

Key Events

Cardiovasculars

Last Updated: 25th June 2007

Date	Event
24 th – 27 th March 2007	American College of Cardiology, 56 th Session
19 th June 2007	Court ruling on Plavix patent challenge by Apotex

Court Upholds Plavix Patent

Wood Mackenzie View

On 19th June, a federal judge in New York ruled that the patent on blood thinner Plavix was valid, thereby protecting its market exclusivity until November 2011. The ruling came as welcome news to the drug's maker, sanofi-aventis, and its marketing partner Bristol-Myers Squibb, both of whom rely heavily on Plavix as a top-selling product. In 2005, worldwide Plavix sales totalled \$6.3 billion, making it the second best-selling prescription drug in the world behind Pfizer's Lipitor. In 2006, however, the "at risk" launch in the US of a generic version of Plavix (clopidogrel bisulfate) by Canadian company Apotex resulted in a 38% YoY decline in reported Plavix sales in that market. This event was a blow to both sanofi-aventis and BMS, who co-promote the product in the US, triggering each to lower earnings guidance for the year 2006. Today's victory, therefore, removes a significant overhang from both companies and, in our opinion, increases the likelihood of a BMS takeout, with partner sanofi-aventis a likely suitor, amongst others such as Pfizer or GlaxoSmithKline.

Background

On 8th August 2006, Canadian generic drug maker Apotex launched generic clopidogrel "at risk" after antitrust regulators rejected a proposed settlement between Apotex, sanofi-aventis and Bristol-Myers Squibb. Although a judge granted a preliminary injunction against sales of the generic three weeks later, Apotex had already flooded the market with over six months' worth of its lower-priced product. In fact, within the first week of launch, generic clopidogrel had gained approximately 75% share of new prescriptions. As a result, both BMS and sanofi-aventis lowered their 2006 earnings guidance by 20% and 9%, respectively.

For BMS, that was just the beginning of its troubles. The Board of Directors went on to oust CEO Peter Dolan and General Counsel Richard Willard in September, based on recommendation by the federal monitor that was overseeing the Company at that time. In Dolan's place, they named James Cornelius, the former head of Guidant Corp, as interim CEO. This raised suspicions that BMS was planning to put itself up for sale, as Cornelius was most recently known for orchestrating the sale of Guidant to Boston Scientific. Meanwhile, the Antitrust Division of the US Department of Justice launched an investigation into Bristol-Myers' proposed settlement with Apotex over the Plavix patent litigation. (The Company reached a settlement with the DOJ on 11th June, admitting that a former senior executive tried to get Apotex to halt generic production and agreeing to pay a \$1 million fine).

When Judge Sydney H. Stein was assigned to preside over the patent case between the three companies beginning 22nd January 2007, sentiment turned in favour of sanofi-aventis and BMS, as he was the same judge to grant the preliminary injunction against Apotex's generic in the fall. Sure enough, on 19th June, Judge Stein ruled to uphold Plavix's patent until its scheduled expiration in November 2011. Furthermore, Apotex was prohibited from producing any additional generic clopidogrel in the US, and a hearing will be scheduled to determine what damages the generic company will be liable for. However, any damages payable are likely to be significantly lower than the standard "triple damages" imposed for an at-risk launch, due to concessions made by both sanofi-aventis and BMS during the settlement negotiations. Apotex announced that it will immediately appeal the US court decision.

What does this ruling mean for BMS?

Needless to say, this ruling was a victory for Bristol-Myers Squibb, who in 2005 recorded about 70% of US Plavix sales (sanofi-aventis recorded the remainder). As such, Plavix accounted for 25% of the Company's ethical drug sales and nearly one-third of its profit in 2005. After losing patent exclusivity on several blockbuster drugs over the past several years, including its second best-seller Pravachol in April 2006, Plavix has become an even more important product to BMS over time. With its patent now virtually safe from generic competition for the next four years, the Company faces no more major patent expirations until then. In addition, it has one of the most robust late-stage pipelines within the industry, focused on serious unmet medical needs particularly in the oncology, metabolic and cardiovascular therapy areas. In fact, the Company's potential new breast cancer drug, ixabepilone, received priority review status from the US FDA also on 19th June. With a line-up of new drugs expected to launch in the next few years, Bristol's growth prospects are looking up (29% earnings growth expected this year), making it an attractive target for some of its large pharmaceutical peers who are struggling to come up with new growth drivers. In fact, so far this year, BMS has inked two separate collaboration agreements with AstraZeneca and Pfizer for its novel diabetes and cardiovascular compounds, respectively.

What next?

Since hitting a low last August when Apotex launched its generic product, Bristol's share price has risen nearly 60%, and is now the most highly valued of all the large pharmaceutical companies in our universe. This premium most likely reflects the assumed likelihood that the Company will be acquired. At Wood Mackenzie, we believe there is a good chance of this happening, especially given the recent shake-up in management. While James Cornelius recently announced his decision to stay on in a permanent role as CEO until 2009, we feel this was merely a strategic move to buy the Company more time to find a potential acquirer. However, with a market cap approaching \$63 billion, the pool of potential bidders narrows.

In our view, Pfizer is the most likely acquirer of BMS, given its strong cash position (\$28 bn in cash and \$13 bn in expected annual cash flow), lack of near-term growth drivers and need to cut costs. The joint collaboration they recently entered to develop apixaban also strengthens the ties between these two New York-based companies. In addition, part of Pfizer's restructuring plan is to shift from primary care markets to focus on specialty area markets – a strategy Bristol-Myers Squibb implemented several years ago. As such, BMS has the specialty care sales force already in place, creating the perfect synergistic opportunity for Pfizer, who also aims to cut 10,000 people from its workforce. Although Pfizer has said publicly that it is not interested in making another large acquisition at this time, we think that BMS's robust late-stage pipeline and the potential for synergies makes it an attractive target for Pfizer, especially in the face of Lipitor's pending patent expiration in 2011.

In January, a report ran in a French publication claiming that sanofi-aventis was in merger talks with BMS, prompting the latter to hire investment bankers to advise on a deal. However, we think that if sanofi-aventis were to bid for its Plavix partner, it would've done so prior to the Plavix ruling, when the stock was cheaper. Nevertheless, we do not rule sanofi-aventis out of the running, as the acquisition of Bristol-Myers Squibb would still bring many advantages. First, sanofi-aventis is in dire need of late-stage pipeline candidates, particularly in the wake of the recent setback for its obesity drug Acomplia. Secondly, such a merger would expand the French company's presence in the US, a faster-growing market than Europe. Finally, the two companies have a history of working together via collaborations on Plavix and Avapro/Avalide, and have complimentary portfolios in diabetes, oncology and CNS. The risks we see in this pairing are cultural fit and sanofi-aventis's already hefty debt load (\$9bn at the end of 2006).

Other potential suitors include GlaxoSmithKline (GSK) and Novartis, both of whom would like to increase their presence in the US market and have suffered recent setbacks in the diabetes market. GSK has been losing sales from Avandia after it was linked to cardiovascular problems, and it has no internal late-stage backup candidate. Novartis has experienced repeated delays in getting approval for its diabetes drug, Galvus. The withdrawal of Zelnorm in the US market was an additional setback for Novartis, and further increases the Company's need for a deeper understanding of regulatory practices in the US. However, several portfolio overlaps (Diovan/Avapro, Gleeevec/Sprycel and Galvus/saxagliptin) could result in product divestitures that would be potentially dilutive to a BMS-Novartis deal. Also, CFO Raymond Breu said there were no major acquisitions on the horizon for the Company. GSK, on the other hand, has two big holes in the oncology and cardiovascular areas, which Bristol's portfolio would fill in nicely. In addition, CEO Jean-Pierre Garnier is set to retire in May 2008, and BMS CFO Andrew Bonfield was the former CFO at SmithKline Beecham.

With the Plavix cloud now lifted from Bristol-Myers Squibb, it looks to be clear skies ahead for this once-troubled company. As such, we see BMS as an attractive acquisition target for several of its pharmaceutical peers, and thus there is likely to be a wide pool of applicants. In the end, we expect that the pairing will most likely be determined by strategic and cultural fit, opportunity for synergies and maximum return to shareholders.

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Breaking data from the ACC

Wood Mackenzie's View

In March 2007, Wood Mackenzie joined nearly 30,000 cardiologists at the 56th session of the American College of Cardiology in New Orleans. In our opinion, the most important breaking data discussed at the meeting arose from the controversial **COURAGE** trial investigating the use of angioplasty in patients with stable coronary disease, and the torcetrapib **ILLUSTRATE** and **RADIANCE** imaging trials. While the COURAGE trial demonstrated no difference between PCI (percutaneous coronary intervention) and aggressive medical therapy in this patient group (apart from a temporary improvement in angina relief), the implications of the trial were hotly debated, with cardiologists largely polarised over the potential impact of the results on the rates of PCI across the US.

Turning to torcetrapib, even if development of the compound had already been terminated by Pfizer, the results of these imaging trials were eagerly awaited – particularly by other companies developing CETP inhibitors. The results revealed increases in HDL of around 60%, but none of the trials hit their primary endpoint of slowing disease progression over atorvastatin monotherapy. When combined with blood pressure increases of between 2.1 and 5.1mm Hg and more serious adverse events (notably from the larger ILLUMINATE trial), the presentations certainly left many unanswered questions for both this product and class of compounds. However, the data presented on torcetrapib did appear to leave the door open for other CETP inhibitors in development.

PCI versus medical therapy – to stent or not to stent?

Percutaneous coronary intervention (PCI) or angioplasty, describes the opening up of blocked or obstructed arteries in the heart via a catheter inserted in an artery in the groin. Following PCI, a cylindrical metal stent is fitted to keep the artery open. PCI has been shown to be effective in relieving angina in patients with symptomatic coronary artery disease (CAD) and reducing mortality in high-risk patients. However, PCIs are also widely performed on patients with stable CAD – estimated to be anything from 35% to 80% of all PCIs performed in the US every year. This patient population was investigated by the Clinical Outcome Utilizing Revascularisation and Aggressive Drug Evaluation (**COURAGE**) trial, which found no benefit from PCI in addition to optimal medical therapy versus medical therapy alone over five years.

PCI did result in a temporary improvement in stable angina relief over the first three years, but after five years there was no difference in the two treatment groups. While short term relief in symptoms of angina will be welcomed by patients, many may now question whether their operation is entirely necessary. Payers may also begin looking more closely at the patients undergoing PCI to determine whether they are receiving the most cost-effective treatment. However, advocates of PCI criticised the trial design and reiterated the symptomatic relief of chest pain provided by PCI procedures.

While the COURAGE trial began to answer an important question in determining the role of PCI in treating stable CAD patients, the extent to which the results will be implemented is far from clear and has further divided the cardiology community. Despite many doctors dismissing the results, we believe overall the number of PCIs undertaken in stable patients will fall – as patients and insurers question the necessity of intervention.

Torcetrapib failure – molecule or mechanism?

One of the most eagerly awaited sessions was the Monday morning Late-Breaking Clinical Trials II session, during which results of Pfizer's cholesterol ester transfer protein (CETP), torcetrapib, were presented – the **ILLUSTRATE** and **RADIANCE** trials. These trials demonstrated that adding torcetrapib to atorvastatin, caused an increase in HDL levels of around 60% over atorvastatin alone. However, this unprecedented rise in HDL did not lead to a corresponding reduction in atherosclerosis above that observed with atorvastatin monotherapy (see Figure 1).

Figure 1: Discontinued Phase III trials involving torcetrapib

Compound*	Trial	Type	Primary endpoint / trial design	Outcome
Torcetrapib + atorvastatin	ILLUSTRATE (1188 patients)	Imaging trial	Change in % atheroma volume as measured by coronary IVUS over 24 months in patients with coronary heart disease	No difference in volume, or atherosclerosis progression. Blood pressure (BP) increased (+4.6mm Hg).
Torcetrapib + atorvastatin	RADIANCE-1 (904 patients)	Imaging trial	Rate of change in maximum cIMT in patients with heterozygous familial hypercholesterolemia over 24 months	Worse disease progression in torcetrapib arm for secondary endpoint of max & mean cIMT. Increase in BP (+2.8mm Hg) and serious adverse events
Torcetrapib + atorvastatin	RADIANCE-2 (752 patients)	Imaging trial	Rate of change in maximum cIMT in patients with mixed dyslipidaemia over 24 months	Trend towards disease progression in torcetrapib arm for secondary endpoint of mean cIMT. Increase in BP (+5.1mmHg) and serious adverse events
Torcetrapib + atorvastatin	ILLUMINATE (13,000 patients)	Morbidity & mortality	Occurrence of cardiovascular events in patients with coronary heart disease, or risk equivalents	Yet to be released, but trial stopped early due to increase in deaths of 60% with torcetrapib

* all trials were conducted against atorvastatin monotherapy, cIMT – carotid intra-medial thickness, IVUS –Intravascular ultrasonography

As well as the lack of efficacy, there was also concern over whether the raised blood pressure observed in these trials was a feature limited to torcetrapib or a wider class effect. In this regard, it was noteworthy that data presented by Prof. Daniel Rader (University of Pennsylvania School of Medicine) during the Louis F Bishop lecture demonstrated that infusion of Merck's CETP inhibitor, MK-0859, in preclinical models did not lead to an increase in blood pressure. Hence, it is possible that the blood pressure effect is specific to the torcetrapib molecule.

Whether the mortality effects are also torcetrapib-specific, or represent a feature of all CETP inhibitors, remains to be seen. More light is expected to be shed on the mechanism of torcetrapib-induced deaths when the results of the final morbidity and mortality trial, **ILLUMINATE**, are published later this year.

HDL – quantity or quality?

Although low HDL has been shown to be an independent risk factor for coronary heart disease, the torcetrapib trials demonstrate that more work is needed to understand the type of HDL which should be targeted for increase. That high levels of HDL observed in these trials failed to slow plaque progression greater than atorvastatin monotherapy will surely be a disappointment to Pfizer and the other companies with CETP inhibitors in development (see Figure 2). Furthermore, these results raise the possibility that a CETP-induced increase in HDL levels is not a clinically relevant objective.

Figure 2: Other development candidates seeking to increase HDL levels

Compound	Phase	Company	Comment
MK-0859	Phase II	Merck & Co	CETP inhibitor - reportedly not associated with increases in blood pressure
R-1658 / JTT-705	Phase II	Roche	CETP inhibitor – initial dose fixing trial complete and extension planned
CP-778875	Phase II	Pfizer	Patient recruitment ongoing
CETi-1	Phase II	AVANT Therapeutics	Synthetic peptide vaccine currently undergoing reformulation
FM-VP4	Phase II	Forbes Medi-Tech	CETP inhibitor – completed POC trials
CSL-111	Phase I	CSL	Reconstituted HDL (rHDL) – ERASE trial presented at ACC 2007
CP-800,569	Phase I	Pfizer	CETP inhibitor – novel formulation – preclinical studies revealed no BP increase
PF-3,185,043	Phase I	Pfizer	CETP inhibitor – torcetrapib analogue – preclinical studies revealed no BP increase
BAY-60-5521	Phase I	Bayer Schering	CETP inhibitor
JTT-302	Phase I	Japan Tobacco	CETP inhibitor

Despite the setback to the CETP-inhibitor class, we expect HDL to continue to be the subject of intense investigation. We suggest that R&D efforts will need to examine not only increasing the levels of HDL but also modifying its composition. Indeed, it is known that HDL plays a role in host defence and immunity and that some compositional changes boost its pro-inflammatory properties. A greater understanding of the lipoproteins comprising the HDL molecule and the effect of changing composition will greatly enhance the chances of success for development compounds in this lucrative field.

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Wood Mackenzie attending ACC in New Orleans

An analysis of the key findings from the conference, including new clinical data, changes to treatment guidelines, emerging products and companies in the CV space will be released shortly after the conference.

Breaking clinical trial data expected to be released:

- **AGI-1067** / AstraZeneca / **ARISE** – Phase III trial that targeted a 20% reduction in death due to CV events in patients with coronary artery disease. On 19th March AZ announced the trial had not meet its primary endpoint. However, the company did not state the level of reduction that was achieved – a 20% reduction was always a high hurdle to get over and now that this has been missed the future of this product is in doubt. AZ have 45 days following the completion of the trial analysis to consider the future of its collaboration with AtheroGenics.
- **torcetrapib** / Pfizer / **ILLUSTRATE** / **RADIANCE-1/-2** – although Pfizer has already terminated development of torcetrapib, the results from these imaging studies are eagerly awaited given their importance for other CETP inhibitors in development. However, we do not expect any regulatory guidance for the CETP class until data from the (failed) morbidity and mortality trial, **ILLUMINATE**, are also released later in the year.
- **Crestor** (rosuvastatin) / AstraZeneca / **METEOR** – designed to assess the reduction in progression of atherosclerosis in the carotid artery in low-risk patients. AZ filed for approval with the US and EU authorities in January 2007 for an atherosclerosis indication, mainly based on the results of the **METEOR** trial. Should results be positive we expect any upside to be small, given the difficulty AZ will face in penetrating this low-risk patient group without hard outcome data.
- **Ranexa** (ranolazine) / CV Therapeutics / **MERLIN TIMI-36** – this trial was designed to support an application for first-line use in the treatment of acute coronary syndrome (ACS). However, the company has already announced that ranolazine missed its primary endpoint in this trial. Ranexa was launched in the US in March 2006 and was the first angina product approved for many years. The company continues to pursue a label expansion for the anti-angina product and will present the full results at the ACC. However, given the disappointing top-line results, we do not expect Ranexa to be approved for ACS on the basis of this trial.

Breaking developments in markets and diseases – key questions to be answered:

- *What is the future of **anti-thrombotic therapy** in acute coronary syndrome?* – includes the most recent thoughts on the role of LMWH, bivalirudin, Factor Xa inhibitors, direct thrombin inhibitors, fibrinolytics, Glycoprotein IIb/IIIa inhibitors, and P2Y12 antagonists.
- *“Is **metabolic syndrome** really a syndrome?”, “Is diet or weight-loss therapy the best treatment for patients?”* – the focus of key debates, with additional sessions on the state of obesity and metabolic syndrome in children.
- *Is **raising HDL** still a viable therapeutic target in the post-torcetrapib world?* – the focus of a keynote session: “Targeting HDL to Prevent Coronary Disease: Where Do We Go From Here?”.

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