Closer Look

MEMORANDUM

AstraZeneca 1Q14 - Bydureon up ~47% but Onglyza down 4%; strong Farxiga launch in US; Forxiga re-launching in Germany - April 25, 2014

Executive Highlights

- Diabetes revenue totaled $347 million in 1Q14, with AZ recording ~50% of the BMS/AZ alliance revenue in January and 100% of revenue in February and March after the acquisition of BMS' diabetes portfolio closed.
- Onglyza franchise suffered first ever decline in revenue (~4%) while Bydureon saw significant growth (~47%). Management commented that it intends to focus energy on Bydureon and Farxiga with less focus on Onglyza - presumably that means less focus on Onglyza as monotherapy.
- SGLT-2 Farxiga had a strong US launch with the strongest non-insulin NBRx trends since Januvia's launch; Forxiga is being re-launched in Germany after successful (!) re-arbitration on pricing.
- The first presentation of phase 3 data for saxagliptin/dapagliflozin (SGLT-2/DPP-4 inhibitor combination) is expected at ADA 2014.
- Disappointingly, Bydureon once-monthly formulation no longer shows up in AZ's pipeline.

AstraZeneca reported 1Q14 financial results yesterday morning in a call led by CEO Pascal Soriot. The call covered the first quarter during which AZ gained full control over the diabetes assets recently acquired from BMS (the deal closed on February 3, 2014). AZ's portion of the revenue from the diabetes assets totaled $347 million in 1Q14, reflecting ~50% of total product revenue from January and 100% of revenue from February and March.

Based on our estimates of what total product revenue would have been in 1Q14 (hopefully we will get exact numbers on Tuesday, April 29 when BMS reports its 1Q14 results), it seems that the Onglyza franchise may have suffered its first ever decline in revenue (-4% YOY). By contrast, Bydureon finally seems to be getting its sea legs; it saw significant growth, both in terms of revenue (up ~47% by our estimates - see below for details of our calculations) and share of total prescriptions (19.6%, up 2.4 percentage points from December 2013). The launch of Bydureon's dual chambered pen in the US is on track for 2H14. A Japanese filing is expected in 2Q14, and a CHMP opinion by the end of the year (4Q14). The Bydureon auto injector, the once-weekly suspension formula, is still on track for a 2015 US/EU submission. However, we were quite disappointed to see that the once-monthly formulation no longer apperas in AZ's pipeline. However, management did not explicitly say whether it has been discontinued, and we hope for the sake of patients that it has not. Management proudly announced a strong launch of Farxiga in the US, stating that it has had the best new to brand prescription (NBRx) penetration in non-insulin anti-diabetics since the launch of Merck's Januvia. Quite notably, management also noted that it is re-launching Forxiga in Germany after successful resolution of price renegotiations. AZ did not break out Farxiga/Forxiga revenue.

Also quite notably, management remarked that it is devoting less attention to Onglyza and focusing efforts on Bydureon and Farxiga/Forxiga. This decision seems understandable given that growth prospects for the GLP-1 agonist and SGLT-2 inhibitor classes are much greater than for the DPP-4 inhibitor class, whose growth has been slowing over the past year.

Finally, we were excited to hear that the company plans to present the first set of phase 3 data for its saxagliptin/dapagliflozin fixed-dose combination this June at ADA. The study was conducted in patients with type 2 diabetes and A1c >8%.

In this report, we bring you our top five highlights from the conference call, followed by select Q&A.

Table of Contents

TOP FIVE HIGHLIGHTS

1. AZ recorded Onglyza Franchise revenue of $162 million globally with $106 million from US and $56 million internationally. AZ's 1Q14 results for diabetes products reflect ~50% of sales January and all sales from February and March since the acquisition of diabetes assets from BMS closed on February 3, 2014. Extrapolating this value out to three months would suggest that BMS and AZ's combined Onglyza revenue in 1Q14 was around $194 million (BMS reports results on Tuesday, April 29 when we will hopefully learn the exact amount), which would represent ~4% YOY decline and ~13% sequential decline for the franchise. This is the first ever YOY decline for the Onglyza franchise. Total prescriptions for Onglyza declined 3% for 1Q14 compared to 1Q13. Share of total prescriptions also decreased slightly to 15.8% in March 2013, down 0.5 percentage points since December 2013.

- **Notably, management remarked that it is devoting less attention to Onglyza and focusing efforts on Bydureon and Farxiga/Forxiga.** This decision seems understandable given that growth prospects for the GLP-1 agonist and SGLT-2 inhibitor classes are much greater than for the DPP-4 inhibitor class, whose growth has been slowing over the past year. That said, we assume that combinations would be a growing focus that would include DPP-4 inhibitors.

2. AZ's SGLT-2 inhibitor Farxiga (known as Forxiga outside the US) has had a successful launch in the US, has been approved in Japan, and, quite notably, is being re-launched in Germany. AZ did not break out Farxiga/Forxiga revenue; BMS in the past had broken out Forxiga revenue.

- **According to AZ's presentation, Farxiga's NBRx (new to brand prescription) share penetration is the best out of all non-insulin anti-diabetic agents since the launch of Merck's Januvia.** Farxiga seems to be expanding the US SGLT-2 inhibitor class with two out of five people starting Farxiga being new to the class. One of AZ's slides implies that Farxiga has added 27% growth in new prescription (NRx) volume to the SGLT-2 inhibitor class over Invokana NRx. NRx for Farxiga was right around 5,000 in early April (we presume this was NRx on a per-month basis, but AZ's slide does not specify). As a reminder, Farxiga was approved in the US in January 2014.
- **Management disclosed that Forxiga is being re-launched in Germany.** Forxiga had been withdrawn from the German market after failing to reach a price agreement with the German Federal Joint Committee, but management noted during Q&A that its re-arbitration process was successful, which has allowed a re-launch. While the exact price was not shared, management suggested that it was similar to that of Januvia.
- **As a reminder, Forxiga was approved in Japan on March 24, 2014.** As per AZ's agreement with Ono Pharmaceutical from December 2013, the two companies will co-promote Forxiga in Japan.
- **As a reminder, Xigduo (Forxiga/metformin IR) was recently approved in the EU** (as the first SGLT-2 inhibitor/metformin FDC). Xigduo XR approval in the US is expected in 4Q14.
- **Other companies with SGLT-2 inhibitors include** J&J (Invokana, approved in the US and EU), Lilly/BI's (empagliflozin, FDA CRL due to manufacturing issues at BI's plant and positive

CHMP opinion in the EU), Pfizer/Merck (ertugliflozin, phase 3), Astellas/Kotobuki (ipragliflozin, approved in Japan), Taisho (luseogliflozin, submitted in Japan), Islet Pharma/BHV Pharma/Kissei's remogliflozin etabonate (phase 2 - recently reported results), Theracos (EGT0001442, phase 2), Lexicon (SGLT-1/SGLT-2 dual inhibitor LX4211, phase 3-ready upon partnering), and Novartis (SGLT-1/SGLT-2 dual inhibitor LIK066, phase 2).

3. AZ will present a phase 3 study for its saxagliptin/dapagliflozin fixed-dose combination as a late-breaker at ADA 2014 (the first phase 3 data for the compound to be released). The study was conducted in type 2 diabetes patients with A1c >8%. The trial pits the combination on top of metformin against a single agent (either saxagliptin or dapagliflozin alone) on top of metformin. The combination remains on track to be filed in the US/EU in 4Q14.

- **The SGLT-2/DPP-4 inhibitor FDC combination comes with several advantages:** (i) it combines insulin-dependent and insulin-independent modes of action to increase glycemic efficacy; (ii) both component classes are associated with a low risk of hypoglycemia; and (iii) the SGLT-2 inhibitor component should confer beneficial weight and blood pressure effects. However, the SGLT-2 component also slightly "muddies" the DPP-4 inhibitor's clean tolerability profile - SGLT-2 inhibitors come with an increased risk for genitourinary infections, although these infections are generally easy to treat and rarely cause treatment discontinuation. We believe that the SGLT-2 inhibitor/DPP-4 inhibitor combination may have one of the best benefit/risk profiles of any currently available once-daily oral treatment for type 2 diabetes.
- **Lilly/BI recently announced the FDA submission of their SGLT-2 inhibitor/DPP-4 inhibitor FDC, empagliflozin/linagliptin,** making a US approval in early 2015 possible. Merck and Pfizer partnered up in early 2013 to develop Pfizer's SGLT-2 inhibitor ertugliflozin (now phase 3), and should ertugliflozin ultimately succeed, the companies will pursue a Januvia/ertugliflozin FDC. J&J does not have an in-house DPP-4 inhibitor to pair with its SGLT-2 inhibitor (Invokana). Takeda and Novartis currently do not have in-house SGLT-2 inhibitors to pair with their DPP-4 inhibitors. We continue to believe Takeda and J&J would be natural partners on this front to make an SGLT-2 inhibitor/DPP-4 inhibitor FDC with Invokana and Takeda's Nesina. Novartis is developing an early stage SGLT-1/SGLT-2 dual inhibitor in-house, so it may ultimately elect to develop a Galvus FDC with this agent. Lexicon's LX4211 (another SGLT-1/SGLT-2 dual inhibitor) is another candidate that could possibly be combined with a DPP-4 inhibitor.

4. AZ recorded exenatide franchise sales of $158 million with $121 million from the US and $37 million OUS. As a reminder, AZ's 1Q14 results for diabetes products reflect only a portion of sales from January and all sales from February and March. We estimate that BMS and AZ's combined exenatide revenue in 1Q14 was around $189.6 million, which would represent ~3% YOY decline[1] and ~4% sequential decline. The decline was driven by Byetta; in contrast, Bydureon saw healthy growth.

- **Bydureon saw growth in 1Q14 both in terms of revenue and share of total prescriptions.** AZ's 1Q14 Bydureon revenue totaled $80 million with $69 million coming from the US and $11 million from international sources. Extrapolating to include both BMS and AZ's 1Q14 Bydureon revenue, we estimate that total worldwide Bydureon revenue reached ~$96 million in 1Q14, which would represent ~47%[2] YOY growth and a ~3% sequential rise.
- **Bydureon's share of total prescriptions was 19.6% in March 2014**, up 2.4 percentage points since December 2013, largely due to its position on the Express Scripts formulary (where it has replaced Novo Nordisk's Victoza). Management remarked in Q&A that it obtained this share gain with minimal price-cutting.
    - **Management still has not specified a launch date for the Bydureon dual-chambered pen, but narrowed down the time window to 2H14 (at the time of approval, AZ stated that it would be launched "later this year").** The dual-chambered pen will eliminate the need for patient-end reconstitution and should improve the convenience factor for patients, although it still requires a significant amount of preparation time (~15 minutes, including waiting for the product to come to room

temperature). The currently available formulation requires patients to perform complicated a multi-step reconstitution procedure. A filing in Japan is expected in 2Q14 and a CHMP opinion in 4Q14.

    - **AZ's supplemental materials indicated that the Bydureon auto injector, the once-weekly suspension formulation, is still on track for 2015 US/EU submission.** Management did not provide an update on the once-monthly Bydureon formulation, and it no longer appears on AZ's updated pipeline.

- **Byetta, in contrast, showed a decline in both YOY and sequential revenue.** AZ reported total Byetta revenue at $78 million, with $52 million coming from the US and $26 million from outside the US. Extrapolating to three months, we estimate that BMS and AZ's combined 1Q14 Byetta revenue was ~$94 million, with ~$63 million from the US and ~$31 million from international sales. For worldwide Byetta sales, this represents a ~27% YOY decline and ~11% sequential decline from 4Q13.
- **Competition in the GLP-1 agonist field is becoming more heated, although there is significant differentiation between the agents currently available and in development.** Agents may be distinguished by action profile (long vs. short-acting, with short-acting agents being more effective for lowering postprandial glucose and long-acting agents more effective for lowering fasting glucose), frequency of administration, convenience of injection device, glycemic efficacy, weight loss efficacy (somewhat correlates with molecule size), and tolerability profile.
- **Until last month, Bydureon had been the only approved once-weekly GLP-1 agonist.** GSK's once-weekly albiglutide received approval in Europe in March 2014 under the trade name Eperzan and in the US on April 15, 2014 under the trade name Tanzeum. GSK plans to begin launches in the EU and US in 3Q14. Albiglutide's main advantage is its great tolerability profile - in phase 3 it had nausea rates nearly on par with placebo, three-fold lower than was seen with market-leader Victoza (Novo Nordisk's once-daily GLP-1 agonist). Lilly submitted its once-weekly dulaglutide to the FDA in October 2013, suggesting it could be approved later this year. Should Lilly's agent be approved, it may represent the biggest competitive threat to Bydureon: dulaglutide recently became the first GLP-1 agonist to demonstrate glycemic non-inferiority to Victoza and it will have the most convenient injection device of all of the once-weekly GLP-1 agonists (a one-step pen, in contrast to the Bydureon and albiglutide pens that require multiple steps and a ~15 minute wait time). Novo Nordisk has a once-weekly agent, semaglutide, in phase 3 development whose glycemic and weight loss efficacy is expected to be similar to or better than Novo Nordisk's once-daily Victoza.

5. Management reiterated its expected timeline for its two diabetic nephropathy candidates. Roxadustat is expected to enter phase 3 this year, while AZD1722 is expected to enter phase 3 in 2015 (pending an investment decision). The company hopes to file in the US in 2018.

HONORABLE MENTION

1. CEO Pascal Soriot made a comment during Q&A that implied that he thinks that there are cases where big pharma mergers do work and create value. While he obviously did not specifically address rumors related to Pfizer's purported $100 billion bid to purchase AZ, the comment did not suggest that he was wholly opposed to the idea of big pharma mergers. That said, he may also just have been speaking from his experience with Roche and Genentech, which has worked at well.

2. Myalept (metreleptin) is on track for EU filing in 4Q14. *As a reminder, the US* FDA approved Myalept in February 2014 for generalized lipodystrophy - a very rare disease characterized by severe metabolic disruptions (e.g., triglycerides in the thousands) due to a lack of leptin. *Myalept is a leptin analog that ameliorates the leptin deficiency*.

Table 1: AstraZeneca Diabetes and Diabetes Complication Drug Pipeline

Drug Name	Class	Indication	Status/Timeline

Bydureon dual-chambered pen	Once-weekly GLP-1 agonist	Type 2 diabetes	Approved in US; launch planned for 2H14. Filed in EU with decision expected in 4Q14. Expected to file in Japan in 2Q14.
Xigduo (Forxiga/ metformin)	SGLT-2 inhibitor/ metformin fixed dose combination	Type 2 diabetes	IR version approved in EU; decision on XR version in US expected 4Q14
Onglyza/Forxiga (saxagliptin/dapagliflozin)	DPP-4 inhibitor/SGLT-2 inhibitor fixed dose combination	Type 2 diabetes	Data to be presented at ADA in June 2014; filing planned for 4Q14
Bydureon once-weekly suspension	Once-weekly GLP-1 agonist	Type 2 diabetes	Filing planned in 2015
Bydureon once-monthly suspension	Once-monthly GLP-1 agonist	Type 2 diabetes	Last known to be in phase 2; no longer appears in AZ's pipeline
Roxadustat (FG-4592)	Hypoxia-inducible factor (HIF) inhibitor	End stage renal disease (ESRD)	Phase 3 initiation expected in 2014; filing in China expected in 2016; filing in US expected in 2018
AZD1722	NHE3 inhibitor	Chronic kidney disease (CKD)	Phase 2 initiated in 1Q13; phase 3 initiation planned for 2015, pending investment decision

QUESTIONS AND ANSWERS

Q: Can you comment on any net price effects you have seen on Bydureon in this year?

A: As far as pricing, the Express Scripts win was certainly not linked - as I have said before - to a large discount we offered. Actually, we didn't. In fact, so far this year the price effect is relatively small. We have a -1% price effect, and we estimate that the price will be more or less stable for the rest of the year. As far as the Bydureon dual chamber pen, our plan at this point is to launch it later this year. We haven't given a specific date, and as soon as we have clarity we will communicate the timeline. But at this point, unfortunately, it's a bit too early to comment.

Q: I think a majority of big pharma companies have talked in recent years about how mergers between big pharma companies destroy more value than they create, due to things such as a disruption to R&D. I suppose you could look at the merger between Roche and Genentech as an exception. Would you generally agree with the majority of your peer companies that these sorts of big tie-ups are too messy to really create value?

A: It would actually be difficult for me to tell you that I do believe that large mergers do not create value first of all because I'm a pragmatic person and I think this, it's never really good to have a sort of a philosophy that applies to everything. I think you've got to be practical and look at things case by case. Because you mentioned the Roche-Genentech merger - I wanted to mention that I led that integration, and I believe that it worked and created value. I think it really depends on the companies you merge and whether or not you can integrate them. There are many questions you need to ask: Are there true synergies you can merge? Are the two companies complementary from a geographic and category viewpoint? Can you bring the two cultures together? Can you operationalize the integration? There's never really a simple answer to those questions. These questions need to be answered on a case-by-case basis.

Q: I just wanted to get a sense of your moving resources from Onglyza to Farxiga as you're launching the drug - should we think of this as a more long-term reorganization? Or do we think of it as resources, and therefore support, moving back to Onglyza? Or does your Diabetes Care business in general need more resources?

A: It is clear that our focus is on Farxiga and Bydureon in the US. That has led to the results you saw with Farxiga. It's also fair to say that you see a rather flattish picture for Onglyza, also as a result of this resource allocation. It's clear that our focus will remain on Farxiga and Bydureon. I would just attract your attention to data we will present at the ADA in June combining Farxiga and Onglyza in a combination on top of metformin and compared to single-agent on top of metformin. That might also give you an idea of the potential that exists in combining those agents. These are our separate mono-therapies and in the fixed combination regimen.

Q: Your net finance charge, excluding the royalties, is very similar in the first quarter of this year to the fourth quarter of last year, yet you will have been paying for the BMS deal for at least part of the quarter. Is there anything unrepresentative about that first quarter, or is the full year-end net financial charge four times the first quarter?

A: We are in Europe, and we need a little bit more time to address your finance question. However, we can tell you a little bit about Forxiga in Germany. The US is of course important, but we are also doing very well in Germany - incredibly well, in fact - with Forxiga and Xigduo.

What I have mentioned in the annual results in the first quarter is that we were in an arbitration process in Germany. I'm happy to report that we came to a resolution and, as a consequence of that, we are in the phase of relaunching Forxiga in Germany. This is going extremely well. It's clearly tracking on the value basis the line of Januvia (Merck's sitagliptin). We are very pleased. On top of that, we were also very pleased to see progress with Xigduo, the fixed-dose combination of dapagliflozin and metformin. Both products are doing extremely well in the general market.

Q: In Germany, does that mean you have a Januvia-type price?

A: We had an active negotiation, as always. We are not disclosing exactly where we landed in terms of pricing, but it is more or less in the Januvia range.

-- by Jessica Dong, Katherine Sanders, Hannah Martin, and Kelly Close

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[1] Total exenatide franchise revenue from 1Q13 was $195 million, the sum of Lilly's international sales of $58 million and BMS' US sales of $136 million and BMS' international sales of $1 million.

[2] The comparison to 1Q13 is based off of an estimate of the split between Bydureon and Byetta sales. At that time, BMS was in the process of transitioning international rights to Bydureon from Lilly. Lilly, for 1Q13, disclosed that it received a total of $57.6 million in international exenatide revenue but did not disclose the split between Byetta and Bydureon. We applied the 4Q12 split to 1Q13, producing the estimate that Lilly recorded about $13.5 million in Bydureon sales and $44.1 million in Byetta sales. In 1Q13 BMS recorded $85 million in worldwide Byetta sales ($84 million US and $1 million OUS) and $52 million in Bydureon sales (all in the US).