

Key Events

Metabolism

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Date	Event	Status
22 nd -26 th June 2007	American Diabetes Association 67 th Annual Scientific Sessions, Chicago, Illinois	Reported
13 th June 2007	FDA advisory committee votes against approving Zimulti	Reported
21 st May 2007	NEJM article on Avandia safety	Reported
26 th February 2007	US FDA issues an approvable letter for Novartis' Galvus, requesting additional data	Reported
14 th November 2007	World Diabetes Day: Diabetes in Children and Adolescents	To be reported

ADA meeting underlines unmet need in diabetes

The American Diabetes Association (ADA) held its annual conference in Chicago this year and we went along to find out more about the latest developments in this therapy area. We identified three key themes that best encapsulate our findings: 1) the need for earlier, more aggressive treatment, 2) the demand for novel treatment approaches and 3) whether this demand can be satisfied against a backdrop of increasing concerns over drug safety.

Pre-diabetes represents a major new commercial opportunity

With regards to the first of these - the call for earlier, more aggressive treatment - it is well known that diabetes mellitus increases the risk of cardiovascular disease and death, but a study from Australia showed that "pre-diabetes" - a condition marked by impaired fasting glucose and impaired glucose tolerance - also significantly increases a person's risk of dying from cardiovascular disease. Other studies presented at the meeting demonstrated that, with early detection and effective intervention, diabetes can be prevented or delayed.

The ADA has changed its guidelines accordingly. Last September, with its European counterpart, the EASD, it recommended that, as well as diet and exercise, patients newly diagnosed with Type II diabetes should also be prescribed metformin - the gold standard oral anti-diabetic. Now, the ADA has gone a step further and is advocating the use of metformin in the pre-diabetic population (again, alongside diet and exercise).

So, what is the significance of this? Well, we believe this marks an important milestone because it now means that, for the first time, doctors are being advised to use drugs as a preventative measure in the battle against diabetes.

The US Centers for Disease Control (or the CDC) estimates that 54m Americans have some form of pre-diabetes, many of whom will progress to fully-fledged diabetes within three years. Clearly, this represents a major new target market for pharmaceutical companies. Indeed, at the conference, we saw data from the DREAM trial showing GlaxoSmithKline's Avandia (rosiglitazone) reduces the risk of developing Type II diabetes by around 60% compared to placebo. Takeda is seeking to demonstrate the same effect with Actos (pioglitazone) in the ACT NOW trial, and Novartis also presented data showing its DPP-IV inhibitor Galvus (vildagliptin) has some efficacy in this setting.

However, while there is already some off-label use in this indication, we believe the FDA and other regulatory agencies have to recognise "pre-diabetes" as a medical condition before the pharmaceutical companies can secure this additional claim and tap into this lucrative patient population.

Demand remains for novel treatment approaches and technologies

Our second key theme looks at the demand for novel treatment approaches. Even aside from pre-diabetes, there remains an enormous level of unmet medical need in treating diabetes itself, as well as its related complications. The US, for example, is facing a dangerous epidemic and, to illustrate that point, the CDC presented epidemiological data showing that there are an estimated 21m Americans with diabetes and, of those, 30% remain undiagnosed. Furthermore, the prevalence of diabetes in the US has increased 5% annually since 1990 (other reports estimate that the current growth rate is more like 7%).

Dr David Nathan, a key opinion leader in the field, made the point that, despite the influx of newer product classes over the last decade, the three oldest product classes - namely, insulin, the sulphonylureas and metformin - remain the most effective at lowering blood-glucose levels. However, another presentation at the conference suggested that the level of diabetes control has improved. A study conducted by Quest Diagnostics, using data gleaned from four million people, showed that more than half of diabetics reached recommended targets for controlling blood sugar last year, compared to around a third in 2001. Whether this improvement is down to the newer product classes is not clear, but it is certainly true that anti-diabetics are used most effectively in multiple combinations, targeting the different underlying mechanisms of the disease.

Two of the newest product classes doing battle at the ADA this year were the GLP-1 analogues and the DPP-IV inhibitors. The two are pitted against each other because, essentially, they work in the same way. GLP-1 is the hormone released by the gut following meals, whereupon it promotes insulin production (amongst other things). GLP-1 analogues simulate this action, but over a longer period of time, and the DPP-IV inhibitors simply prevent the breakdown of the body's own GLP-1.

Table 1: GLP-1 analogues versus DPP-IV inhibitors

	GLP-1 analogues	DPP-IV inhibitors
Administration	Injection twice daily	Tablet once a day
HbA1c	0.8-1.8%	0.5-1.1%
Weight-loss	3-5kg	Neutral
Effect on beta-cell mass	Robust	Probable
Side effects	Nausea	Skin reactions in some developmental compounds Effects on kidney not fully established

Source: Company documents

As you'll see from the slide, the GLP-1 analogues must be given by injection, whereas the DPP-IV inhibitors have the advantage of being orally available. However, the GLP-1 analogues are proven to cause weight-loss, while the DPP-IV inhibitors are only weight neutral. And the problem with the DPP-IV inhibitors is that, unless they are highly specific to DPP-IV, they can be a blunt instrument. We believe Merck & Co.'s Januvia is the cleanest, most selective DPP-IV inhibitor developed so far. And, indeed, it is the only one approved in the US so far. Some of the other DPP-IV inhibitors still in development appear to cause certain skin reactions, a side effect that may be explained by a poorer specificity for DPP-IV.

At the conference, we saw data supporting Januvia's continued expansion into newer indications, as well as interesting data for Novartis's Galvus – for instance, showing how it significantly reduces blood pressure in hypertensive patients. However, Novartis' Galvus received an approvable letter in February, in which the FDA requested an additional trial in patients with kidney impairment. None of this all-important safety data was available yet, though. The other DPP-IV inhibitor creating a splash at the conference was BMS and AstraZeneca's saxagliptin. Phase III data showed that, in combination with metformin, the drug caused a statistically significant improvement in glycaemic control compared to metformin alone.

Novo Nordisk presented some exciting data on its novel GLP-1 analogue liraglutide. Data from the first of five Phase III trials showed liraglutide was superior to sanofi-aventis' Lantus (an insulin formulation) when it came to lowering blood-glucose levels. The reduction in HbA1c (or glycosylated haemoglobin) was more than 0.2 percentage points better than in the insulin group – which (surprisingly to us) is actually a statistically significant difference. Also, at the end of the study, the difference in weight between the two groups was 3.5kg – again, a statistically significant difference in favour of liraglutide.

Table 2: Byetta versus liraglutide

	Byetta	liraglutide
Regulatory status	Launched in 2005	In Phase III trials, due to launch 2009/2010
HbA1c	Comparable to sanofi-aventis' Lantus (insulin glargine)	Superior to sanofi-aventis' Lantus (insulin glargine)
Weight-loss	2.6kg over four months (with oral anti-diabetics)	2kg over six months (with oral anti-diabetics)
Effect on beta-cell mass	Injection twice daily (once-weekly LAR formulation due in 2010)	Injection once daily
Side effects	Nausea (57% in Phase III trials)	Nausea (10-15% in Phase III)

Source: Company documents

The problem for Novo Nordisk is that liraglutide will not be the first GLP-1 analogue to reach the market. Amylin/Eli Lilly's Byetta (exenatide) gained US approval in April 2005 - for treating patients with Type II diabetics not achieving adequate control with metformin and/or a sulphonylurea. Liraglutide has the advantage of a once-daily dosing schedule, whereas Byetta must be administered twice a day. And liraglutide appears to be associated with a lower incidence of nausea (around 10-15% of patients versus over half taking Byetta). However, Amylin and Eli Lilly are developing a once-weekly long-acting release formulation that could be on the market just six to 12 months after liraglutide is launched (which we expect to be in late 2009 or early 2010).

Aside from the GLP-1 analogues and the DPP-IV inhibitors, BMS and AstraZeneca's dapagliflozin also created some excitement at the meeting. It is the first in a new class of compounds called the sodium-glucose uptake transporter-2 (SGLT-2) inhibitors - which block glucose re-absorption in the kidney. Phase II data presented at the conference showed a dose-dependent reduction in fasting serum glucose and a dose-dependent increase in the amount of glucose excreted in the urine. However, adverse events included two vaginal infections. We believe that, because the drug causes an increased concentration of glucose in the urine, urinary tract infections may be an issue with this class of products. UTIs are already a common symptom of diabetes and they are often how the condition is diagnosed in the first place.

Drug-safety concerns may delay approvals

The third and final key theme we have identified is drug safety. In May, the *New England Journal of Medicine* published a meta-analysis, which found that GlaxoSmithKline's Avandia is associated with an increased risk of heart attacks and cardiovascular-related deaths. Given the media furore that followed in the weeks running up to the conference, the issue of drug safety was always going to be a major talking point. The ADA responded to events by adding a panel discussion on the subject to the conference agenda. With the author of the meta-analysis, Steve Nissen, claiming top billing on the panel, it came as no surprise that this was the most keenly attended event of the meeting.

Dr Nissen said that, like all meta-analyses, there were flaws in his study, but he gave a robust defence of his decision to publish the findings, claiming he felt it his duty to share the data with the scientific community. Some members of the audience felt his decision was wrong, largely because it would cause patients to drop out of the RECORD trial – the only trial designed to accurately assess the long-term cardiovascular risk with taking Avandia. It has also caused confusion amongst patients, they argued. Interestingly, when asked if they would start patients on Avandia, other panel members said they would not – at least until the cardiovascular risks were better defined. However, they also said they would be reluctant to take a well controlled patient off the drug.

We had hoped GlaxoSmithKline would present the findings of its own meta-analysis on the cardiovascular safety of Avandia. After all, it would be interesting to see what methodology the company used. We were also hoping to see the results of the meta-analysis Takeda has conducted on Actos – Avandia's closest rival. But both companies are clearly waiting until 30th July, when the FDA is scheduled to hold an advisory committee meeting to discuss the cardiovascular safety of this class of drugs.

What is interesting is that, in light of the fall-out from the Avandia scare, Merck & Co. felt compelled to present the results of a meta-analysis looking at Januvia. The study showed Januvia's cardiovascular profile is as safe as other oral anti-diabetics on the market. But we do not believe Januvia's cardiovascular profile has ever been in doubt – because, if anything, its mechanism of action is likely to have a cardio-protective effect. Of more concern, though, is the drug's kidney toxicity profile as, in clinical trials, it appeared to cause raised creatinine levels in some patients.

We believe the Avandia scare may have a lasting impact on the way diabetes drugs are approved from now on. There was a lot of debate at the conference on the validity of using a reduction in HbA1c levels as the benchmark the regulatory agencies use for assessing the efficacy of diabetes drugs. It is a surrogate endpoint – which is to say it is a laboratory measurement of a drug's efficacy that may correlate with a real endpoint but has no guaranteed relationship.

Many now argue that, because they are used chronically over many years, diabetes drugs should follow a regulatory pathway that incorporates a measure of longer-term outcomes, such as mortality. Clearly, these sorts of trials are very expensive because they involve many thousands of patients and take years to complete. Given the unmet medical need in this area, the diabetes community must decide if it can afford the sorts of delays that these new measures would incur in bringing novel therapies to market.

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Wood Mackenzie attending annual meeting of the ADA in Chicago

Wood Mackenzie will be attending the 67th Annual Meeting of the American Diabetes Association in Chicago, between 22nd and 26th June 2007. We will be reporting on the key findings of the conference, including changes to current clinical guidelines, breaking clinical data and new R&D candidates. Following a string of recent controversies and setbacks in this area, this year's conference promises to be one of the most exciting yet.

Possible highlights include:

GlaxoSmithKline's Avandia and Takeda/Eli Lilly's Actos

In May 2007, the *New England Journal of Medicine* published a meta-analysis of 42 clinical studies involving GlaxoSmithKline's Avandia (rosiglitazone). The paper concluded that the anti-diabetic was associated with an increased risk of heart attacks and cardiovascular-related deaths. The findings sparked a media furore, which resulted in a sharp decline in Avandia prescriptions and a Congressional hearing into how GSK and the FDA handled the drug's safety data. GSK has staunchly defended its franchise, arguing that long-term studies (e.g. DREAM, ADOPT and an interim analysis of RECORD) show Avandia's cardiovascular risks are no different from other diabetes treatments on the market. In addition, the company has conducted its own meta-analysis (also involving 42 clinical trials), which has been filed with both the EU and US regulatory agencies, but has yet to be made public.

- Will GSK take this opportunity to present its own meta-analysis – and what methodology will it have used?

After all, the FDA claimed GSK's meta-analysis had found a 31% increase in the risk of cardiovascular events, but the agency's own analysis of the data put the risk at closer to 40%. So there appears to be some conflict there – and with the *NEJM* paper, which found a 43% increased risk of heart attacks. Interestingly, Takeda is also now conducting a meta-analysis of Actos cardiovascular events ahead of an FDA advisory committee meeting on 30th July, when the panel will assess the cardiovascular risk of the glitazones.

- Will Takeda take this opportunity to present *its* meta-analysis on Actos – and what methodology will it have used?

Merck & Co.'s Januvia

Januvia is the first-in-class DPP-IV inhibitor that secured US approval in October last year, and has since already gained approval for use in combination with a number of other anti-diabetics. However, the US consumer group Public Citizen is advising diabetics not to take the drug until the long-term safety is better understood. The group argues that, of the 2,650 patients exposed to Januvia in trials prior to approval, only 164 took the 100mg dose for more than two years. It also notes that the FDA expressed concerns about the increased creatinine levels and recommended routine monitoring for these.

- Will Merck & Co. provide some long-term safety data on the drug?
- Will Merck & Co. provide further trial data supporting the drug's ongoing indication expansion?

Novartis' Galvus

In February 2007, the FDA issued an approvable letter for the Novartis diabetes drug, Galvus (vildagliptin), requesting additional data including an extra trial in patients with renal impairment. The news came as a major blow for the Swiss drug manufacturer as it meant losing further ground to Merck & Co.'s rival DPP-IV inhibitor, Januvia (sitagliptin), which was launched in the US in October 2006. Galvus had already been delayed by three months in November when the FDA asked for proof that skin reactions observed in pre-clinical trials were not replicated in human studies. With this latest setback, though, the product is unlikely to reach the US market before the start of 2009.

- Will Novartis present any additional safety data to support its filing?
- Given Januvia's first-to-market advantage, will Novartis reveal how it plans to position its product?

Bristol Myers Squibb/AstraZeneca's saxagliptin and dapagliflozin

In January 2007, AstraZeneca and Bristol-Myers Squibb announced a broad diabetes R&D and commercialisation collaboration - one of the largest deals to date in 2007. The deal covers two BMS compounds: saxagliptin, a DPP-IV inhibitor, currently in Phase III clinical trials, and dapagliflozin, a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, in Phase IIb trials. At the meeting, we are expecting Phase III data for saxagliptin, as well as Phase IIa data for dapagliflozin.

- Will Phase III data show saxagliptin offers any advantages over the other DPP-IV inhibitors (i.e. Merck & Co.'s Januvia or Novartis' Galvus)?
- Dapagliflozin belongs to a novel product class. Will it show any advantages over existing oral anti-diabetics?

sanofi-aventis' Acomplia/Zimulti

In June 2007, an FDA advisory panel voted unanimously against recommending approval for sanofi-aventis' obesity treatment, the CB-1 receptor antagonist, Zimulti (rimonabant). The committee found that, while the 20mg dose of Zimulti did result in significant weight loss, those taking the treatment were twice as likely to experience thoughts of suicide as those on placebo. The drug was also found to double the risk of psychiatric side effects (including depression, anxiety and insomnia), as well as causing an increased risk of neurological disorders. The FDA will make a final decision on whether to approve Zimulti on 26th July 2007. The European Medicines Evaluation Agency (EMA) also now plans to review the safety of the drug, which was approved in the EU last year.

- What does the future hold for Acomplia/Zimulti?
- Does the nature of the side effects cast doubt on the future of other CB-1 receptor antagonists in development (e.g. sanofi-aventis' follow-on AVE1625, Merck & Co.'s tranaband and Pfizer's CP-945598)?

Inhaled insulins

Last year, Pfizer's Exubera became the first inhaled insulin to reach the market, following lengthy regulatory delays. A primary-care rollout in the US followed in January 2007, but first-quarter sales were a very disappointing \$5m. Exubera replaces the short-acting insulin injections taken at mealtimes - it is inhaled before meals to reduce post-prandial blood glucose 'spikes'. However, patients still need to inject a long-acting insulin at bedtime. This limitation perhaps explains why the product has failed to elicit much excitement from diabetologists. In response, Pfizer has launched a campaign to help educate doctors on the benefits of the novel delivery device. One such benefit Pfizer has already claimed is improved compliance. Poor patient compliance means complications such as blindness, kidney failure, neuropathy and heart disease are common amongst diabetics.

- Will we see any compliance data for Exubera to help boost acceptance amongst diabetologists?

We believe Exubera's competitors may be the biggest beneficiaries of Pfizer's awareness campaign. Novo Nordisk's AERx iDMS and Eli Lilly/Alkermes's products are both in Phase III trials and could be on the market from 2009.

- Will we see any Phase III data for Lilly's Air inhaled insulin and Novo Nordisk's AERx-iDMS?

Diabetes - addressing the need

The recent setbacks we have seen with Galvus and Acomplia/Zimulti emphasise the challenges that pharmaceutical companies face in developing safe and effective medicines in this area. Indeed, as the Avandia scare shows, even approved drugs can carry a risk that goes undetected during clinical trials and may only surface once long-term data has been gathered. Much of the commentary surrounding the Avandia story has criticised the current regulatory pathway for developing anti-diabetics – namely, a sustained reduction in blood glucose levels. Some argue that the approval process should assess the reduction in complications caused by diabetes. Clearly, by investigating these outcomes the overall time and cost to bring a drug to market would be increased dramatically.

- How will recent events shape the future development of diabetes treatments?

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FDA's advisory committee votes unanimously against approval for Zimulti

Wood Mackenzie view

On 13th June 2007, a Food and Drug Administration (FDA) advisory panel voted 14-0 against recommending approval for sanofi-aventis' obesity treatment, the CB-1 receptor antagonist Zimulti (rimonabant). The committee reviewing the application found that, while the 20mg dose of Zimulti did result in significant weight loss, people who took the treatment were twice as likely to have thoughts of suicide as those on placebo. The drug was also found to double the risk of psychiatric side effects (including depression, anxiety and insomnia), as well as causing an increased risk of neurological disorders (such as seizures). Thus, the committee concluded that the company failed to provide enough safety data for the drug, or demonstrate that the product's benefits outweighed its risks. The FDA will make a final decision on whether to approve Zimulti on 26th July 2007. The agency is not required to follow the advice of the committee, but given this was a unanimous decision, we believe the drug is highly unlikely to get the go-ahead. The nature of the side effects also casts doubt on other CB-1 receptor antagonists in development (e.g. Merck & Co.'s tranabant and Pfizer's CP-945598).

Background

Zimulti has already been approved in 37 countries, and is now available in 18 of those (including Europe and Argentina), where it is known as Acomplia. The drug was originally filed for US approval in April 2005 – for weight loss and smoking cessation. The agency rejected the application for smoking cessation, but it issued an "approvable letter" for the weight-loss indication. The letter requested additional data due to concerns surrounding the increased frequencies of psychiatric adverse events, including suicidality, an ill-defined constellation of neurological signs and symptoms, and seizures. This additional data was submitted to the FDA in October 2006.

Efficacy

Four Phase III studies formed the basis of the efficacy assessment for Zimulti: RIO Europe, RIO Lipids, RIO Diabetes, and RIO North America. In all four, the primary efficacy endpoint was the absolute change in body weight from baseline to year one. At the 20mg dose, Zimulti on average helped patients lose between 3.9kg and 5.4kg, with 49-58% of subjects losing at least 5% of their baseline body weight (versus 15-20% of those on placebo). Thus, the committee concluded that the 20mg dose was associated with both a statistically and clinically significant weight loss. However, it is worth noting that they also felt the drug was no more effective than the two weight-loss drugs already on the market – namely Abbott's Meridia (sibutramine) and Roche's Xenical (orlistat) (see Table 1). The 5mg dose was not nearly as effective and, in any case, had already been rejected following the original review.

Table 1: Approved weight-loss medications in the US

Medication	Route of administration	Year of approval	Mean weight loss (kg)
Meridia	Oral	1997	6.4
Xenical	Oral	1996	6.1

Source: Company documents

Sanofi-aventis was also seeking approval in Type II diabetes, dyslipidaemia and metabolic syndrome. It cited improvements in HDL-cholesterol and triglyceride levels, as well as a statistically significant 0.7% reduction in HbA1c (glycosylated haemoglobin) in overweight and obese Type II diabetics. Again, we would point out that conventional oral anti-diabetics (e.g. sulfonylureas and metformin) are capable of achieving better reductions in HbA1c (see Table 2). And besides, it is not clear whether the improvement Zimulti causes is as a direct pharmacologic effect or simply a consequence of the weight loss. It is also worth acknowledging that Eli Lilly's GLP-1 analogue Byetta (exenatide) causes both a reduction in HbA1c *and* some weight loss.

Table 2: Approved anti-diabetes medications in the US

Medication	Route of administration	Year of approval	Efficacy as monotherapy - %age reduction in HbA1c
Insulin	Parenteral	1921	>2.5
Inhaled insulin	Pulmonary	2006	1.5
Sulfonylureas	Oral	1946	1.5
Metformin	Oral	1995	1.5
Alpha-glycosidase inhibitors	Oral	1995	0.5-0.8
Glitazones	Oral	1997	0.8-1.0
Glinides	Oral	1997	1.0-1.5
GLP analogues	Parenteral	2005	0.6
Amylin analogues	Parenteral	2005	0.6
DPP-IV inhibitors	Oral	2006	0.5-0.9

Source: *New England Journal of Medicine*

As an interesting aside, on page 9 of the FDA briefing documents, under the Pharmacokinetics heading, the document states that: "Blacks had 75% higher clearance than non-Black patients and consequently the area under the curve (AUC) was predicted to be 43% lower than in non-Blacks." To us, that suggests the drug is likely to be a lot less effective in black patients. Although it says around 6-7% of subjects in the trials were black, we couldn't find any efficacy data for these patients. Yet the relative incidence of obesity, alongside other cardiovascular risk factors, is much higher amongst African-Americans and so these patients would no doubt represent a sizeable chunk of sanofi-aventis' target population in the US.

Safety concerns

Given the efficacy of Zimulti is already well documented, the advisory committee meeting was always likely to focus on the safety profile of the drug. And to anyone who read the briefing documents posted on the FDA's website ahead of the meeting, the unanimous decision will have come as no surprise. The documents showed that the drug effectively doubled the risk of psychiatric side effects (including depression, anxiety and insomnia), as well as causing an increased risk of neurological disorders (such as seizures). In fact, some 26% of patients on 20mg Zimulti reported having a psychiatric event.

Perhaps most worrying of all, though, people who took the drug were found to be twice as likely to have thoughts of suicide as those who took a placebo. Indeed, sanofi-aventis conceded that three patients taking the drug had killed themselves during clinical trials. A fourth suicide has also been reported after the drug went on sale in Europe, but has yet to be confirmed. The panel disagreed with sanofi-aventis' claim that the increase in cases of psychiatric adverse events was attributable to depression or other disorders not directly caused by Zimulti. FDA medical reviewer Dr Amy Egan stated that she strongly believes there is a causal relationship, noting that 88% of patients who reported psychiatric problems when taking the treatment did not have a history of depression.

The committee was also anxious about the lack of long-term data in large numbers of patients. In all, only 441 patients stayed on the 20mg dose of Zimulti for a period of two years or more; the drop-out rate in the first year of the RIO trials ranged from 34-47%. Yet the trial was not designed to follow patients who discontinued their treatment – many due to adverse events. For instance, patients who required treatment for depression were automatically withdrawn, but not followed to the trial's conclusion. This unsettled the panel as it implied that data on adverse events, especially on depression and anxiety, will have been lost. Given the centrally-acting nature of Zimulti, panel members criticised the trial design for failing to provide adequate means of characterising these adverse events. Several members went on to suggest that even the CRESCENDO trial – a cardiovascular outcomes trial due to report in 2010 – would fail to quantify the risks as it is not set up to monitor these types of events.

Trouble in Europe?

The day after the FDA advisory committee delivered its verdict, the European Medicines Evaluation Agency (EMA) stated that it too would be reviewing the safety of the drug. Acomplia was approved last year in the EU, where it generated sales of \$20m in the first quarter of 2007, with over 130,000 using the product since it was launched in June 2006. However, the post-approval safety data in the briefing documents echo some of the worrying findings from the clinical trials. As of 11th May 2007, there had been 15 reports of suicidal ideation, six reports of psychotic behaviour (including a man who tried to strangle his daughter) and five reports of aggression (including a man who beat his wife). Furthermore, sanofi-aventis has reportedly seen a 40% drop-out rate in the European markets where the product is on sale. Acomplia has had problems securing re-imburement (notably in Germany), so that drop-out could conceivably be down to cost. But a more likely explanation now seems to be the side-effect profile.

Conclusion

Zimulti is a first-in-class CB-1 receptor antagonist that acts centrally on the brain's endocannabinoid system. It exploits research into marijuana use, which has been shown to activate the cannabinoid receptors in the brain causing users to experience the "munchies." By blocking the CB-1 receptor, Zimulti is designed to curb hunger. However, as is always the case with the central nervous system, it is not as simple as that. The endocannabinoid system is also involved in modulating depression, phobias and anxiety, amongst other things. Findings from the clinical trials involving Zimulti – alongside the post-marketing reports from Europe – suggest there is still a lot to learn before adequately characterising the psychiatric and neurological risks involved with using the drug.

The FDA will make a final decision on whether to approve the drug on 26th July 2007, and we believe that decision will be negative. Alongside the EMEA's impending safety review, that casts some doubt over Acomplia/Zimulti's commercial future (we have reduced our 2013 forecast from \$1,500m to \$149m). But it also questions the viability of the other CB-1 receptor antagonists in development, including sanofi-aventis' follow-up compound AVE1625 and Merck & Co.'s tranabant and Pfizer's 945598. Interestingly, the advisory committee's vote came on the same day as GlaxoSmithKline launched Alli, an over-the-counter version of Roche's Xenical. Xenical and Meridia remain the only prescription drugs approved for weight-loss in the US. Yet both are associated with troublesome side effects of their own: in Xenical's case, diarrhoea and gas, in Meridia's, high blood pressure. Thus, for the growing number of overweight Americans, of which a third are now defined as clinically obese, there is no quick fix - diet and exercise remains the safest and most effective treatment option on offer.

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New England Journal of Medicine article on Avandia safety

Wood Mackenzie view

A paper published in the *New England Journal of Medicine (NEJM)* has raised concerns over the cardiovascular risks with using GlaxoSmithKline's (GSK's) Avandia (rosiglitazone). The meta-analysis has some major flaws, as the authors admit, but the article has created a media furore - especially in the US, where the issue of drug safety is particularly sensitive following the withdrawal of Merck & Co.'s Vioxx in September 2004. Although the timing of the publication has come in for criticism from some high-profile physicians, nearly all now agree that questions surrounding Avandia's cardiovascular safety profile need to be answered. The RECORD trial was designed to do just that, but it is not clear whether that data will ever materialise after reports of an exodus of participants from the trial. Until GSK can provide concrete reassurance of its product's safety, sales will dwindle, with Takeda's rival thiazolidinedione Actos (pioglitazone) likely to be the key beneficiary.

New England Journal of Medicine article

On 21st May 2007, the *NEJM* published an article entitled "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes", which was authored by Steven Nissen and Kathy Wolski from the Cleveland Clinic. Steven Nissen is an influential US cardiologist and is President of the American College of Cardiology. He has previously published high-profile articles on the cardiovascular safety profiles of Merck & Co.'s Vioxx (rofecoxib), which was later withdrawn, and Pargluva (muraglitazar), which was subsequently rejected by the FDA.

The authors conducted a meta-analysis of 42 clinical studies involving GSK's rosiglitazone (brand name, Avandia) to investigate the incidence of myocardial infarction and death from cardiovascular causes. The analysis suggested that there was a 43% increase in the risk of myocardial infarction ($p=0.03$) and a 64% increase in the risk of death from cardiovascular causes ($p=0.06$) in Avandia-treated patients, compared to the control group.

Importantly, the authors did highlight a number of flaws in their analysis, namely the lack of access to source data, the weakness of meta-analyses generally, the size and length of many of the trials, the lack of definition for myocardial infarction and the fact that the trials were not designed to study cardiovascular outcomes. However, they did conclude that there is an urgent need to evaluate the potential cardiovascular risks for Avandia and that patients and providers should carefully consider the potential risks of using this drug until cardiovascular safety has been established.

Study creates a scare

News of the findings precipitated widespread coverage in the media - especially in the US, where the furore led to something approaching panic among patients. And since the article was published, shares in GSK have fallen over 9%, fuelled by early prescription data suggesting the drug's share of new scripts had all but disappeared. Given that drug safety has become a major political issue since the withdrawal of Vioxx, the article also elicited a damning response from the US Senate Committee on Finance. Both the FDA and GSK have been invited to appear before the committee to explain the timelines around the submission of safety data to the FDA and to answer allegations that GSK sought to silence independent scientists about risks associated with Avandia.

The FDA responded by stating that GSK had submitted a similar meta-analysis of 42 randomised, controlled trials (mostly of six months' duration) and that results had shown that patients treated with Avandia may have a 30-40% greater risk of heart attack and other related events than those on placebo or other anti-diabetic therapies. Subsequently, a spokesperson from the agency confirmed that an FDA review of early studies involving Avandia showed that the compound could raise the risk of cardiovascular adverse events by about 40% (versus 31%, according to GSK's analysis). However, the FDA has to review findings from additional studies before reaching any conclusions, and deciding how to proceed. Nonetheless, the spokesperson added that "if [the risk] is real, and if 40% more people with diabetes are at risk of ischemic cardiovascular events, then this is in fact significant to us and would be very important information and we would act accordingly." An advisory committee meeting is scheduled for later in June.

The Lancet urges calm

An editorial published in the *Lancet* called for a more measured response to Nissen's findings. It points out that the two most reliable studies to inform decision-making are DREAM and ADOPT. The DREAM study showed MI rates of 0.6% for the Avandia group versus 0.3% for controls, and the MI/stroke/cardiovascular composite occurred in 1.2% of Avandia patients versus 0.9% of control patients. Although the two studies suggest some increased cardiovascular risk, neither result reached statistical significance. The only significantly relevant finding in the ADOPT trial was an excess of congestive heart failure episodes for Avandia-treated patients compared with glyburide (22 versus nine events).

"Taken together, these results, although based on very small numbers of events, certainly raise a signal of concern and indicate the need for more reliable information about rosiglitazone's safety. But the FDA, physicians, and patients can reasonably await the results of RECORD, a phase III trial designed specifically to study cardiovascular outcomes. Until the results of RECORD are in, it would be premature to over interpret a meta-analysis that the authors and *NEJM* editorialists all acknowledge contains important weaknesses. To avoid unnecessary panic among patients, a calmer and more considered approach to the safety of rosiglitazone is needed. Alarmist headlines and confident declarations help nobody," the *Lancet* editorial concludes.

Given the flaws in the data, many high-profile physicians have also questioned the *NEJM*'s decision to publish the meta-analysis. As one of the world's leading medical journals, they argue that it has a duty to present study findings in a more responsible manner. Writing in the *Wall Street Journal*, former deputy commissioner of the FDA, Scott Gottlieb, went one step further, contending that the study authors, the *NEJM* and certain politicians had tried to upstage the FDA. Gottlieb asserts that Nissen's manuscript was filed with the *NEJM* on 1st May, but neither the FDA nor GSK were made aware of the findings. The journal then expedited a review of the paper and commissioned a commentary from two well-known critics of the FDA's drug safety record, Dr Curt Furberg and Dr Bruce Psaty. The article was published on 21st May, just two days before the FDA was scheduled to issue a safety statement regarding Avandia.

GSK issues robust response

- For its part, GSK issued a robust response to the *NEJM* findings, later supported by a letter to the *Lancet*, in which it provided additional cardiovascular safety data from several large-scale clinical trials. The company also made several key points in defence of its Avandia franchise, which included:
 - The recent meta-analysis published in the *NEJM* failed to mention that the actual number of heart attacks represents a very low frequency of events – 0.6% for both Avandia and the control group (Avandia 86 out of 14,371; control 72 out of 11,634).
 - Further analyses from ADOPT and DREAM – two long-term prospective clinical trials – show that the incidence of ischemic cardiovascular events with Avandia is comparable to the two gold standard medicines used to treat type 2 diabetes (metformin or a sulfonylurea) in the ADOPT study, and to placebo in the DREAM study.
 - Findings from a soon-to-be-published study, using a managed care database of more than 30,000 diabetes patients in a real-world setting, show the incidence of hospitalisations for heart attack, and/or for a surgery known as revascularisation for patients on Avandia is the same as for other diabetes treatments.
 - The independent safety monitoring board for the RECORD trial – a large, long-term clinical trial, which has been designed to look at cardiovascular outcomes in people with diabetes – reviewed an interim analysis of cardiovascular endpoints in all study participants, and determined that the study should be allowed to continue.

So is Avandia guilty?

The cardiovascular safety profile of Avandia has been in the foreground since the product was approved in 1999. The FDA has been monitoring heart-related adverse events (such as fluid retention, oedema and congestive heart failure), and has updated the labelling on several occasions, most recently in 2006 when a warning was added about a potential increase in heart attacks and heart-related chest pain. The *NEJM* article has raised further questions about the cardiovascular safety of the product, but it is important to remember that, as the authors themselves admit, the statistical methodology used has some major flaws. Aside from the shortcomings Nissen and Wolski highlight, we would argue that excluding the trials in which patients had no adverse events in either group could also bias the results.

The RECORD trial, which started in 2000, should provide more definitive answers. It is a large-scale, prospective study designed to evaluate cardiovascular outcomes. An interim analysis found no cardiovascular safety signal, but the full data are not expected until 2009. Whether those data will ever materialise is not clear, though, after investigators reported that patients are dropping out of the trial following the findings presented in the *NEJM* article. If the RECORD trial is under threat, then it could be a major problem for GSK as the study was to provide the most reliable assessment yet of Avandia's cardiovascular safety profile. Without these data, it is doubtful whether the product would ever shake off its reputation for causing more heart attacks - in patients already more susceptible to such events.

The impact on Avandia and other diabetes drugs

Early prescription data already suggest Avandia's share of new prescriptions in the US oral diabetes market has shrunk from around 10% to zero. Given the litigious nature of the US market, it comes as no surprise that physicians have stopped putting patients on the drug. Despite a robust response from GSK, we believe it is unlikely that the company will be able to stem the tide of sentiment the media furore has created and that sales of Avandia will suffer as a result.

In 2006, GSK's product (including Avandamet and Avandaryl) generated global sales of \$2,574m, up 7% YoY. For 2007, we were forecasting sales of \$2,849m, but have revised this figure to \$2,269m (Source: Wood Mackenzie's *Productview*). For 2010, we now expect global sales of \$1,722m (versus \$3,414m previously) and for 2013 we are predicting sales to fall to \$769m (versus \$2,930m), accelerated by the US patent expiring in 2011. It is worth mentioning that, in 2006, 73% of sales stemmed from the US market – where, unfortunately for GSK, this recent safety scare is sure to have a far more pronounced effect on sales.

The question is: which products are going to pick up the slack from Avandia's lost sales? Takeda's Actos (pioglitazone) is the only other thiazolidinedione approved (the former Sankyo's Rezulin (troglitazone) was withdrawn in 2000, two years after launch, due to liver toxicity issues). The concern for Takeda is that the cardiovascular safety signal observed for Avandia may be viewed as a class effect – especially after Bristol-Myers Squibb/Merck & Co.'s Pargluva (muraglitazar) was rejected by the FDA in 2005 due to an increase in cardiovascular events. Interestingly, it was another analysis by Steven Nissen – this time reported in the *Journal of the American Medical Association* – that alerted the agency to these risks with Pargluva.

Although Avandia and Actos have the same basic mechanism of action, we believe the two have different effects on patients. True, like Avandia, Actos can cause oedema and is contraindicated in patients with heart failure. But in the PROactive study – a three-year trial investigating cardiovascular outcomes – the Takeda drug was found to cause a 16% *reduction* in heart attacks, stroke and death (p=0.027). When the results were published in September 2005, the PROactive trial was criticised for failing to meet its primary endpoint, a combination of seven different macrovascular events of varying clinical importance.

In light of the concerns surrounding Avandia, though, the secondary endpoint (i.e. the reduction in heart attacks, stroke and death) has taken on a greater importance. One theory centres around the drugs' influence on LDL-cholesterol levels to explain their differing effects on cardiovascular events. In PROactive, Actos was found to increase LDL levels by just 2% (and lowered triglyceride levels), whereas Avandia has been shown to raise LDL levels by as much as 18%. That said, this would be unlikely to have caused a cardiovascular event in the short timeframe of many of the Avandia studies included in the analysis.

Whatever the reason, we believe Actos does demonstrate an improved cardiovascular profile over Avandia, and that, consequently, it is likely to be the key beneficiary from the recent media furore surrounding GSK's product. For instance, for 2007 we were forecasting global sales of \$2,665m for Actos, whereas we now expect it to generate sales of \$3,128m. For 2010, we are now expecting sales of \$4,453 (versus \$3,414m previously). And for 2013, we are predicting sales of \$2,339m (versus \$2,332m previously), following patent expiries in the US and UK in 2011. Other products likely to benefit include Merck & Co.'s Januvia (sitagliptin) and Eli Lilly's Byetta (exenatide), not to mention generic metformin.

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US FDA issues an approvable letter for Novartis' Galvus, requesting additional data

Wood Mackenzie view

US regulators have requested additional data on the Novartis diabetes drug, Galvus (vildagliptin), including an additional trial in patients with renal impairment. The news comes as a major blow for the Swiss drug manufacturer as it means losing further ground to Merck & Co.'s rival DPP-IV inhibitor, Januvia (sitagliptin), which was launched in the US in October 2006. Galvus was already delayed by three months in November when the US Food and Drug Administration (FDA) asked for proof that skin reactions observed in pre-clinical trials were not replicated in human studies. With this latest setback, though, the product is unlikely to reach the US market before the start of 2009.

FDA is concerned over metabolite levels

For its part, Novartis claims to be confident in the safety and efficacy profile for Galvus, which has been the subject of a global clinical trial programme involving over 8,000 patients (5,500 of which have been treated with Galvus). The company told Wood Mackenzie that: "there is no renal issue with Galvus." What the FDA is concerned about, though, is the high levels of the metabolite LAY151 in the plasma of patients with renal impairment. Some 75% of Galvus is hydrolysed into LAY151 and excreted via the kidney; the rest remains unchanged and is excreted via the kidneys (20%) and faeces (5%).

Although details of the size and duration of the additional trial have yet to emerge, we understand that Novartis will have to provide additional pre-clinical and efficacy data that clarifies the process by which Galvus is metabolised into LAY151 and to characterise what effect LAY151 has on the body thereafter. For instance, is there a link between LAY151 and the skin lesions observed in pre-clinical trials? The company hopes to provide more guidance on the likely timelines for the additional trial work at its first quarter results on 23rd April 2007.

Merck tackled this issue head on

Merck appears to have adopted a savvier approach to its regulatory submission, addressing this issue head on. Recognising that Januvia is predominantly eliminated by the kidney, it undertook a 54-week study investigating lower doses of its drug in patients with moderate and severe renal insufficiency "to achieve plasma concentrations of Januvia...similar to those in patients with normal renal function." At the American Diabetes Association meeting in June 2006, the company revealed that the efficacy with adjusted doses of Januvia was similar to that in the other trials. That is reflected in the labelling, which stipulates that renally impaired patients should take 25mg or 50mg a day, rather than the standard 100mg.

Merck retains the upper hand

As the first two compounds in this promising new product class, Januvia and Galvus were pitted against each other in a high-profile race to reach the market. Yet, at every step of the way, Januvia has always had the edge. The drug was even filed for approval just a fortnight before Galvus (in January 2006) and it does not appear to cause the necrotic skin lesions that have been reported in primate studies involving other DPP-IV inhibitors, including Galvus.

Consequently, Merck's product was approved first – in October 2006 – and the company has seized on this advantage. Merck sales reps were detailing Januvia within 36 hours of approval and 70% of target physicians were reached within the first eight days of promotion. The company is also waiting on approval of fixed-dose combination with metformin, called Janumet, which is due in March 2007 (Novartis was only planning to file its own Galvus-metformin combination in the first quarter 2007).

Januvia has also been recommended for approval in Europe, in January 2007, and Merck has since sought to build on its position by filing for two additional indications in the US. The first is for using Januvia in combination with metformin as an initial therapy, the other is as an add-on therapy to a sulfonylurea, when it does not provide adequate glycaemic control; or as an add-on therapy to the combination of a sulfonylurea plus metformin, when the dual therapy fails to provide adequate control.

In the race for supremacy between the two DPP-IV inhibitors, being the first to market was always going to be a major advantage – but developing fixed-dose combinations and securing additional indications for use with other anti-diabetic agents were also key components of the strategy. Merck has trumped Novartis on every one of these, but these latest events illustrate that it is Merck's belt-and-braces approach to regulatory affairs that has really made the difference. Novartis' head of development, James Shannon, has speculated that FDA will only ask for a small new study, involving less than 100 patients and lasting only a few months. However, we believe the agency is more likely to use Merck's 54-week study in renally impaired subjects as a proxy. On that basis, we do not expect Novartis to re-submit Galvus until the second half of 2008. That suggests it may not reach the market now until the start of 2009 – around the same time as Bristol-Myers Squibb/AstraZeneca's saxagliptin. Indeed, the Galvus news was in part responsible for Merck's decision to lift its earnings per share expectations by 2% \$2.55-\$2.65, excluding exceptional items, just a few days later.

Conclusion

The Galvus setback typifies the challenge that pharmaceutical companies face in developing safe and effective treatments for a disease that is rapidly reaching epidemic proportions. The dual PPAR agonists represent another novel class of oral anti-diabetics that have failed to reach the market due to side-effect concerns. In a high-profile upset in November 2005, Bristol-Myers Squibb/Merck & Co.'s Pargluva (muraglitazar) failed to secure approval in the US due to a cardiovascular safety signal. And just a few months later, in February 2006, AstraZeneca terminated its dual PPAR Galida (tesaglitazar) due to renal toxicity issues. Other dual PPARs have suffered a similar fate, casting heavy doubt over the commercial potential of this class.

Even those that have been approved carry risks of their own. Just last week it emerged that 9.3% of women taking Avandia (rosiglitazone) in the 4,000-patient ADOPT trial experienced a fracture, versus 5.1% on metformin and 3.5% on glyburide. The product's labelling will no doubt be updated to include warnings of these risks – alongside existing warnings for an increased incidence of oedema, cardiac failure, and other cardiovascular adverse events.

The story of the first glitazone to reach the market – Sankyo's Rezulin (troglitazone) – serves as another cautionary tale. Approved in 1998, it was withdrawn from the market just two years later due to hepatotoxicity issues. These did not appear in the clinical trials programme, only surfacing after the product was launched on the wider market, in many hundreds of thousands of patients. The example highlights the shortcomings of clinical trials and suggests that Januvia is by no means out of the woods yet.

Even aside from these side effects, a recent commentary in the *New England Journal of Medicine* makes the point that all these new products are in fact no more effective in glycaemic control than the older medications. In an article entitled "Finding New Treatments For Diabetes – How Many, How Fast...How Good?" (1st February 2007), the author, David Nathan, argues that: "ironically, the two oral anti-diabetes medicines that are most effective in lowering glycaemia are also the oldest and were discovered accidentally, without the benefit of our contemporary understanding of the mechanisms of actions or of the pathophysiology of Type II diabetes."

They are the sulfonylureas and the biguanides. However, the article ignores two key points: a) that these older medications are associated with troublesome side effects (notably weight gain and hypoglycaemia), and b) that the oral anti-diabetics are used most effectively in multiple combinations, targeting the different underlying mechanisms of the disease. The DPP-IV inhibitors cause no weight gain, while the GLP-1 inhibitors (i.e. Eli Lilly's Byetta) in fact promote weight loss – highly advantageous in the treatment of diabetes. Although these represent only small, incremental improvements, the industry remains committed to seeking further advances in the disease – especially given the incidence of diabetes has risen by 54% in the last seven years.

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