

Key Events

Central Nervous System

Last Updated: 4th June 2007

Date	Event	Status
April 28 – May 6, 2007	59 th Annual Meeting of the American Academy of Neurology (AAN)	Reported
May 19 – May 24, 2007	160 th Annual Meeting of the American Psychiatric Association (APA)	Reported
June 16 – June 20, 2007	17 th Meeting of the European Neurological Society (ENS)	To be reported
October 7 – October 10, 2007	132 nd Annual Meeting of the American Neurological Association (ANA)	To be reported

Report from the 160th Annual Meeting of the American Psychiatric Association

Wood Mackenzie View

The general impression taken from the 160th Annual Meeting of the American Psychiatric Association meeting in San Diego was that despite the presentation of a lot of interesting data, there was little that could be viewed as ground-breaking or sensational. This was particularly evident in large-market disease states such as depression and schizophrenia – and reflects the current state of late-stage R&D in many psychiatric disease areas.

Rather, the overwhelming message that came out of the majority of presentations on the treatment of psychiatric illness was that of refinement and segmentation. This included the identification of treatment-responsive populations in bipolar disorder as well as the ranking of the atypical anti-psychotics on an efficacy/side-effect axis, which both provide additional information in order to tailor treatment to specific patient need. This theme was also present when looking at late-stage development candidates in a number of disease areas, including schizophrenia and ADHD – where new products were viewed positively by many physicians, but, in almost all cases, the candidates were not perceived as being superior to existing therapies. Instead, these new products were expected to provide additional options to address the wide range of treatment needs in many psychiatric disorders.

Alongside this was the growing concern over the safety issues dogging many psychiatric treatments in widespread use – these include suicidal ideation in patients taking anti-depressants, metabolic and cardiovascular implications of the atypical anti-psychotics, and the potentially severe psychiatric and cardiovascular side-effects of ADHD medications. In addition, almost every discussion of optimal treatment paradigms included a reference to the range of co-morbidities associated with many psychiatric conditions (i.e. pain or insomnia in depression) and the need to treat all aspects of a particular condition in order to enhance patient outcomes. All of these issues were used to call first for increased monitoring of patients, and if necessary, an increase in the use of “polypharmacy” to address all aspects of patient need. There was also a constant call for the increased use of cognitive behavioural therapies (CBT) to accompany pharmaceutical use in the treatment of psychiatric conditions, as many felt there was a growing reliance on drug treatment that reduced physician time with the patient and decreased the likelihood of a sustained positive outcome.

In short, it appears that the “practice” of psychiatry is becoming increasingly important as co-morbidities, drug safety issues, and population segmentation drives a potentially complex mix of drug and behavioural therapies in order to address an individual patient requirements.

Key Clinical Results

Shire leads the way in ADHD and reports data on its key development products.

Shire's ADHD products were well represented at this year's APA with data being presented on its whole range of marketed and developmental products. Data for all products was broadly positive and should all candidates reach the market it would certainly provide Shire with the broadest range of treatments for ADHD. Key ADHD findings presented at APA include:

- **Vyvanse demonstrated long term effectiveness at 12 months and inter-patient pharmacokinetics was improved compared to Adderall XR** – Data from a one-year open-label study demonstrated that maintenance treatment of 30-70mg of lisdexamfetamine in children 6-12 years old reduced mean ADHD-RS scores by 70% after 12 months. Also, Phase II data looking at the pharmacokinetics of lisdexamfetamine confirmed it was effective with once-daily dosing and that when compared to Adderall XR the inter-patient plasma concentration variability of d-amphetamine was lower and more predictable. A more consistent plasma level and 12-hour duration of action was considered by the physicians present to be an important; however, following the DEA's recent decision to class Vyvanse as schedule CII it may be difficult for Shire to sufficiently differentiate the product in order to encourage a strong switch from Adderall XR.

- **Daytrana is good option to oral ADHD treatments given positive one-year safety and tolerability data** – Data presented came from a 12-month open label extension to four studies and demonstrated that transdermal methylphenidate (MPH) was effective in maintaining improvements in ADHD-RS scores out to one-year. Additional testing demonstrated that the prevalence of adverse events was infrequent but confirmed that side-effects were generally consistent with other MPH treatments, including increases in blood pressure and other cardiac measures. As the efficacy and safety profile appears similar to oral treatments, it confirms our earlier impression that use of the product will be limited to patients who are unwilling or unable to take tablets. Furthermore, it was highlighted by one physician that is often necessary to contact insurers and justify the need for a transdermal product in order to gain reimbursement, something that may further restrict the product's uptake.
- **Non-stimulant, extended-release guanfacine, shows promise in children 6-17 years old with ADHD; however, effect is still less than existing amphetamine treatments** – The results presented came from two, short-term, placebo-controlled studies (up to 9 weeks) examining the efficacy and safety of 1-4mg of extended release guanfacine. In both trials patients were started on 1mg and then titrated up to the randomised dose, were held at this dose for a period of time and then tapered back down to 1mg. Patients in both trials demonstrated a dose-dependent improvement in ADHD-RS IV scores compared to placebo. Similarly, in physician and parent-evaluated scoring of clinical efficacy there were placebo-adjusted improvements on the order of 20-40% across all doses. The safety data collected in the two studies showed no severe adverse events and the primary complaints were sedative in nature – i.e. somnolence (27-32%) and fatigue (9-18%). There were also mean decreases in heart rate, and systolic and diastolic blood pressure but these were minimal and thought not to be clinically meaningful. While the results of these studies show disease improvements well below those normally associated with methylphenidate treatments, the approval of guanfacine would provide a much needed alternative for patients intolerant to stimulants.

BMS/Otsuka explore wider use of Abilify – adolescent schizophrenia, bipolar I disorder monotherapy, and major depressive disorder

The debate continues over the risk/benefit profile of all atypical antipsychotics, focusing in particular on the risk of weight gain and other metabolic changes. As such, data continues to be generated on the metabolic profile of aripiprazole. Results presented at the APA showed that Abilify was associated with a low incidence of diabetes-related adverse events, equivalent to that seen for haloperidol or ziprasidone (Pfizer's Geodon). In addition, in patients switching from Eli Lilly's Zyprexa, data showed that at 16 weeks there was a mean decrease in body weight, as well as an associated decrease in total triglyceride levels and non-HDL-C lipids in the Abilify treated group. That said, metabolic benefits came at a price as Clinical Global Impressions Scales for Improvement (CGI-I) were better in Zyprexa-treated patients.

Given the positive metabolic profile of the product compared to other atypicals BMS/Otsuka are exploring Abilify's use in a range of conditions where the atypicals have demonstrated efficacy but are currently only used off-label :

- **Abilify was effective as an adjunct therapy in MDD (major depressive disease) patients with an incomplete response to antidepressants** – Data comes from a Phase III trial involving patients that had reported an inadequate response on up to three antidepressants, including GSK's Paxil, Pfizer's Zoloft, Forest's Lexapro, Lilly's Prozac, and Wyeth's Effexor XR. After antidepressant treatment for eight weeks patients were randomised to Abilify (5mg, titrating to 2-15mg) plus antidepressant or placebo plus antidepressant. Results showed that the addition of Abilify improved both response and remission rates - 33.7% of Abilify patients showed a response compared with 23.8% of patients on placebo and 26% of patients achieved remission in the Abilify group compared to 15.7% in the placebo group.
- **There is a dose-dependant improvement in PANSS scores for adolescent patients taking Abilify** - Phase III data examining the efficacy and tolerability of Abilify (10 or 30mg) in adolescent (aged 13-17) schizophrenia patients showed a significant improvement at six weeks in a number of physician-evaluated and quality of life diseases measures, including the primary endpoint of a mean change from baseline in the positive and negative symptom scale (PANSS). The improvements seen were dose dependant, with the 30mg dose (titrated from starting dose of 2mg over 11 days) separating from baseline after one week of treatment. The positive metabolic profile of Abilify was again confirmed in this study and the incidence of clinically significant weight gain (>7% increase from baseline), although greater in treatment groups, was not significantly different to placebo.
- **Abilify monotherapy is as effective as lithium in bipolar I mania but no better than placebo in bipolar I depression** – Data from three studies (CN138-135, 096, 146) demonstrated that aripiprazole monotherapy (15 or 30mg/day) was as effective as lithium (900-1500mg/day) in the treatment and maintenance of acute bipolar treatment. The Abilify treated group showed an improvement at day two compared to placebo and this effect was maintained to the end of the 12-week study. Conversely, in bipolar patients with a major depressive episode, Abilify at 10mg/day (titrated to 5-30mg/day) was no better than placebo in the primary measure of MADRS total score at the end of the 8-week study; however, there was statistical separation at various time points up to week 6. This loss of efficacy could suggest that a change in dosing may elicit a more sustained response.

At present it is not known whether BMS/Otsuka will pursue approval for these indications as the atypicals are already often used off-label. However, as concern over the side-effects associated with atypical use has potentially restricted indication expansion, aripiprazole's positive safety profile in comparison to other treatments could provide a clear opportunity. As such, if BMS/Otsuka can continue to confirm the product's efficacy and relatively good metabolic profile it is likely that Abilify would become the treatment of choice in these difficult-to-treat patient populations.

Additional data on Lundbeck/Merck's insomnia treatment gaboxadol provides few clues to product's failure

Despite small delays in the development of Lundbeck/Merck's selective extrasynaptic GABA_A agonist, gaboxadol, the product was perceived by many as providing a novel alternative to existing insomnia treatments. As a result, the termination of programme in Q1 2007 came as quite a surprise. Although both Lundbeck and Merck presented positive Phase III efficacy data on the treatment at this year's APA, it became clear that it was the culmination of a number of issues that brought about the termination of the project.

- **Gaboxadol 5-15mg improved sleep onset and total sleep time in adults and the elderly with primary insomnia; also decreased wakefulness-after-sleep-onset (WASO) scores in a model of transient insomnia** – The results presented came from three studies conducted by both Lundbeck and Merck examining gaboxadol in three populations and over time periods that ranged from four weeks to three months. In general, the results showed an improvement in both sleep onset and maintenance compared to placebo; however, this was primarily restricted to the highest doses – the three-month study showed efficacy at 15mg but not at 10mg.
- **Discontinuation of gaboxadol's development was the result of several complicating factors highlighted in pivotal Phase III trials** – The decision to terminate the development of gaboxadol was taken after a review of clinical data coming out of key Phase III trials, and an FDA requested trial looking at gaboxadol's abuse potential. Data showed an increase in psychiatric adverse events, particularly in patients who had taken a dose higher than that prescribed in clinical trials. There was some debate at the conference as to why patients would take higher than therapeutic doses and this centred on the product's novel mechanism of action as a potential cause. It was proposed that a similar trend has been seen in those taking Takeda's melatonin receptor agonist Ramelteon, where patients who have experience of traditional hypnotics, do not perceive the same sedating effects that normally herald sleep onset and as a result sometimes augment the prescribed dose even though it is not required. Regardless, of the reason, given the product's lack of efficacy at 10mg and potential side effects at 3-4x therapeutic doses, it suggested a relatively narrow therapeutic window. In addition, other studies conducted by Merck discovered significant sex-related differences in drug plasma concentrations, with women having drug levels up to three-fold higher than men, further complicating the dosing profile of the product. The end result was the termination of gaboxadol for the treatment of sleep disorders.

Both Merck and Lundbeck remain committed to publishing further results from these studies and we would expect additional data to become available throughout the year. Although this product has failed it is not yet clear whether this is a class effect or whether similar GABA_A agonists may yet provide a viable option to existing treatments.

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Report from the 59th Annual Meeting of the American Academy of Neurology

Wood Mackenzie View

There has traditionally been a significant gap between the ability to diagnose and the ability to treat many neurological disorders. Despite this fact, great strides forward have been made in recent years to elucidate the underlying disease mechanisms and as such neurologists are now, more than ever, able to provide real treatment options for their patients. This was one of the main themes that came out of the 59th Annual Meeting of the American Academy of Neurology, held in Boston earlier this month.

While the general mood of the meeting was positive, part of the opening lecture from AAN President, Dr. Thomas R Swift, polled leading members of the AAN on when they thought there would be a cure for debilitating neurological conditions such as Alzheimer's, Parkinson's, and multiple sclerosis. The answer was unanimous in its vagueness – none of those polled were able to realistically foresee a time when these conditions would no longer be a concern and one respondent noted that as human lifespan extends, the brain is becoming the rate-limiting organ. This echoed the overarching message of the conference: there remains a significant unmet need in the treatment of all neurological disorders.

It was proposed that to address this need will require continued investment in the basic understanding of the brain, support of neurology as a specialty, and greater awareness from regulatory and reimbursement agencies when examining treatment options of the profound impact these conditions have on both the individual and the wider society. Although progress has been made in recent years and indeed clinical findings at this year's conference, particularly in the area of multiple sclerosis, point to a number of improved treatments on the horizon the goal of neurology in the near term will remain disease management rather than cure.

Key Clinical Results in Multiple Sclerosis

Multiple sclerosis became one of the key focuses at this year's AAN as data was presented on a number of marketed products as well as key development products – the highlights of this data are below.

The role of the B-cell in autoimmune neurological disorders

One of the Hot Topics at this week's AAN meeting focused on the growing amount of research examining the role of the B-cell in neurological auto-immune disorders. Data was presented on Genentech/Biogen Idec/Roche's targeting B-cell therapy **rituximab** and its use in conditions such as Stiff Person Syndrome, paraproteinemic peripheral neuropathy, and neuromyelitis optica. Of greatest interest however, was the Phase I and Phase II data on the safety, tolerability, and efficacy of rituximab in relapsing remitting multiple sclerosis (RRMS). For RRMS, 1000 mg of rituximab, infused twice over a two week period and again after 6 months, was shown to be well tolerated, with low grade adverse events associated primarily with the infusion. In terms of efficacy, rituximab depleted all circulating B-cells by 2 months and this depletion did not begin to recover for up to eight months. What this meant in terms of disease progression was a significant decrease in Gd-enhancing lesions at all time points (the primary endpoint) and a 91% decrease overall, compared to placebo. Importantly, rituximab also reduced the relative risk of relapse by approximately 58% compared to placebo.

While this data clearly points to a pivotal role of the B-cell mediating in the progression of MS it also demonstrates that rituximab treatment had greater efficacy in preventing relapse than currently available treatments such as Copaxone and the interferons. Indeed, given the established safety profile of the drug, we believe rituximab will only have to demonstrate similar efficacy in its Phase III programme to ensure its place as a leading MS treatment.

Alemtuzumab demonstrates strong efficacy in RRMS but incidence of ITP causes concern

One of the surprising results of the conference came in the form of Phase II interim data from the CAMMS223 study of the use of the anti-IL2 therapy alemtuzumab (Genzyme/Bayer's Campath) in the treatment of RRMS. The data showed that patients taking high dose alemtuzumab (24 mg/d IV for five days, then for three days in subsequent yearly treatments) demonstrated an 87% reduction in the risk of relapse and a 66% reduction in the risk for progression of clinically significant disability. While on the surface these results appeared broadly similar to what was presented earlier in the day for rituximab, the CAMMS223 trial utilised an active control rather than placebo and therefore these were the benefits seen over an above one of the leading interferon products, Pfizer/Merck Serono's Rebif.

However, overshadowing this result was further information on alemtuzumab's ability to cause immune thrombocytopenic purpura (ITP), which arose in six of 216 patients (2.8%) and resulted in one fatality. Furthermore, additional data presented at the conference on the higher level of thyroid-related adverse events in the alemtuzumab group. That said, there was a real buzz in the audience following the presentation of these results and we believe that if Bayer/Genzyme can incorporate an effective ITP management plan as part of any Phase III programme the impressive efficacy demonstrated to date should outweigh the safety concerns.

Positive Tysabri safety data and what patients perceive as an "acceptable" treatment risk in MS

Several posters were presented at this year's AAN looking at data from the TOUCH Prescribing Program and the TYGRIS study examining the safety and efficacy of Tysabri treatment in RRMS. The results demonstrate that since the product was re-launched there have been no new reported cases of progressive multiple leucoencephalopathy (PML), with approximately 10,000 patients currently on therapy worldwide.

Also, as part of the ongoing monitoring of patients treated with Tysabri, additional data was presented that examined the efficacy of treatment at three years. The results from this extension study demonstrated that the annualized relapse rate for patients treated with Tysabri over the three-year period was 0.23, translating into an average of one relapse every 4.3 years and the effect on the cumulative probability of disability progression was also significantly decreased in Tysabri treated patients at three years.

In addition to a growing body of evidence showing the safety of Tysabri it appears as though attitudes to risk are changing, at least among patients. Additional studies presented at the meeting demonstrated that when patients were polled on their view of acceptable risk in treatment they were comfortable with the relative risk of Tysabri treatment in order to gain the additional efficacy the product affords. However, although patients may be willing to embrace the new treatment, panel discussions on the subject later in the week demonstrated that many neurologists remain wary of Tysabri's risks. As a result of these findings, we are increasingly optimistic about Tysabri's potential but we believe that Biogen Idec/Elan will need to continue to monitor the product's safety and at the same time educate physicians, possibly in conjunction with the strong patient advocacy groups.

Other Clinical Results

Safinamide shows efficacy as adjunct therapy in early stage PD – In a Phase III dose finding study of the addition of Newron/Merck Serono's **safinamide** to a single dopamine agonist in the treatment of Parkinson's disease, two doses were examined – low dose: 50-100mg/day and high dose: 150-200mg/day. Oddly, only the low dose was shown to be effective, with the high dose not differing from placebo. The results showed that the low dose of safinamide significantly improved motor symptoms as measured by UPDRS III as well as improving quality of life measures and the UPDRS II Activities in Daily Living Scores when compared to placebo. Furthermore, in cognitive testing it was demonstrated that safinamide-treated patients performed better than patients who received dopamine agonist monotherapy. Patients will have the opportunity to enter into a one-year extension study as part of the continuing Phase III programme. Given the unmet need in Parkinson's treatment we believe that any additional efficacy in motor improvement and cognitive function will be embraced. In addition, if Newron and Merck can demonstrate that these improvements in early PD can slow or mediate disease progression then there is a significant opportunity for safinamide.

Zolmitriptan is effective as an acute and prophylactic treatment in menstrual migraine – Data from two studies in women who suffer from migraine in the peri-menstrual period showed that AstraZeneca's **Zomig** was significantly more effective than placebo in producing a headache response and pain free rates at two hours post dose. In addition, given the predictability of these headaches, a second study examined two doses of zolmitriptan– 2.5mg tid or 2.5mg bid – which was to begin 2 days before the expected onset of menses and would continue for seven days. Results showed that both doses significantly reduced the number of attacks compared to placebo with the higher dose demonstrating slightly greater efficacy over three cycles.

These results certainly point to the efficacy of Zomig in the treatment of menstrual migraine but also point to the fact that this is probably a triptan class effect. If so, this could have an impact on the likes of Endo's Frova (frovatriptan), which is currently awaiting approval from the FDA of its sNDA in menstrual migraine – if approved it would be the first triptan approved for this indication. However, if it becomes generally accepted that this is a broader class effect it will likely decrease Frova's competitive advantage in this space.

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