YOY decline in the basal insulin market overall. In 4Q17, combined revenue grew 18% YOY and 10% sequentially to $561 million (from a base of $475 million in 4Q16 and $510 million in 3Q17). This was an easy sequential comparison, following 10% QOQ decline in 3Q17. Moreover, growth in 4Q17 was entirely driven by Tresiba (+31% YOY to $302 million), as Toujeo took an unexpected dip (-4% YOY to $259 million). That said, both franchises showed a strong financial performance in 2017 overall (Tresiba +80% YOY to $1.1 billion, Toujeo +26% YOY to $926 million), and the advanced products now account for 22% of the $2.5 billion basal insulin market, up from 18% in 4Q16 and 21% in 3Q17. Tresiba captured 54% of next-gen pooled sales in 4Q, and Toujeo captured the remaining 46%. Tresiba's market share by value has climbed steadily (47% in 4Q16), and it also outpaced Toujeo in market share by volume over the past year, holding 11% of total basal insulin prescriptions (TRx) in the US as of January 2018 compared to Toujeo's 8%. Notably, Novo Nordisk met its goal of surpassing 10% TRx with Tresiba by year-end. Tresiba's growth could accelerate in 2018 pending FDA approval of a hypoglycemia claim for the insulin degludec label. An FDA decision is expected in 1Q18. The EMA approved this label change based on DEVOTE data in 3Q17, and we have our fingers crossed for a parallel decision in the US, though the specifics are still to be determined. To be sure, reflecting a hypoglycemia benefit for a diabetes product is

unchartered territory for regulators, but we hope FDA responds positively considering the tremendous quality of life impact of hypoglycemia for patients.

- **Head-to-head RCTs sponsored by each company are underway.** Novo Nordisk appears to be capitalizing on hypoglycemia data to differentiate Tresiba from first-gen products and from Sanofi's next-gen Toujeo: A phase 3 study was posted on ClinicalTrials.gov in March 2017, randomizing participants (n=1,590) to Tresiba or Toujeo for 52 weeks with a primary endpoint of severe or blood glucose-confirmed symptomatic hypoglycemia. This Novo Nordisk-sponsored trial is expected to complete in October 2018, and management implied that results will be available in 4Q18. Sanofi's EVP of Diabetes & Cardiovascular Mr. Stefan Oelrich highlighted topline data from the BRIGHT study (n=929) during Q&A. We got our first glimpse at these results at IDF 2017: Toujeo met its primary endpoint of non-inferiority to Tresiba in terms of A1c-lowering over 24 weeks; hypoglycemia was a secondary endpoint, but no relevant data has been disclosed. Mr. Oelrich announced that full results from BRIGHT will be presented at ADA 2018 in Orlando. He also briefly discussed Sanofi's real-world evidence campaign, which has revealed lower rates of severe hypoglycemia with Toujeo vs. Lantus (the LIGHTNING program) and similar rates with Toujeo vs. Tresiba (DELIVER-D). Mr. Oelrich argued that Toujeo will maintain its competitive edge on the market, even if Tresiba wins a hypoglycemia claim in 1Q18, because of its compelling clinical profile and clear superiority over first-generation basals. We certainly agree that both Tresiba and Toujeo are so much better than what came before. We wouldn't be at all surprised if Toujeo comes with some hypoglycemia benefit over Lantus, given its more stable PK/PD profile, although Novo Nordisk is ahead of the game in showing this key advantage to Tresiba. What we've gathered from thought leaders, clinicians, and some patients is that insulin degludec is a "better" product in many ways (a true 24-hour PK/PD profile, more flexibility around missed doses, higher patient satisfaction scores), but Toujeo is the preferred option for many people who are familiar with glargine and with Sanofi's SoloStar pens - plus, we emphasize again, it's a big step above Lantus and other first-gens.

4. Rapid-Acting Insulins Rise 4% YOY in 2017 as Market Continues to Fluctuate, Hovering Around $6.4 Billion for Full Year and $1.6 Billion/Quarter; Next-Gen Fiasp Just-Launched in US, Biosimilar Admelog On Its Heels

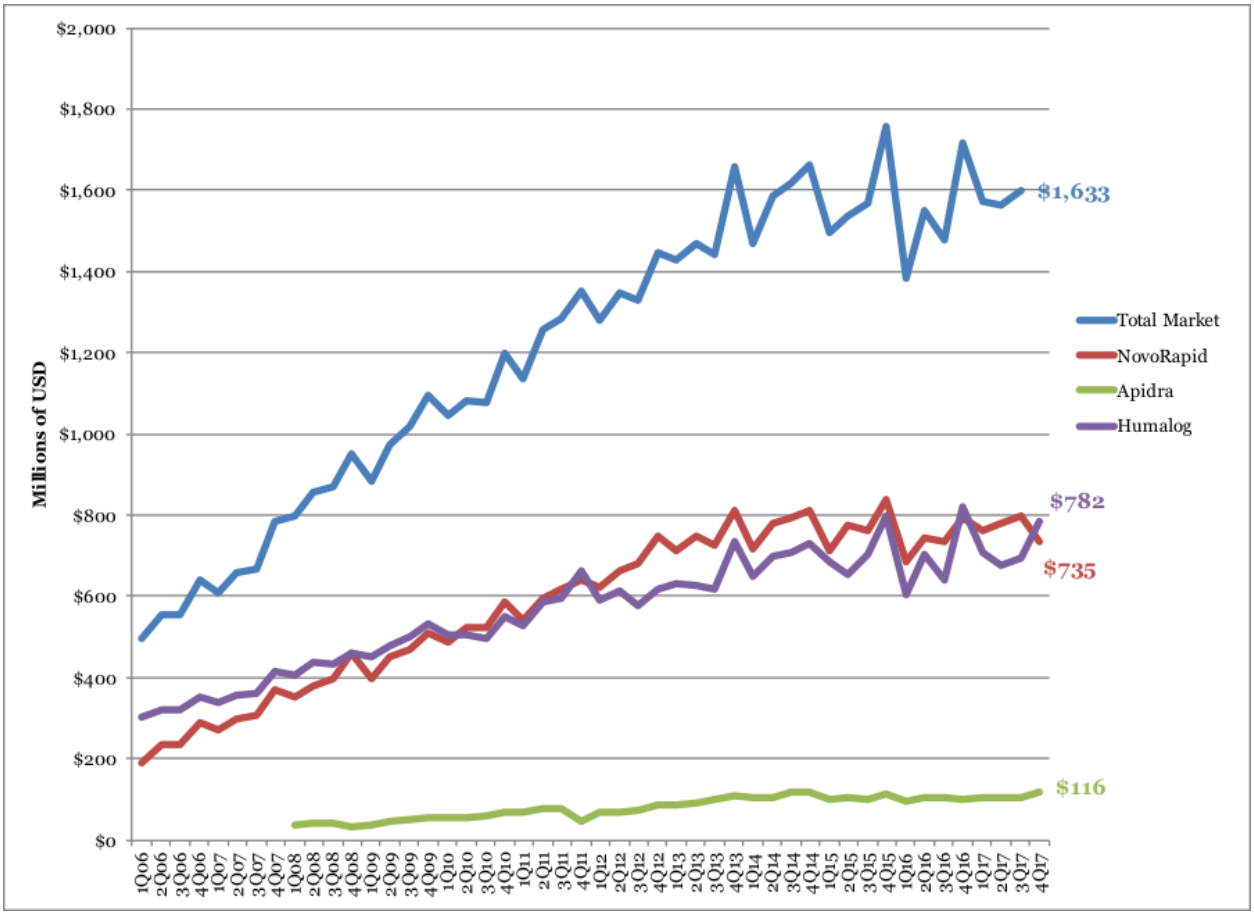
Pooled sales of major mealtime insulin products (Novo Nordisk, Lilly, Sanofi) rose a modest 4% YOY in 2017, totaling $6.4 billion (vs. $6.1 billion in 2016). This growth comes against an easy comparison of 4% decline between 2015 and 2016. In other words, the 2017 financial performance of rapid-acting insulins is more so a sign of fluctuating class sales rather than renewed growth. For additional context, the market summed to $6.3 billion in 2014 and $6.4 billion in 2015. Mealtime insulin products are subject to intense pricing pressure in the US (we've heard from all three manufacturers that payer contracts are more exclusive the rapid-acting category vs. any other diabetes drug class) as well as increasing competition from GLP-1 agonists and SGLT-2 inhibitors, advanced therapies that address postprandial glucose excursions without added hypoglycemia risk. To this end, the GLP-1 market surpassed the rapid-acting insulin market in 2017 ($6.5 billion total vs. $6.4 billion total) and in 4Q17 ($1.9 billion vs. $1.6 billion). Pooled revenue from rapid-acting insulins fell 5% YOY and grew 2% sequentially in 4Q17 to $1.6 billion (vs. $1.7 billion in 4Q16 and just under $1.6 billion in 3Q17). Once again, we emphasize the fluctuations in this market, a trend that's also depicted clearly on the graph below. Sales of Lilly's Humalog (insulin lispro) fell 6% YOY in 4Q17 to $782 million, reflecting 48% of total class sales. Novo Nordisk's NovoLog (insulin aspart) fell 11% YOY to $735 million, reflecting 45% of total class sales. Lastly, Sanofi's Apidra (insulin glulisine) grew 2% YOY and 9% sequentially to $116 million, reflecting 7% of total class sales.

- **Very notably, Novo Nordisk's next-gen Fiasp (faster-acting insulin aspart) was just launched in the US following FDA approval at the tail end of 3Q17.** The company has yet to break out Fiasp sales, but wraps these into reported revenue from the new-generation insulin portfolio (comprised of Tresiba, Xultophy, Ryzodeg, and Fiasp). We thus estimate OUS Fiasp sales at <$20 million for the full year 2017, but we expect this franchise to take off now that the product is

available in the US, the largest market for diabetes worldwide. Fiasp is the first injectable prandial insulin approved without a pre-meal dosing recommendation on its label, which affords greater flexibility and convenience to patients (a dose can be taken up to 20 minutes after a meal begins). We imagine Fiasp could help mitigate fear of hypoglycemia, since the faster-offset/shorter tail ensures that less residual bolus insulin lingers in the bloodstream. This is not trivial - 79% of type 1 patients and 58% of type 2 patients lower their insulin doses following an episode of severe hypoglycemia, leading to suboptimal glycemic control, and 72% of PCPs alongside 79% of diabetes care specialists say they'd treat hyperglycemia more aggressively if fear of hypo wasn't a factor. Fiasp could be empowering on the patient side and on the provider side, helping both parties feel more successful in diabetes care. Also exciting, Novo Nordisk has decided to price Fiasp on par with NovoLog across all global markets, including the US, which should help support real-world uptake and payer negotiations. Reimbursement will be gradually built up over the course of 2018 and beyond. For much more detail, see our recent report on Fiasp's US launch.

- **Sanofi will also launch the first biosimilar mealtime insulin in 2018: Admelog is a biosimilar formulation of Lilly's Humalog (insulin lispro).** The product received full FDA approval in December 2017, and although management hasn't been super specific about launch timing, Sanofi's 4Q17 presentation slides suggest that Admelog revenue should be expected in 2H18 financial results. We imagine this biosimilar market entry could cause ripples in the rapid-acting insulin class, but an appreciable impact on market dynamics may not be visible until 2019, as Sanofi will have to build up reimbursement. To be sure, neither Admelog nor Fiasp will be immune to the commercial challenges affecting all rapid-acting insulins. Lilly CEO Mr. Dave Ricks spoke to this at JPM, suggesting that pricing pressure is so intense around prandial insulin that Humalog and NovoLog are "already on the floor, with some of the lowest pricing in the market." Mr. Ricks went on to explain how this distinguishes the Humalog/Admelog story from the Lantus/Basaglar story - Humalog may already be priced competitively and may be able to maintain its current reimbursement status, even in 2019 and beyond, while Lantus faced a major headwind with the CVS Health and UnitedHealthcare formulary exclusions in 2017. Presumably, Admelog will be priced at a 15%-20% discount relative to Humalog. We'll be watching closely to see how the Humalog business responds to Admelog's US launch. The product is already available in Europe under brand name Insulin lispro Sanofi.

Figure 3. Rapid-Acting Insulin Market (1Q06-4Q17)



5. Basal Insulin/GLP-1 Fixed-Ratio Combinations: Disappointing First Year of $143 Million Revenue; +45% Sequentially to $54 Million in 4Q17

Basal insulin/GLP-1 agonist fixed-ratio combinations - a class comprised of Novo Nordisk's Xultophy (insulin degludec/liraglutide) and Sanofi's Soliqua (insulin glargine/lixisenatide) - rose 45% sequentially to $54 million in pooled revenue for 4Q17. In its first year of reported sales, the class grew from $19 million in 1Q17, to $33 million in 2Q17, to $37 million in 3Q17, and now to $54 million. Total 2017 sales were $143 million. Xultophy sales have comprised the majority of this revenue, at 79% of combined sales in 1Q17, 85% in 2Q17, 76% in 3Q17, and 80% in 4Q17. This is despite a lack of explicit commercial investment in the product from Novo Nordisk. Indeed, management has been consistently clear that they're focused on growing Victoza and Tresiba separately before turning to the combination. To our understanding, Sanofi has been much more committed to Soliqua - making its commercial performance (+13% sequentially to only $11 million for 4Q) all the more disappointing. During Sanofi's prepared remarks, management commented that Soliqua's launch is progressing slower than expected, and we suspect both Xultophy and Soliqua are facing significant headwinds in terms of (i) securing reimbursement and access, and (ii) overcoming HCP reluctance toward and lack of familiarity with titratable, injectable combination therapy. Throughout 2017, we were disappointed in the sluggish growth of this class, which carries incredible glucose-lowering efficacy and an improved side-effect profile vs. either drug alone. That said, there is some glimmer of hope: In France, Xultophy (but not Tresiba) gained market access and has grown to claim 14% of the basal insulin market by value there. In Greece, Tresiba holds 23% and Xultophy 20% of the basal insulin market by value - it's clear that patients and providers can, in the real world, adopt and use these combinations. We'll be keeping a close eye on how Novo Nordisk and Sanofi prioritize and promote Xultophy and Soliqua in 2018 and beyond.

- **When launched in the US, Soliqua was priced at parity with standalone GLP-1 agonists, around $20-$25/day, while Xultophy was priced at a premium, around $31/day.** It seems likely that these numbers have gone up a bit since each company announced its pricing strategy: At our local CVS, we found list prices of $794 for Soliqua and $1,170 for Xultophy, per five-pen box, which translates to $26/day and $39/day, respectively (if a person uses all five pens in a month). For comparison, Trulicity and Bydureon are both listed around $800/month ($27/day), and Victoza is ~$643/month ($21/day). That said, we understand list prices may differ somewhat between pharmacies, and we recognize that these prices don't reflect insurance coverage or patient discounts. This also suggests to us that reimbursement remains poor for fixed-ratio combination products, because ostensibly, Soliqua costs about the same as leading once-weekly GLP-1s, and yet revenue is disappointingly low. We saw enormous revenue potential when these fixed-ratio agents hit the market: Our late 2016 estimate was $1-$3 billion in the US by ~2020, which now seems all but impossible.

Financial Highlights

6. Sanofi's Diabetes Portfolio Falls 16% YOY in 4Q17, -11% YOY in 2017; Signals Challenging Quarter and Year; Decline Driven by Lantus Losses, Somewhat Buffered by Toujeo

In 4Q17, Sanofi's total diabetes sales declined 21% YOY as reported (-16% operationally) to €1.5 billion ($1.8 billion), from a base of €1.9 billion ($2 billion) in 4Q16. The portfolio was flat (-1%) sequentially. Looking at 2017 as a whole, Sanofi's diabetes sales of €6.4 billion ($7.2 billion) dropped 13% YOY as reported (11% operationally) from €7.3 billion ($8.1 billion) in 2016. US sales were hit especially hard, dropping 24% YOY as reported (23% operationally) to €3.1 billion ($3.5 billion) from €4.1 billion ($4.6 billion) in 2016. Management emphasized that a stronger 4Q16 performance in the US (+7% YOY) amplified the expected YOY loss in 4Q17: For the quarter, US sales declined 36% YOY as reported (-30% operationally) to €730 million ($875 million), and management cited approximately 20% YOY revenue decline in the US for the first nine months of 2017. Diabetes sales in other geographies were relatively flat in 4Q17, though management highlighted an 8% YOY rise in emerging markets and a "slight" 1% YOY rise in Europe. Management noted reduced Medicare Part D coverage for Sanofi's diabetes products beginning January 1 - specifically, Lantus and Toujeo - as well as a continued but expected decline in average net price (indicating high rebates going to PBMs/payers). These variables lead us to expect another less-than-stellar year from Sanofi Diabetes in 2018. The one bright spot in Sanofi's diabetes portfolio globally comes from next-gen basal insulin Toujeo, which still somewhat underwhelmed with $925 million in sales for 2017, up only 26% YOY compared to 2016, though it is gaining market share globally (according to management's comments). Adjacent to diabetes, Regeneron-partnered PCSK9 inhibitor Praluent is also growing, slowly but surely (+67% YOY for the full year, +54% YOY for the fourth quarter). We're looking forward to ODYSSEY Outcomes CVOT results to be presented as a late-breaker at ACC. You can read about these individual products in more detail below.

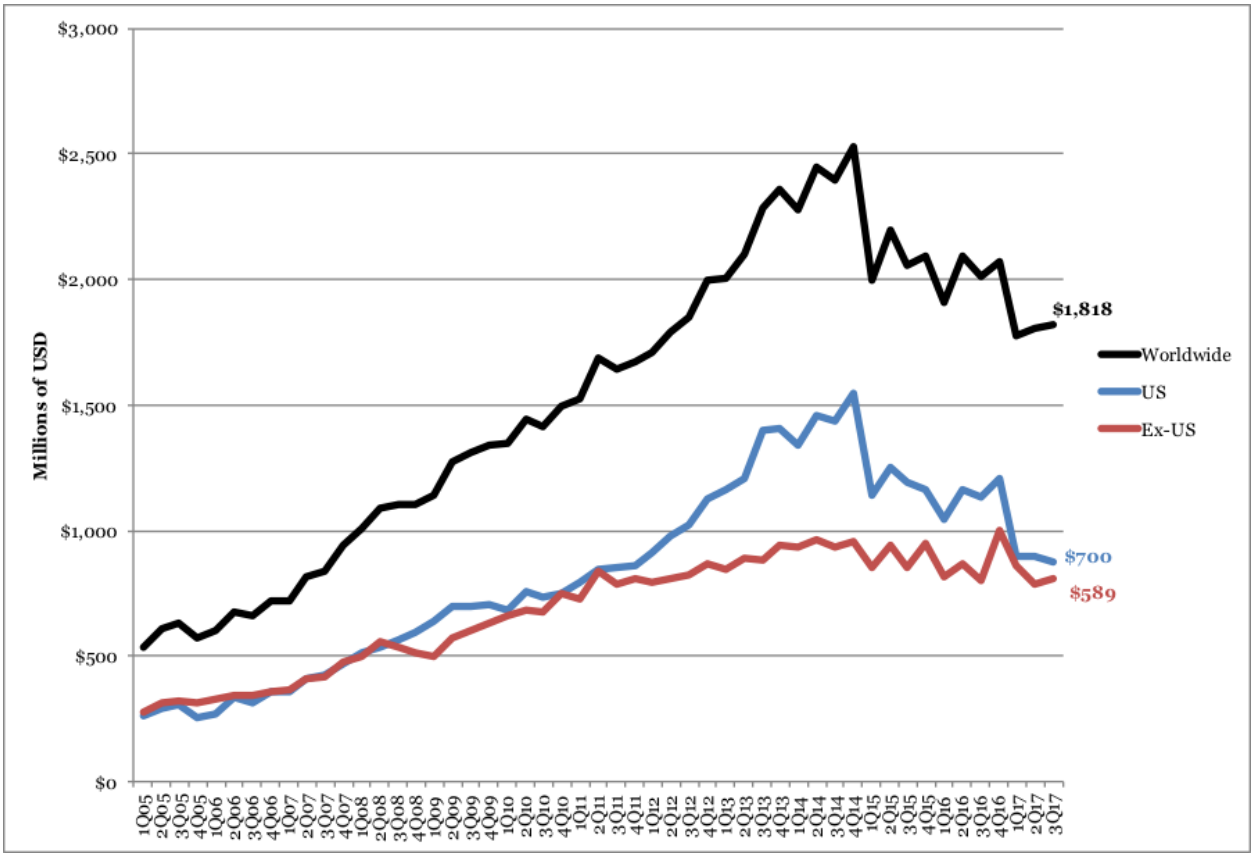
- **The full year revenue of -11% YOY to $7.2 billion comes in below Sanofi's latest guidance of 6%-8% annual loss in the diabetes business over 2015-2018. That said, the overall diabetes portfolio fell a smaller 3% YOY in 2016 and grew a modest 4% YOY in 2015, so there is some averaging out.** On the call, management shared that Sanofi is still on track to meet its revised guidance of minus 6%-8% for the full four-year period, projecting a 9% decline YOY in 2018.

7. Lantus Drops 21% YOY in 4Q17, -18% YOY in 2017; Revenue Down to $5.2 Billion for Full Year; Sluggish Lantus Sales Drive Decline for Sanofi's Overall Diabetes Portfolio

Sales of basal insulin Lantus (insulin glargine) fell 27% YOY as reported (21% operationally) and 4% sequentially in 4Q17 to €1.1 billion ($1.3 billion), down from €1.5 billion ($1.6 billion) in 4Q16 and €1.1 billion ($1.3 billion) in 3Q17. Full year Lantus revenue fell 19% YOY as reported (18% operationally) to €4.6 billion ($5.2 billion) from €5.7 billion ($6.3 billion) in 2016. During Q&A, EVP of Diabetes & Cardiovascular Mr. Stefan Oelrich commented that losses in both prescription volume and revenue are progressing as expected - he underscored that this downward trajectory for the Lantus business is not at all a surprise. Management specifically pointed to biosimilar competition from Lilly/BI's Basaglar (biosimilar insulin glargine), and to exclusion from the CVS Health and UnitedHealthcare formularies (Lantus is also excluded on the Medicare Part D formulary for 2018 - another headwind). These revenue losses are by far the most significant factor contributing to the overall decline in Sanofi's diabetes portfolio (-11% YOY in 2017, -16% YOY in 4Q17). US sales have been hit particularly hard by formulary exclusions and lower average net price (indicating high rebates, now characteristic of the insulin market), with Lantus sales down 36% YOY as reported (31% operationally) in 4Q17 to €584 million ($700 million). Europe has fared somewhat better, dropping 8% YOY (as reported and operationally) to €183 million ($219 million) in 4Q17; Sanofi cited biosimilar competition and Toujeo switching as most important in this market. Lantus has ultimately been on the decline since ~2014, facing an onslaught of new market entries, including next-generation basal insulins Tresiba (Novo Nordisk) and Toujeo (Sanofi), and now biosimilar Basaglar (Lilly/BI). We expect the decline will only intensify as more patients switch to cheaper biosimilar insulins, and as more biosimilar options reach the market.

- **Sanofi has filed patent infringement lawsuits against (i) Merck for its biosimilar insulin glargine Lusduna Nexvue and (ii) Mylan for its Biocon-partnered biosimilar glargine.** Lusduna Nexvue received tentative FDA approval in July 2017, meaning the product can be launched in US pharmacies pending lawsuit resolution; Mylan's has not received tentative approval but recently received a positive CHMP opinion for the EU. It took ~30 months after Sanofi initially filed its lawsuit against Lilly/BI for Basaglar to launch in the US, so it could be a while before the Merck and Mylan/Biocon products reach the US market, but they're nevertheless on the horizon. Previously, Mr. Oelrich suggested that FDA may be granting interchangeability designations to biosimilar basals by 2020, which would allow a pharmacist to switch patients between products without consulting the prescriber. On the other hand, Lilly's Head of Diabetes and SVP Mr. Enrique Conterno has argued that interchangeability for biosimilar insulins won't be a factor until much further into the future.
- **Sanofi's insulin glargine franchise (Lantus + Toujeo) fell 15% YOY in 4Q17, driven by declining Lantus sales.** Meanwhile, Toujeo revenue fell by a smaller margin YOY (-9% as reported, -4% operationally) to €216 million ($259 million) - more below. The insulin glargine business was flat sequentially between 3Q17 and 4Q17. In 2017 overall, Lantus + Toujeo sales of $6.2 billion represented 12% YOY decline from $7 billion in 2016 overall. Since Toujeo revenue grew on the year, this once again shows how Lantus is driving decline for Sanofi Diabetes.

Figure 4. Lantus Sales (1Q05-4Q17)



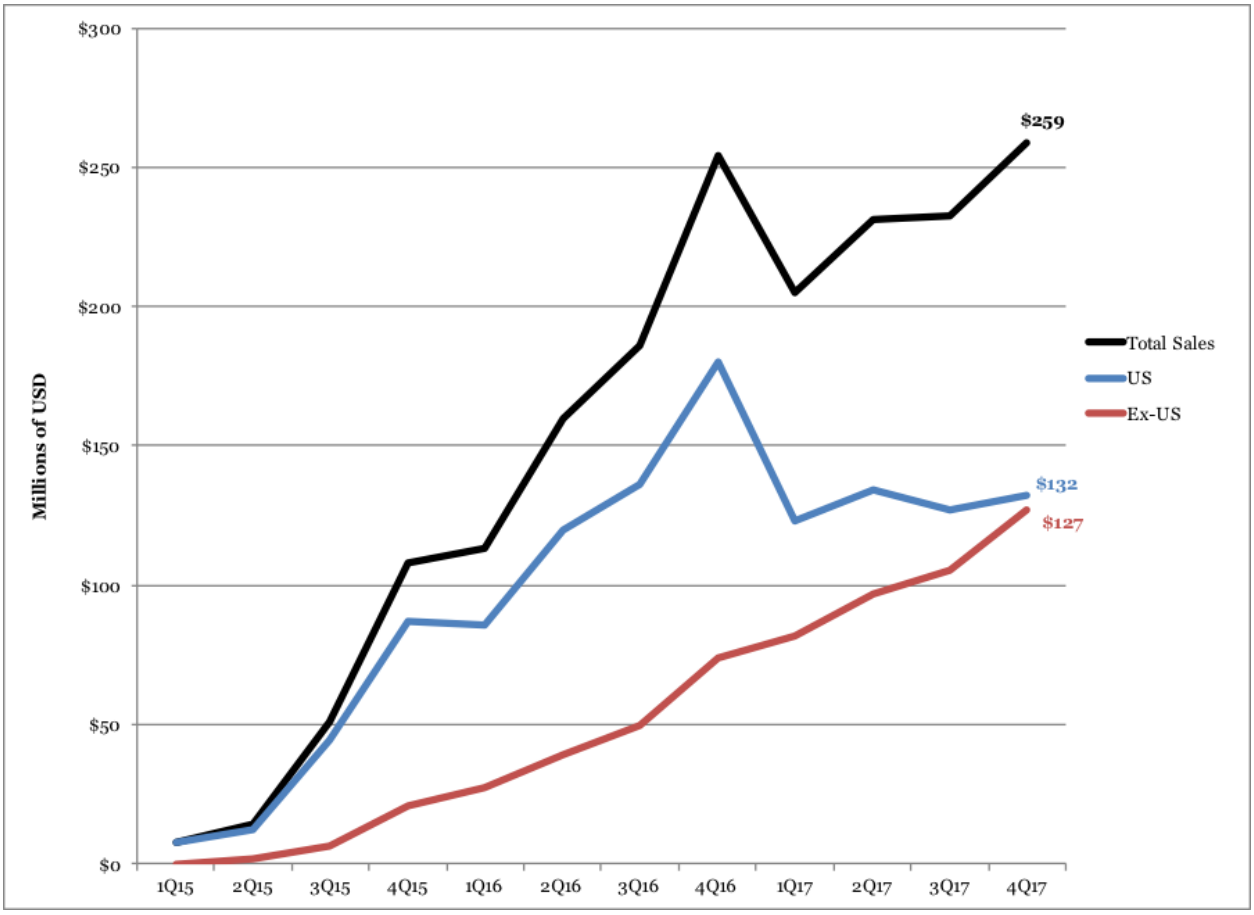
8. Toujeo Sales Fall 4% YOY in 4Q17, but Climb 27% YOY in 2017 to $926 Million Globally; Headwinds in the US Drive Revenue Down 30% in 4Q

Despite a weak performance in 4Q17, when sales fell 9% YOY as reported (-4% operationally) to €216 million ($259 million), Toujeo was a bright spot in Sanofi's diabetes portfolio for 2017 overall, growing 26% YOY as reported (+27% operationally) to €816 million ($926 million). Management highlighted strength in Europe and emerging markets, where Toujeo revenue climbed 81% YOY (posting €217 million, or $246 million) and quadrupled YOY (to €79 million, or $90 million), respectively. This positive performance was offset by 2% YOY decline in the US market, to €455 million ($516 million) vs. €475 million ($526 million) in 2016. US revenue was a thorn for the global Toujeo business in 4Q17 as well: In the US, sales dropped 35% YOY as reported (-30% operationally) to €110 million ($132 million). Meanwhile, sales in Europe grew 51% YOY to €63 million ($74 million) and sales in emerging markets grew 73% YOY to €25 million ($30 million). Sequentially, total global Toujeo sales rose 2% against a very easy comparison of 12% QOQ decline in 3Q17 (to $233 million). Toujeo's share of total basal insulin prescriptions in the US (TRx) was 8% as of January 2018, down from 9% as of October 2017 (slide 9) - another indication of US headwinds for the product (in contrast, Tresiba's TRx rose from 9% to 11% between October 2017 and January 2018). Management explained that Sanofi is "seeing the expected impact of loss in Medicare Part D since January 1," with an unspecified dip in prescriptions in the Medicare segment. Broadly, pricing pressure continues to swirl around insulins in the US, leading to higher rebating and lower realized price per prescription for the manufacturer; we suspect this was another factor muting Tresiba's 2017 growth and spurring the 4Q17 decline.

- **During Q&A, Mr. Oelrich expressed confidence in Toujeo's clinical profile and argued that it will maintain its competitive edge on the market if/when Novo Nordisk's Tresiba receives a hypoglycemia claim.** FDA is evaluating relative risk reduction for severe hypoglycemia with Tresiba vs. Lantus as seen in the DEVOTE and SWITCH studies, and a final decision for the US label is expected in 1Q18. This would certainly stimulate growth for Tresiba, but

Mr. Oelrich didn't seem worried about any adverse impact on Toujeo. He highlighted topline data from the BRIGHT study (n=929), discussed during a corporate symposium at IDF 2017, in which Toujeo met its primary endpoint of non-inferiority to Tresiba in terms of A1c-lowering over 24 weeks. Hypoglycemia was a secondary endpoint in BRIGHT, but to-date, this data hasn't been disclosed. Mr. Oelrich announced that full results from BRIGHT will be presented at ADA 2018 in Orlando. He also briefly discussed Sanofi's real-world evidence campaign, which has revealed lower rates of severe hypoglycemia with Toujeo vs. Lantus (the LIGHTNING program) and similar rates with Toujeo vs. Tresiba (DELIVER-D). Without a doubt, we see Toujeo as a very important product for diabetes care, bringing many patients an advanced basal insulin option with a more stable PK/PD profile compared to earlier options. It's clearly an important product for Sanofi Diabetes. We're skeptical that it will demonstrate the same level of overall efficacy as Tresiba (thought leaders seem to agree that insulin degludec has a flatter 24-hour profile), considering A1c and beyond-A1c effects all together, but the take-home message here is that both next-gen basals are so much better than what came before. We'd like to see both businesses grow substantially in 2018, with spikes in volume and sales.

Figure 5. Toujeo Sales (1Q15-4Q17)



9. Soliqua Disappoints with Only $30 Million in 2017; 4Q17 Sales Rise Merely 13% Sequentially to $11 Million; Issues of Access and HCP Reluctance Toward Fixed-Ratio Combos

Soliqua sales of €9 million ($11 million) in 4Q17 grew 13% sequentially from €8 million ($9 million) in 3Q17. In its first year on the market, the fixed-ratio combination (insulin glargine/lixisenatide) posted only €26 million ($30 million) in sales, essentially all from the US. We noted minus €1 million in 4Q17 sales for the "rest of the world" segment, and it's not clear what this means.

Sequential growth was 25% in 2Q17 and 60% in 3Q17. This is very underwhelming for a product so early in its launch cycle (Soliqua became available in the US in January 2017), and it speaks to both poor market access as well as HCP reluctance (especially in the US) to prescribe fixed-ratio combination therapy. Sanofi's slides noted that launch is progressing more slowly than expected - Soliqua has only been launched in "some European countries" and clearly hasn't taken hold in the US - and our sense is that both payers and providers aren't entirely sure how to handle these fixed-ratio combinations (also Novo Nordisk's Xultophy). Soliqua was not discussed on the call, but in the past, Sanofi has highlighted its peer-to-peer medical education efforts that could overcome provider reluctance, and has given an update on covered lives (up to 65% for commercial insurance and 25% within Medicare Part D as of 3Q17, though this doesn't speak to co-pays, which are at least as important). We've perceived Sanofi's commitment to Soliqua, so far, as much greater than Novo Nordisk's commitment to Xultophy (insulin degludec/liraglutide); the thinking has seemed to be that standalone GLP-1 agonist Lyxumia (lixisenatide), which never took off commercially, could find a new life in Soliqua. We're hoping the lack of discussion on the 4Q17 call is not reflective of waning enthusiasm for Soliqua among Sanofi management, though we are curious how they view the product now that promising once-weekly GLP-1 agonist efpeglenatide has been advanced into phase 3. Ultimately, we're disappointed that neither Soliqua nor Xultophy have become more widespread within real-world diabetes care, given their remarkable clinical profile - impressive glucose-lowering with less hypoglycemia risk and a milder side-effect profile compared to either basal insulin or GLP-1 monotherapy.

- **Soliqua's US label is relatively restrictive, indicating the combination only for type 2 diabetes patients not at goal on basal insulin glargine or lixisenatide monotherapy, presenting another serious barrier to uptake.** In contrast, the EMA-approved label indicates Suliqua for intensification as well as second-line therapy to metformin, reflecting what we see as greater clinical inertia against early intensification in the US compared to Europe. The US indication effectively constricts the number of patient-years during which someone can benefit from Soliqua; earlier initiation of this combo agent (without having to wait for insulin glargine or lixisenatide monotherapy to fail) could prevent long-term complications by offering more quick, efficient glucose-lowering and postprandial control. The Soliqua marketing team is tasked with pitching this product as an intensification option, while also trying to shift the entire diabetes treatment paradigm - no small set of tasks.
- **Sales of standalone GLP-1 agonist Adlyxin (lixisenatide) fell ~29% YOY and sequentially to €5 million ($6 million) in 4Q17.** This was from a base of $7 million in 4Q16 and $8 million 3Q17. For the full year 2017, the product grossed €26 million ($30 million) in total revenue, falling 21% YOY as reported from $37 million in 2016. Adlyxin claimed <1% of the GLP-1 agonist market, which combined for ~$6.5 billion in revenue for 2017.

10. Praluent Sails through Headwinds to $63 Million in 4Q17, +54% YOY; Revenue Rises 67% Over 2016 to $194 Million in 2017 Sales; ODYSSEY Outcomes Data Coming at ACC 2018; Planned Filing for CV Indication in 3Q18

Sales of Regeneron-partnered PCSK9 inhibitor Praluent (alirocumab) grew 43% YOY as reported (54% operationally) and 26% sequentially to €53 million ($63 million) in 4Q17. This was from a base of €37 million ($39 million) in 4Q16 and €42 million ($49 million) in 3Q17. In 2017 overall, Praluent revenue rose 63% YOY as reported (67% operationally) to €171 million ($194 million) vs. €105 million ($116 million) in 2016. US revenue continues to make up the majority of sales (67%), growing 17% YOY as reported (30% operationally) and 25% sequentially in 4Q17 to €35 million ($42 million). For 2017, US sales totaled €116 million ($132 million), representing a 37% YOY rise as reported (40% operationally) over 2016. Ex-US growth was even stronger, with sales more than doubling YOY and rising 29% sequentially in 4Q17 to €18 million ($22 million); 2017 sales nearly tripled YOY from 2016 to €55 million ($62 million). With respect to OUS revenue, ~84% came from Western Europe. Sanofi's slides noted that Praluent launch is, like Soliqua's, progressing slower than expected, following ~two years of sales in the US. Praluent's only competitor in the PCSK9 inhibitor class, Amgen's Repatha (evolocumab), grew 69% YOY in 4Q17 to reach $98 million in sales; we view this as a marginal lead over Praluent considering the promise of these advanced

lipid-lowering drugs, far superior to statins in terms of efficacy. In 3Q17, Praluent held 40% of all PCSK9 inhibitor prescriptions in the US. To be sure, the PCSK9 class has faced enormous headwinds, particularly in access/reimbursement. Both Praluent and Repatha are indicated only (i) as an adjunct to maximally-tolerated statin therapy for people with heterozygous familial hypercholesterolemia or atherosclerotic CV disease who require additional LDL-lowering, or (ii) as an adjunct to other LDL-lowering therapies in patients with homozygous familial hypercholesterolemia. Due to the extremely high list price (~$14,000/year), we've heard that prior authorizations are all but necessary (and rejected as much as 96% of the time) to get access to PCSK9s.

- **Management highlighted that ODYSSEY Outcomes CVOT data will be presented as a late-breaker at ACC 2018 in March.** They suggested that no topline data will be released before then, as results are arriving just in time for the ACC conference and aren't yet available in house, either. Pending positive results, presentation slides reiterated that Sanofi/Regeneron could file with FDA in 3Q18 for Praluent's CV indication (notably, Amgen's Repatha was granted a CV indication in December 2017 for prevention of heart attack, stroke, and coronary revascularization in people with established CV disease). During Q&A, management elaborated on the impact that positive CVOT data could have - not only for the Praluent business, but for the PCSK9 class as a whole.

Pipeline Highlights

11. Sanofi-Led Filing of Sotagliflozin for Type 1 Diabetes Planned for 1Q18

Sanofi's presentation (slide 24) indicated a slightly expedited timeline for sotagliflozin submission to FDA - 1Q18 as opposed to 1H18. The SGLT-1/2 dual inhibitor is partnered with Lexicon for a type 1 diabetes indication (Lexicon led all pivotal studies, including inTandem3 presented by Professor Melanie Davies at EASD 2017). This plan for swift submission doesn't come as a surprise to us, since Lexicon management has said repeatedly that they're targeting "the earliest part of 1H18." Sotagliflozin stands to be the first-to-market oral adjunct therapy for type 1 diabetes, and you can bet we're excited about this one. The agent has shown significant glucose-lowering, weight loss, and reduced total daily insulin dose across the inTandem clinical program. Perhaps the most important benefit is increased time-in-range: Pooled CGM data from inTandem1 and inTandem2 found 5% (1.3 hours) extra time-in-range with the 200 mg dose vs. placebo ($p=0.026$), 12% (2.8 hours) extra with the 400 mg dose vs. placebo ($p<0.001$). In our view, these benefits far outweigh any heightened DKA risk, especially since there's growing consensus among thought leaders that this risk should be manageable in the real world with patient education and diligent monitoring. As we wrote in our 2017 + 2018 reflections piece, the past year featured much more consensus on this topic relative to 2016, which gives us hope. As for the competitive landscape, AZ is planning to file its SGLT-2 inhibitor Farxiga (dapagliflozin) for a type 1 indication in 2H18, based on results from DEPICT 1 (also presented at EASD) and DEPICT 2 (upcoming). Lilly/BI will share data from the phase 3 EASE program investigating Jardiance (empagliflozin) in type 1 diabetes sometime in 2018. We're tempted to put "competitive" in quotes, because we actually see more than enough room for all these products to be successful on the market for type 1. Adjunct treatment to insulin for people with type 1 diabetes feels long overdue (Dr. Chantal Mathieu positioned this as an area of high unmet need during an EASD talk), and we're pleased to see continued commitment from Sanofi/Lexicon, as well as AZ and Lilly/BI. Sanofi is leading the phase 3 program investigating sotagliflozin in type 2 diabetes. There were no updates on this front during the 4Q17 update, but the table below offers a summary of ongoing studies.

Table 4. Phase 3 Program for Sotagliflozin in Type 2 Diabetes

Trial	Estimated Enrollment	Comparator/Design	Estimated Completion
Sotagliflozin as monotherapy	400	Placebo	January 2019

Sotagliflozin as add-on to metformin	500	Placebo, metformin alone	March 2019
Sotagliflozin as add-on to a sulfonylurea	500	Placebo, metformin alone, SU alone	May 2019
SOTA-INS (add-on to insulin)	560	Insulin glargine (Sanofi's Lantus)	May 2019
SOTA-CKD3 (in patients with moderate renal dysfunction)	780	Placebo	September 2019
SOTA-CKD4 (in patients with severe renal dysfunction)	276	Placebo	September 2019
SOTA-GLIM (head-to-head vs. SU)	930	Glimepiride	May 2019
SOTA-EMPA (head-to-head vs. empagliflozin)	700	Empagliflozin (Lilly/ BI's Jardiance)	May 2019
SCORED	10,500	CVOT vs. placebo	March 2022

12. Admelog FDA-Approved as First-to-Market Biosimilar Mealtime Insulin; US Launch Coming Soon

Sanofi received full FDA approval for Admelog (biosimilar insulin lispro) in December 2017, and management suggested that this first-to-market biosimilar mealtime insulin will be an important growth opportunity for the company beginning in 2H18 (slide 31). Previously, Sanofi explained that Admelog might not be a growth driver until 2019, because it would take time to build up reimbursement. After all, the drug was approved very late in 2017, after most payer contracts for 2018 had already been negotiated. It's definitely notable that the company is showing confidence in the new product, and this hints to us that Admelog should be launched in US pharmacies in 1H18 - the sooner the better, if the biosimilar is expected to meaningfully boost pharmaceutical sales in the second half of the year. We're a bit skeptical that Admelog will revive Sanofi Diabetes so quickly, but we do see longer-term potential for the product to sustain the company's insulin business, especially as Lantus sales fall in the wake of biosimilar market entries. Moreover, a biosimilar rapid-acting insulin could be a valuable - and more affordable - addition for patients. Presumably, Admelog will be listed at a 15%-20% discount vs. Humalog, but we'll revisit this discussion once the product is on pharmacy shelves.

- **As background,** this biosimilar was EMA-approved under brand name Insulin lispro Sanofi in July 2017. It was debuted in the EASD 2017 exhibit hall, with an emphasis on lower cost and the familiar SoloStar family of pens. In the US, Admelog first received tentative FDA approval in 3Q17, before Lilly confirmed that it would not pursue a patent infringement lawsuit over Humalog.

13. Once-Weekly GLP-1 Efpeglenatide Advances into Phase 3; Study Expected to Complete January 2020; Autoinjector Developed In House

In early December 2017, Sanofi launched a phase 3 trial of once-weekly GLP-1 agonist candidate efpeglenatide (expected to complete January 2020). This was highly-anticipated, as the phase 3 start was delayed from 4Q16. Although efpeglenatide wasn't discussed during the 4Q17 update, it was highlighted during the company's Analyst Day in December, and was also featured in CEO Mr. Olivier

Brandicourt's JPM remarks. Sanofi has already developed a proprietary autoinjector for the GLP-1 agonist, the MARS platform, and has conducted modeling studies that suggest equivalent efficacy to Novo Nordisk's recently-launched Ozempic (semaglutide once-weekly). We think this conclusion should probably be taken with a grain of salt, since the model compared phase 2 efpeglenatide data to all semaglutide data, including phase 3. Nonetheless, this is an intriguing finding, and we'd certainly love to have another potent, once-weekly GLP-1 agonist available for people with diabetes. Sanofi is clearly invested in this second-generation GLP-1, and management seems to have an eye toward commercialization already (hence the autoinjector and comparisons to a current leading option). See the pooled market highlights above for our comprehensive take on the GLP-1 agonist class.

14. Sanofi Expands R&D to Obesity and NASH with GLP-1/Glucagon Dual Agonist; Phase 3 Obesity Trials Slated for 2018 Start

While not mentioned on the call, CEO Mr. Olivier Brandicourt announced at JPM that phase 3 studies of GLP-1/glucagon dual agonist SAR425899 would begin in 2018. He also shared that a phase 2 proof-of-concept trial in NASH would start this year. In phase 2, the agent stimulated >3.5 kg (~8 lbs) weight loss after four weeks, and while "cross-trial comparison can be misleading," Mr. Brandicourt suggested that this level of weight loss is at least as good if not better than what's achieved with Novo Nordisk's liraglutide (Victoza) or semaglutide (Ozempic). Sanofi's decision to expand R&D into diabetes-adjacent indications like obesity and NASH follows a trend we've noticed in the field: As the market for diabetes drugs becomes more competitive, companies are looking to obesity and NASH as areas of untapped potential, considering how vastly undertreated these diseases are. We note that there's still a substantial portion of the diabetes patient population that doesn't receive adequate medical care - and certainly not the most effective therapies in our toolkit today, such as GLP-1 agonists or SGLT-2 inhibitors - but we're also excited to note Sanofi's commitment to obesity. Management emphasized during the December 2017 Analyst Day that the GLP-1/glucagon dual agonist could make a profound impact for people with obesity, and also underscored that it could be a great value proposition for payers. That latter piece remains to be seen, since reimbursement for obesity drugs today is abysmal, but with more companies working on this, we'll hopefully start to see improved payer coverage.

Table 5. Sanofi Diabetes-Related Pipeline Summary

The table below reflects the latest updates, as far as we are aware, on Sanofi's diabetes/obesity pipeline products. Items highlighted in yellow indicate notable changes to the pipeline in 4Q17.

Candidate	Phase	Timeline/Notes
Admelog (biosimilar insulin lispro)	Approved	FDA-approved in December 2017; US launch expected sometime in 2018; EMA-approved in July 2017 under brand name Insulin lispro Sanofi; SORELLA 1 trial presented at ADA 2016; SORELLA 2 trial results presented at ADA 2017, along with one-year SORELLA 1 data
Sotagliflozin (SGLT-1/2 dual inhibitor)	Phase 3	FDA submission for type 1 indication expected 1Q18; Positive phase 3 results in type 1 (led by Lexicon) presented at

		ADA and EASD 2017; Phase 3 program in type 2 underway, readouts/FDA filing expected 2019
SAR341402 (rapid-acting insulin)	Phase 3	GEMELLI 1 (open-label vs. Novo Nordisk's NovoLog) expected to complete January 2019; FDA submission slated for 2019; Added to pipeline in 4Q16
Efpeglenatide (once-weekly GLP-1 agonist)	Phase 2	Phase 3 trial initiated in 4Q17 (delayed from 4Q16) and expected to complete January 2020; Licensed from Hanmi
SAR425899 (GLP-1/glucagon dual agonist)	Phase 2	Phase 3 trials in obesity scheduled to begin 2H18; Phase 2 proof-of-concept in NASH scheduled for 2018 study start; Phase 2 in type 2 diabetes completed December 2017; Promising phase 1 results presented at ADA 2016
SAR438335 (GLP-1/GIP dual agonist)	Phase 1	Added to pipeline in 3Q15
Once-weekly LAPSInsulin-115/ efpeglenatide combination	Preclinical	Acquired from Hanmi in November 2015; Hanmi is leading early development efforts and Sanofi will revisit this candidate in ~2019 or later

Select Questions & Answers

Q: One question on Lantus. You mentioned a more difficult 1H18 for the product, but what do you think about Novo Nordisk's Tresiba getting a hypoglycemia indication? Couldn't that confer a more difficult 2H18 for your glargine franchise as well?

Mr. Oelrich: Novo Nordisk has worked on separating second-generation basal insulins from first-generation basal insulins. We're pretty much on a very similar strategy with Toujeo, and we're eye-to-eye with Tresiba. We have recently done some really interesting work using real-world evidence that will be presented in the coming weeks, and we've also done a head-to-head trial, the BRIGHT study, and we've talked about topline results. The full data from BRIGHT will be at the ADA meeting this year, and we're waiting for publication as well. From the topline, we know that we achieved our primary endpoint against Tresiba, which shows comparable effectiveness in terms of A1c reduction. We also care greatly about the safety profile of our product, and we look forward to the final presentation at ADA. We're confident that we can very successfully separate Toujeo from first-generation basals. So, I feel quite confident about our share evolution as well. We see strong growth for Toujeo, up more than 50% in Europe, good in emerging markets. We're going in the

right direction. We're in line with what was expected for Lantus, and I don't see that going to change. I'm confident that we have all the clinical data to counter that with Toujeo on our side.

Q: How do you plan to position Praluent once the data from ODYSSEY Outcomes become available? And a follow-up to that - do you have the data internally already? Do you intend to send a press release for topline results? Or will we have to be patient and wait for the ACC late-breaking session?

Mr. Olivier Brandicourt (CEO, Sanofi): Unfortunately, I think you have to be patient. We have a late-breaker that's already booked for March 10, and that's what we're gearing toward.

Mr. Stefan Oelrich (EVP, Diabetes & Cardiovascular, Sanofi): To clarify, we don't have the data yet. We won't have the data at hand until very shortly before the late-breaker, so not only will you have to wait, but we're waiting as well. In terms of potential and positioning, we already think our target patient population for Praluent should be in line with the ODYSSEY Outcomes study population - we're going after high-risk patients and post-familial hypercholesterolemia (FH) patients. We also anticipate that if our trial reads positive, as we believe it will, that could move the needle on guidelines, because it would be the second time a PCSK9 inhibitor proves an outcome benefit. Following the trial, it could also help improve utilization management criteria; we've seen some progress for Repatha on that front throughout 2017, with lower rejection rates for prior authorizations. If we redefine the class with ODYSSEY Outcomes as we expect to do, we anticipate that by end of 2018 or early 2019, the guidelines will change to reflect the full efficacy of PCSK9s. That change will open a new opportunity for us with Praluent.

Q: What kind of data do you think is necessary to really drive the PCSK9 inhibitor market forward? Or do you think it's more a matter of getting the price right?

Mr. Elias Zerhouni (President, Global R&D, Sanofi): That's a very good question. The data that's needed, first and foremost, is outcomes data on the MACE criteria. That's the first endpoint people are going to look at. Are we reducing that to a significant extent in the population we're dealing with? Now, the two populations are also important. One is the FH population, where lifelong CV risk cannot really be mitigated with statins. These individuals have no other option than a PCSK9. The other patients are those who've had an acute CV event within the past year, and that drives event rates that are obviously higher. Ultimately, the thing that you want to show in the data is either a trend or a statistically significant reduction in CV-related mortality related to coronary disease. With Lipitor, this took a while to establish because you need a longer follow-up to collect those mortality events. We'll see in our data what the trends are.

Mr. Brandicourt: We continue to be absolutely convinced that Praluent will change medical practice. ODYSSEY Outcomes could compel payers to adapt their utilization management criteria.

Mr. Oelrich: And just for the record, guidelines are generally expected to change within six months once you have two published studies. Which is why we want to make sure we're published by the ACC.

-- by Ann Carracher, Payal Marathe, and Kelly Close