CLOSER LOOK

MEMORANDUM

Merck 2Q17 - Januvia franchise falls 8% YOY to $1.5B, driven by 11% YOY decline in US; Pooled DPP-4 inhibitor sales drop 4% YOY to $2.5B; SGLT-2 Ertugliflozin highlighted; No mention of Lusduna Nexvue - July 28, 2017

Executive Highlights

- The DPP-4 inhibitor Januvia franchise experienced 8% YOY sales decline in 2Q17, falling to $1.5 billion. This was driven by an 11% YOY drop in US sales of Januvia (sitagliptin) and Janumet (sitagliptin/metformin) to $789 million, even though US prescription volume of these products grew 3% YOY in 2Q17. Management emphasized the adverse impact of US pricing pressure (presumably, patient discounts and high rebates to PBMs) on the Januvia business.
- The DPP-4 inhibitor market as a whole fell 4% YOY to $2.5 billion in 2Q17. Merck's Januvia franchise maintained its 61% share of sales (the same proportion it held in 1Q17).
- Management expressed a great deal of optimism for Merck/Pfizer's upcoming SGLT-2/DPP-4 fixed-dose combination of ertugliflozin/sitagliptin. FDA decisions on standalone ertugliflozin, ertugliflozin/sitagliptin, and ertugliflozin/metformin are anticipated by end of 2017.
- There was no mention of Merck's biosimilar insulin glargine candidate, which recently received tentative FDA approval under brand name Lusduna Nexvue (full approval will have to wait until the lawsuit from Sanofi over infringement of Lantus patents is settled). There was also no mention of MK-2640, the company's glucose-responsive insulin candidate discontinued from phase 1 in 2Q17.

Merck provided its 2Q17 financial update in a recent call led by CEO Mr. Ken Frazier. We brought you our First Look <two hours after the webcast wrapped-up (now's as good a time as any to download our Closer Look app to receive notifications for breaking coverage!). For those of you with keen interest in the Januvia franchise, the DPP-4 inhibitor class, and/or Merck's diabetes pipeline (biosimilar insulin glargine, SGLT-2 inhibitor ertugliflozin, and more), this full report offers a deeper dive. We've also added graphs and a comprehensive pipeline summary table, and we direct you to Merck's press release here, and supplementary databook on 1H17 here.

If you're only going to read one of these six highlights below, we recommend no. 4, our pooled analysis of the DPP-4 inhibitor market in 2Q17 (down 4% YOY to $2.5 billion). Of course, it is all pretty interesting : >, so without further ado…

Financial Highlights

1. Revenue from the DPP-4 inhibitor Januvia franchise fell 8% YOY as reported (7% in constant currencies) to $1.5 billion, driven by an 11% YOY decline in US sales to $789 million. Ex-US sales showed a smaller, 3% YOY decline to $722 million. Management attributed this financial performance to continued pricing pressure in the US, which deflated sales despite 3% YOY volume growth for Januvia (sitagliptin) and Janumet (sitagliptin/metformin) prescriptions: "Each year, pricing pressure gets a little bit harder than the year before. This year is harder than last year, and I suspect next year will be harder than this year."

2. Global sales of standalone Januvia fell 11% YOY to $948 million (down from $1.1 billion in 2Q16). US sales fell a steep 14% YOY to $541 million, while ex-US sales fell 6% YOY to $407 million, in parallel to the geographical trend seen for the overall Januvia franchise. We would love to see the volume numbers here to better understand the field and Merck's leadership, which we suspect is still very high.

3. Fixed-dose combination Janumet sales totaled $563 million, down 1% YOY. As for the overall franchise and for standalone Januvia, this was driven by the US market, where sales fell 4% YOY to $248 million (down from $258 million in 2Q16). Ex-US sales rose 1% YOY to $315 million.

4. On a pooled basis, the DPP-4 inhibitor class fell 4% YOY and grew 13% sequentially to $2.5 billion in 2Q17. This continues the trend of fluctuating sales for all major DPP-4 inhibitor products, likely due in part to increasing competition from SGLT-2 inhibitors and GLP-1 agonists, and certainly partly due to the competitive US pricing environment. Once again the indisputable frontrunner, Merck's Januvia franchise captured 61% of the market by value in 2Q17 (on par with its market share in 1Q17). Lilly/BI's Tradjenta (linagliptin) was in a distant second place with 16% market share by value, followed by Novartis' Galvus (vildagliptin) with 13%, AZ's Onglyza (saxagliptin) with 6%, and Takeda's Nesina (alogliptin) with 5%. Notably, these values are based on our estimate of total Tradjenta franchise revenue, since only Lilly's share is reported publically. We estimate Lilly's share of revenue at ~36% based on Lilly's reported Tradjenta franchise sales for 2015 ($357 million) and global net sales for the franchise in 2015 (€909 million, or ~$1 billion) as reported by BI in a diabetes update.

Pipeline Highlights

5. Management confirmed that an FDA decision on Pfizer-partnered SGLT-2 inhibitor ertugliflozin is expected by year-end, and reinforced that Merck is committed to broadening its diabetes portfolio with this new franchise, which will also include fixed-dose combination tablets with metformin and with sitagliptin. This last combination therapy was highlighted specifically - management positioned it as a distinct advantage that Merck/Pfizer are combining an advanced SGLT-2 agent (showing profound glycemic and weight loss efficacy) with what is by far the market leader in the DPP-4 inhibitor class.

6. We were surprised to hear no mention of Lusduna Nexvue (biosimilar insulin glargine), which just recently received tentative approval from the FDA. Perhaps there was little commentary to be made, since full approval is contingent upon resolution of the patent infringement lawsuit from Sanofi (over Lantus). Merck's glucose-responsive insulin candidate MK-2640 was discontinued in 2Q17, but was not mentioned on the call.

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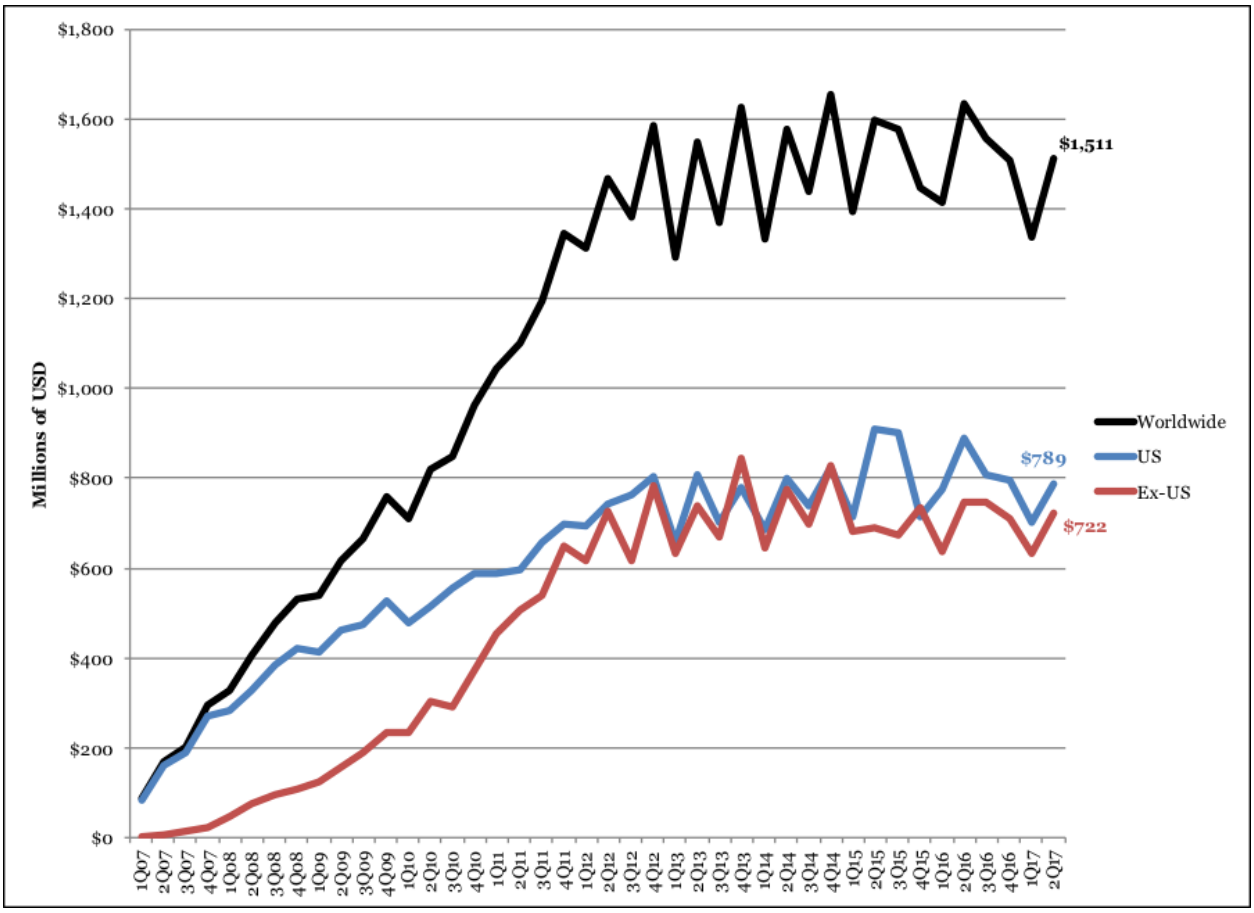
Financial Highlights

1. US PRICING PRESSURE DRIVES JANUVIA FRANCHISE DOWN 8% YOY TO $1.5 BILLION

Revenue from the DPP-4 inhibitor Januvia franchise fell 8% YOY as reported (7% in constant currencies) to $1.5 billion, driven by an 11% YOY decline in US sales to $789 million. Ex-US sales showed a smaller, 3% YOY decline to $722 million. Management attributed this financial performance to continued pricing pressure in the US, which deflated sales despite 3% YOY volume growth for Januvia (sitagliptin) and Janumet (sitagliptin/metformin) prescriptions: "Each year, pricing pressure gets a little bit harder than the year before. This year is harder than last year, and I suspect next year will be harder than this year." We have been learning more about industry investments in patient access, rebates, etc. and we would also say that "pricing pressure" stems not just from PBMs wanting to pay less, but also from investment in more populations getting access (i.e. a greater proportion of prescriptions going to patients on Medicaid). There is a clear pattern in recent earnings calls, with management from many diabetes companies (AZ in 2Q17, J&J in 1Q17 and 2Q17, Lilly in 2Q17, Merck in 1Q17) speaking to the tough pricing environment in the US, to high rebates and discounts. That the Januvia franchise experienced positive volume growth, despite negative revenue growth, provides valuable information from our view that patients in-need are accessing the therapy, although management acknowledged that the 3% volume growth in 2Q17 was "not as strong" as the 4.5% volume growth seen in 2016 on average - we'd love to get the industry numbers on this and "pool" the analysis on volume as we suspect it's also positive.

- **Merck released a Pricing Action Transparency Report in 2016, which says the company's gross US sales were reduced 41% in 2016 due to rebates, discounts, and returns.** Lilly management shared recently that the company returns 50% of pharmaceutical profits in the form of patient discounts or rebates to PBMs, and we know other diabetes companies are paying similar percentages, which have increased substantially in the past few years. We applaud industry players for this transparency (see reports from Merck, Lilly, Novo Nordisk, J&J, and Sanofi), but we also know it's impossible to compare from company to company since they encompass drugs from so many therapeutic areas. Merck's decision to include "returns" in its calculation of 41% reduction in US pharmaceutical sales is not something we've seen before, and represents an additional confounder. Efforts toward transparency are a key step in the right direction, and we'd love to see more consistency in how these values are reported by various companies. We also desperately need transparency from PBMs, as we don't believe this incredibly complicated issue will be solved without collaboration from all players in healthcare. A recent JAMA article showed that 27% of total pharmaceutical sales in the US (including non-diabetes) - a grand sum of $115 billion - was paid by industry to payers and PBMs in 2015. We're eager to understand rebates much better to get a sense of how the complex drug pricing system in the US is impacting recorded revenue by manufacturers, including Merck for Januvia.
- **Sequentially, Januvia franchise sales increased 13% globally, 12% in the US, and 14% ex-US in 2Q17, but this growth from 1Q17 occurred against a very easy comparison.** Between 4Q16 and 1Q17, franchise sales dropped by near-equivalent percentages - 12% worldwide, 12% in the US, and 11% internationally. This speaks to a recent trend of fluctuating revenue for the DPP-4 inhibitor class overall, and we include our pooled class analysis of these agents from 2Q17 below (highlight no. 4). It's also interesting to note how powerful the US market is in influencing Januvia's global financial performance. In 4Q16, for example, 4% YOY growth was attributed to a spike in US revenue, and in 1Q17 (as in 2Q17), a marked drop in US sales was to blame for the decline in global franchise sales. This makes sense, since the US is the largest market for diabetes around the world, but also underscores the sharp impact that commercial challenges stateside can have for diabetes drug manufacturers.

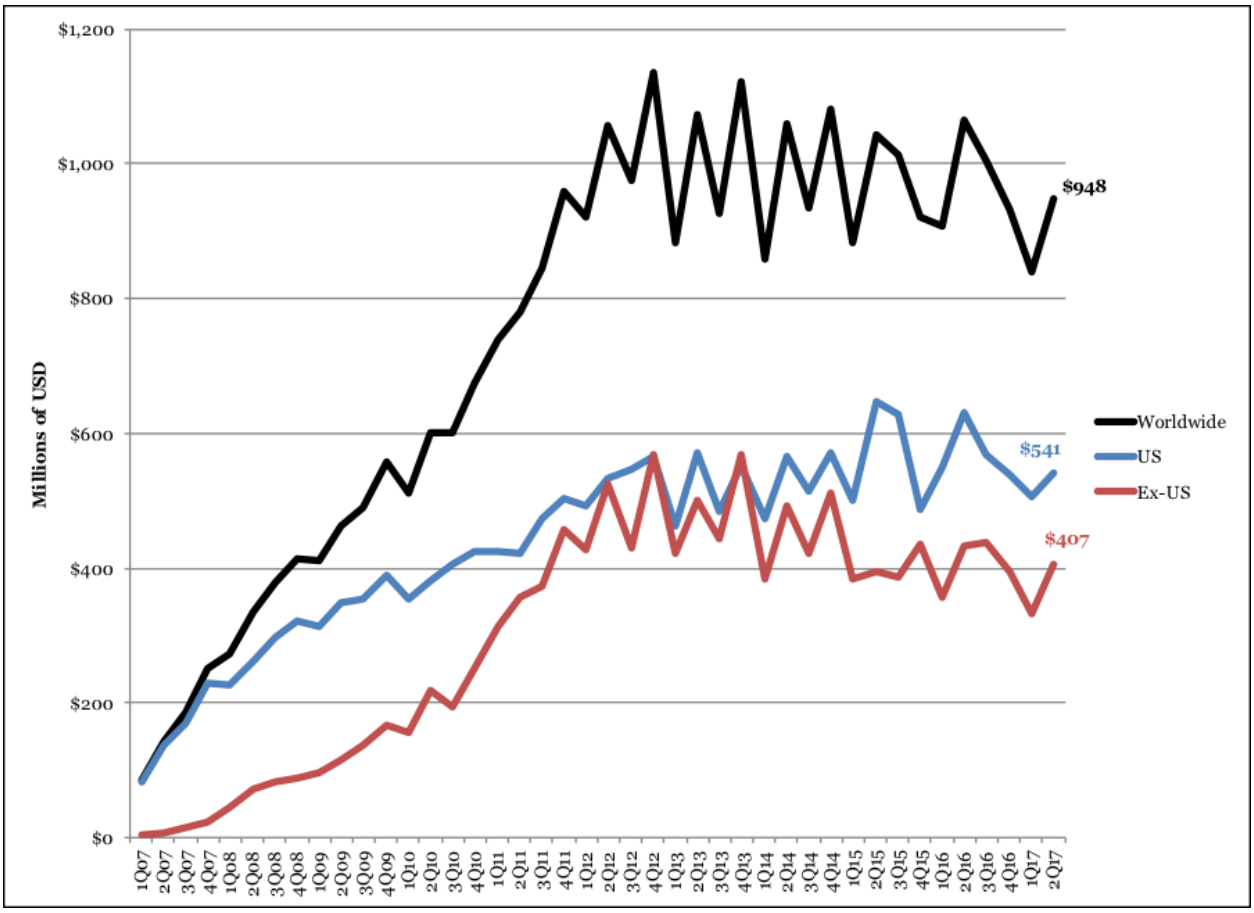
Figure 1: Total Januvia Franchise Sales (1Q07-2Q17)



2. STANDALONE JANUVIA SALES DECLINE 11% YOY TO $948 MILLION; US REVENUE DECLINES 14% YOY TO $541 MILLION

Global sales of standalone Januvia fell 11% YOY to $948 million (down from $1.1 billion in 2Q16). US sales fell a steep 14% YOY to $541 million, while ex-US sales fell 6% YOY to $407 million, in parallel to the geographical trend seen for the overall Januvia franchise. Notably, US Januvia revenue faced a relatively easy YOY comparison in 2Q17, since the product experienced 3% YOY US sales decline in 2Q16. This points to the commercial challenges of pricing pressure, high rebates to PBMs, increased patient discounts, and more segment mix (a greater proportion of prescriptions going to patients on Medicaid) plaguing the US market for pharmaceuticals, and Januvia is no exception. We would love to see the volume numbers here to better understand the field and Merck's leadership, which we suspect is still very high. Sequentially, worldwide sales of standalone Januvia were up 13% against an easy comparison of 10% sequential decline in 1Q17. Januvia accounted for 63% of franchise sales in 2Q17, with the remaining 37% going to fixed-dose combination product Janumet (sitagliptin/metformin).

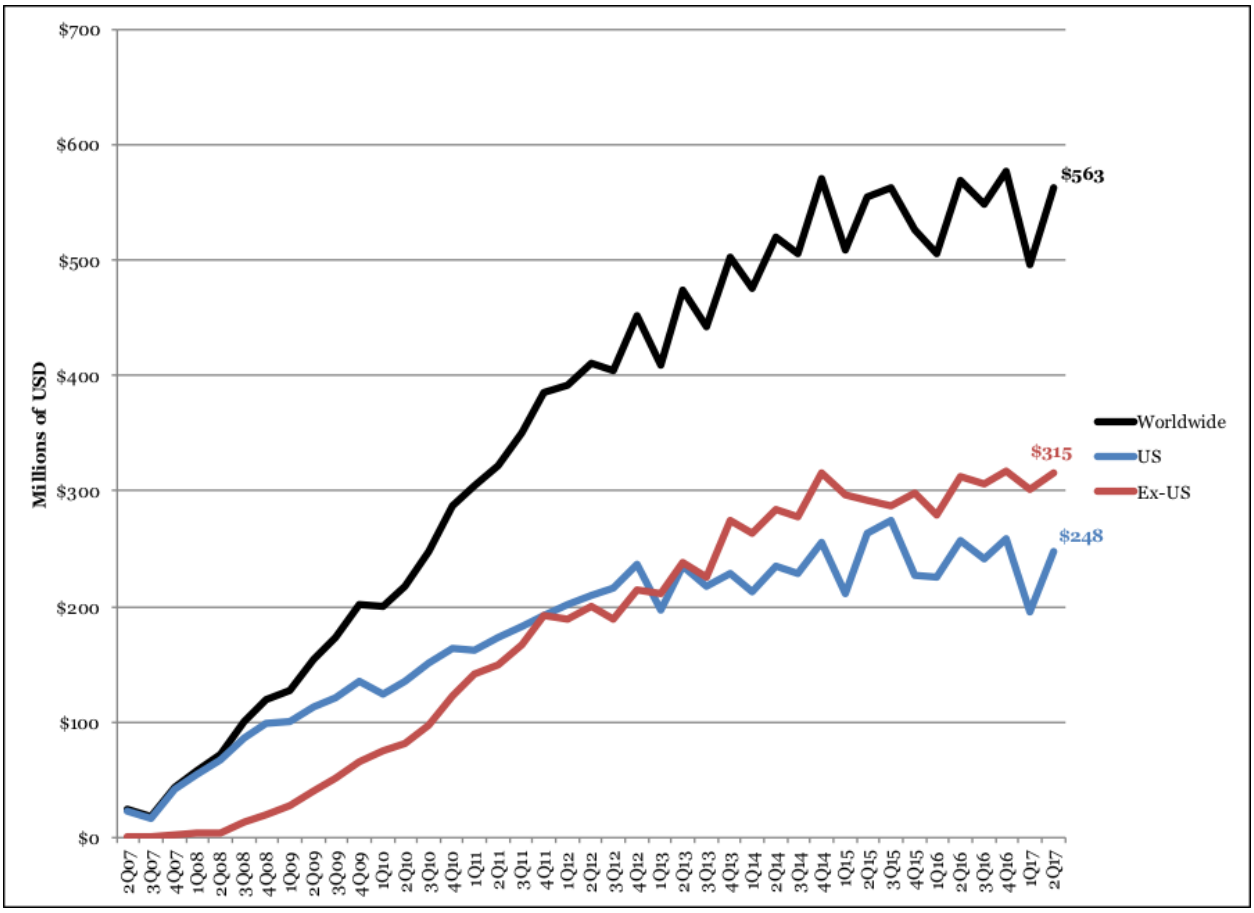
Figure 2: Standalone Januvia Sales (1Q07-2Q17)



3. JANUMET SALES ~FLAT YOY AT $563 MILLION, BUT FALL 4% YOY TO $248 MILLION IN THE US

Fixed-dose combination Janumet sales totaled $563 million, down 1% YOY. As for the overall franchise and for standalone Januvia, this was driven by the US market, where sales fell 4% YOY to $248 million (down from $258 million in 2Q16). Ex-US sales rose 1% YOY to $315 million. Janumet accounted for 37% of overall franchise sales in 2Q17, which is similar to its share throughout 2016 and in 1Q17. While DPP-4/metformin combinations do seem highly-favored among patients and providers, especially ex-US, we think the wave of enthusiasm *could* eventually move toward fixed-dose combinations of a DPP-4 inhibitor with an SGLT-2 inhibitor - latter agent offers enhanced A1c-lowering and weight loss (DPP-4 inhibitors appear less potent on the glycemic front, and are weight neutral). It depends somewhat on pricing, of course. Indeed, Merck management did seem optimistic about its upcoming DPP-4/SGLT-2 fixed-dose combo of sitagliptin with Pfizer-partnered ertugliflozin (the SGLT-2 inhibitor candidate has been filed with the FDA and EMA, and regulatory decisions are expected by the end of 2017) - but these combos have had a slow start overall (not that any have been developed by such a joint marketing powerhouse team as Merck/Pfizer). We'll be curious to see how priorities align between Janumet and the potential new combination pill in 2018 and beyond.

Figure 3: Janumet Sales (2Q07-2Q17)



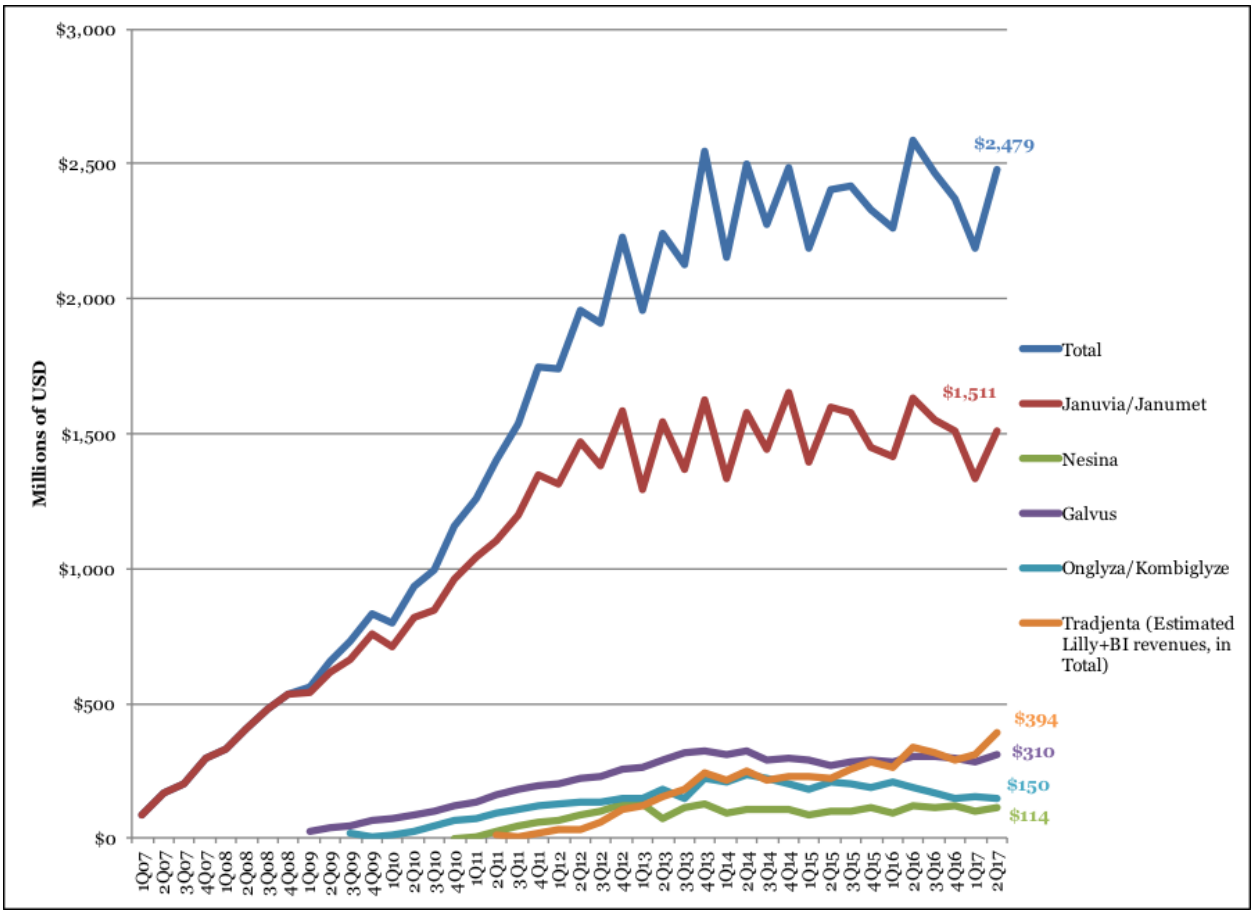
4. POOLED CLASS ANALYSIS: DPP-4 INHIBITOR MARKET TOTALS $2.5 BILLION, DOWN 4% YOY; JANUVIA LEADS WITH 61% MARKET SHARE BY VALUE

On a pooled basis, the DPP-4 inhibitor class fell 4% YOY and grew 13% sequentially to $2.5 billion in 2Q17. This continues the trend of fluctuating sales for all major DPP-4 inhibitor products, likely due in part to increasing competition from SGLT-2 inhibitors and GLP-1 agonists, and certainly partly due to the competitive US pricing environment. Recently, we've heard mixed commentary from thought leaders on the role of DPP-4 inhibitors in diabetes management, and to match this, various companies that manufacture a DPP-4 inhibitor seem to be approaching their products in vastly different ways. At Keystone 2017, Drs. Jay Skyler (University of Miami, FL) and Steven Nissen (Cleveland Clinic, OH) voiced their hesitation to include a DPP-4 inhibitor in a diabetes treatment regimen due to neutral CV effects and a possible signal for heart failure hospitalization. This safety concern was seen primarily in the SAVOR-TIMI study for AZ's Onglyza (saxagliptin), but the hazard ratio for heart failure hospitalization also trended in the wrong direction (favoring placebo) in the EXAMINE trial for Takeda's Nesina (alogliptin), even though it didn't reach statistical significance. Merck's TECOS trial investigating the CV effects of sitagliptin found a neutral hazard ratio of 1.00 for heart failure hospitalization, but the FDA (rather unfortunately) issued a Complete Response Letter for inclusion of these results on the Januvia label. What's more, according to Drs. Skyler and Nissen, is that we now have diabetes therapies available that actually improve CV outcomes - namely, SGLT-2 inhibitors and GLP-1 agonists, the main sources of competition for DPP-4 inhibitors. Other experts have pointed out that DPP-4 agents are most effective for newly-diagnosed patients with type 2 diabetes, but can't compete with the potency of an SGLT-2 or a GLP-1 agent later in the course of disease. That said, Dr. Robert Ratner has defended the niche of DPP-4 inhibitors in diabetes care due to their long history of safety/tolerability - indeed, this therapy class boasts a familiarty factor among patients/providers. DPP-4 inhibitors are also oral agents (as opposed to injectable GLP-1 agonists), and are likely to be generic and therefore much more affordable sooner than SGLT-2 inhibitors. We see both sides to this debate. We'd love to see more patients

access the more advanced classes of GLP-1 agonists and SGLT-2 inhibitors, but we don't anticipate DPP-4 inhibitors are going anywhere anytime soon. DPP-4 inhibitors could be particularly beneficial in elderly patients or in people with renal impairment - Novartis seems to be marketing Galvus (alogliptin) specifically to these pockets of the patient population. The market totaled $9.7 billion in 2016, compared to $2.9 billion for SGLT-2 inhibitors and just under $5 billion for GLP-1 agonists. There's no doubt, though, that these newer classes are growing fast, while DPP-4 inhibitor sales are fluctuating and grew a modest 4% YOY in 2016. AZ management has been particularly explicit that the company will prioritize its SGLT-2 inhibitor business (Farxiga) over its DPP-4 one (Onglyza), going so far as to allow Farxiga to cannibalize some Onglyza sales.

- **Once again the indisputable frontrunner, Merck's Januvia franchise captured 61% of the market by value in 2Q17 (on par with its market share in 1Q17).** Lilly/BI's Tradjenta (linagliptin) was in a distant second place with 16% market share by value, followed by Novartis' Galvus (vildagliptin) with 13%, AZ's Onglyza (saxagliptin) with 6%, and Takeda's Nesina (alogliptin) with 5%. Notably, these values are based on our estimate of total Tradjenta franchise revenue, since only Lilly's share is reported publically. We estimate Lilly's share of revenue at ~36% based on Lilly's reported Tradjenta franchise sales for 2015 ($357 million) and global net sales for the franchise in 2015 (€909 million, or ~$1 billion) as reported by BI in a diabetes update.
- **We'd love to know more details on prescription volume for each of these products as well.** Given the inescapable obstacle of US pricing pressure, volume would be a helpful indicator of how many patients are accessing these therapies, and whether uptake is growing, slowing, or steady from previous quarters.
- **The CARMELINA and CAROLINA CVOTs for Lilly/BI's Tradjenta (linagliptin) are ongoing.** The former compares linagliptin vs. placebo in 8,300 type 2 diabetes patients, and has an expected completion date of December 2017 according to ClinicalTrials.gov. While we anticipate a lot of attention on the heart failure hospitalization data, we're hopeful that results from CARMELINA (coming soon!) will help put these concerns to bed. That said, we'll have to look closely at the results ourselves. The CAROLINA trial is particularly interesting because it compares linagliptin vs. glimepiride (a sulfonylurea). Our fingers are crossed that these findings highlight the inferiority of sulfonylureas compared to more advanced agents, so that payers are pushed toward greater reimbursement of DPP-4 inhibitors, and so that more patients have access to something better than sulfonylureas, which are associated with weight gain, hypoglycemia, beta cell burnout, and possible CV risk. In fact, Dr. Ratner has suggested that CAROLINA results could help knock sulfonylureas out of treatment algorithms: Sulfonylureas maintain their place in algorithms right now because of their generic status and low cost, but more empirical evidence to support their possible health harms, and to show that they might not be cost-effective in the long run (we all know how expensive a hypoglycemia hospitalization can be), could be just the push that guideline-writing committees need. Moreover, DPP-4 inhibitors could be just the replacement for sulfonylureas because they are not so far from generic status, either.

Figure 4: Pooled DPP-4 Inhibitor Sales (1Q07-2Q17)



Pipeline Highlights

5. MERCK TO BROADEN DIABETES PORTFOLIO WITH SGLT-2 INHIBITOR ERTUGLIFLOZIN, PENDING FDA APPROVAL

Management confirmed that an FDA decision on Pfizer-partnered SGLT-2 inhibitor ertugliflozin is expected by year-end, and reinforced that Merck is committed to broadening its diabetes portfolio with this new franchise, which will also include fixed-dose combination tablets with metformin and with sitagliptin. This last combination therapy was highlighted specifically - management positioned it as a distinct advantage that Merck/Pfizer are combining an advanced SGLT-2 agent (showing profound glycemic and weight loss efficacy) with what is by far the market leader in the DPP-4 inhibitor class. We have not seen fixed-dose combinations perform as well as we would have expected in the US (in terms of revenue) and believe a lot of this is due to formulary access, even if they are priced the same as single agents. This is very unhelpful for patients. AZ's Qtern (saxagliptin/dapagliflozin) was FDA-approved in March 2017 but has yet to launch in US pharmacies, while Lilly/BI's Glyxambi (linagliptin/empagliflozin) has never quite taken off commercially. That said, we have high hopes for both Merck and AZ in this particular therapy area: Management from both companies has expressed a great deal of optimism around SGLT-2/ DPP-4 combination treatment, and we're eager to see what each company does in the name of marketing. We've noticed a discrepancy between clinical enthusiasm for fixed-dose and fixed-ratio combinations and commercial uptake of the products, and we see a critical role for industry to play in filling this gap by educating real-world patients/providers on the distinct benefits vs. monotherapy (after all, this concept of fixed-dose and fixed-ratio combination therapies is still relatively knew, and familiarity will have to be cultivated over time).

- **Results from several phase 3 studies in the VERTIS clinical program for ertugliflozin were presented at ADA 2017.** ADA's Chief Scientific, Medical, and Mission Officer Dr. William

Cefalu called out these VERTIS read outs in his "Best of ADA" address at Keystone 2017, emphasizing the terrific efficacy of ertugliflozin and expressing excitement for this agent to join the commercial SGLT-2 inhibitor market. That said, he also underscored that ertugliflozin will likely have to demonstrate CV benefit in order to be a real commercial contender, given that in-class competitors Jardiance (empagliflozin, from Lilly/BI) and Invokana (canagliflozin, from J&J) have already shown significant risk reduction for CV events. The VERTIS CV trial for ertugliflozin is expected to complete in October 2019, while the DECLARE CVOT for AZ's Farxiga (dapagliflozin) is expected to complete earlier, in 2H18. We expect the diabetes field will scrutinize the safety data alongside the CV data from each of these outcomes studies, given the nearly two-fold risk for lower limb amputations associated with canagliflozin in CANVAS (and the fact that the FDA issued a boxed warning in response, while the EMA strengthened amputation warnings for all SGLT-2 inhibitor products).

6. NO OTHER MENTION OF DIABETES PIPELINE, INCLUDING BIOSIMILAR INSULIN GLARGINE LUSDUNA NEXVUE

We were surprised to hear no mention of Lusduna Nexvue (biosimilar insulin glargine), which just recently received tentative approval from the FDA. Perhaps there was little commentary to be made, since full approval is contingent upon resolution of the patent infringement lawsuit from Sanofi (over Lantus). This lawsuit could be settled in one of three ways: (i) Merck and Sanofi reach an agreement, as was the case for Lilly/BI when Sanofi issued a similar lawsuit regarding biosimilar insulin glargine Basaglar - this took nearly 30 months and Merck may just feel it's likely here so this won't impact financials anytime soon; (ii) a court decides in favor of Merck; or (iii) 30 months elapse since the lawsuit was filed in September 2016 (~March 2019). We're excited about the prospect of a second biosimilar basal insulin reaching the market, especially since past experience tells us that at least two generics are needed to meaningfully drive down cost for patients, but we recognize that we may be looking at many more months and possibly more than a year before Lusduna Nexvue hits pharmacy shelves. See our full report on the Lusduna Nexvue (formerly known as MK-1293) tentative FDA approval for more of our thoughts.

- **Notably, Merck's glucose-responsive insulin candidate MK-2640 was officially discontinued in 2Q17.** This didn't come as a huge surprise to us, considering several delays of the phase 1 study, and considering management's silence on the trial after it did finally complete in August 2016. We expect the decision to terminate MK-2640 development was based on insufficient efficacy and possibly safety issues found in phase 1, which speaks to the tremendous challenges up against glucose-responsive insulin (most notably, high hypoglycemia risk). See our insulin competitive landscape for an overview of other glucose-responsive insulins in the preclinical stage.

TABLE 1: MERCK DIABETES PIPELINE SUMMARY

Product	Product Details	Status	Timeline
Lusduna Nexvue (MK-1293)	Biosimilar insulin glargine (Sanofi's Lantus)	Received tentative FDA approval	Tentative FDA approval granted July 2017; Full approval contingent on resolution of Sanofi's patent infringement lawsuit, filed September 2016; Phase 3 data reported at ADA 2016
MK-8835	SGLT-2 inhibitor ertugliflozin	Under review	FDA/EMA decisions expected by end of 2017; Other regulatory filings

			planned for 2017; Phase 3 data reported at EASD 2016
MK-8835A	Ertugliflozin/sitagliptin (Merck's Januvia)	Under review	FDA/EMA decisions expected by end of 2017; Other regulatory filings planned for 2017; Phase 3 data reported at EASD 2016
MK-8835B	Ertugliflozin/metformin	Under review	FDA/EMA decisions expected by end of 2017; Other regulatory filings planned for 2017; Phase 3 data reported at EASD 2016
MK-0431J	Sitagliptin/ipragliflozin	Phase 3	One phase 3 trial in Japanese participants completed November 2016; Another completed March 2017
MK-8521	GLP-1/glucagon receptor co-agonist	Phase 2	Phase 2 trial completed April 2017
MK-2640	Glucose-responsive insulin	Discontinued from phase 1	Discontinued based on insufficient efficacy in phase 1 trial, completed August 2016 following several delays

-- by Payal Marathe and Kelly Close