Takeda’s Recovery Will Be Rooted In Development Partnerships

**BMI View:** Takeda’s attempts to recover from recent losses are firmly rooted in research and development. The NsGene partnership is part of a broad trend of investment in early stage research and, though somewhat counter to the trend of late stage acquisition, these investments are based upon solid, up and coming development. As Takeda stabilises its finances these partnership will become a key growth driver.

Takeda Pharmaceutical Company has announced a research agreement to develop a new form of cell therapy for patients with Parkinson’s disease (PD), in partnership with NsGene. The new therapy will focus on the delivery of recombinant Glial Cell Line-Derived Neurotrophic Factor via implanted, encapsulated cell therapy devices. The agreement marks the second such collaboration Takeda has announced for the development of early stage drugs in 2016 and forms part of the company’s strategy to revitalise its fortunes after making a loss in FY15.

**Partnership Key For NsGene Development**

NsGene is a Denmark based drug discovery company with a heavy focus on developing new solutions to CNS conditions. It has an early stage pipeline of therapeutics, addressing common neurological disorders in need of improved therapeutics including PD, Alzheimer’s disease and neuropathic pain. The company intends to leverage its proprietary platform, Brain Repair Device, to deliver therapeutics across the blood-brain barrier and target these key conditions. A Takeda partnership is a large step for the company and will provide it with a solid base of capital to develop the PD therapeutics and pursue the rest of its pipeline.

**Parkinson’s Has Pressing Need For Late Therapies**

The NsGene PD therapy is still in very early stages, but represents a novel mode of treatment for the disease. Ultimately, all PD treatments are ineffective at reversing disease progression and beyond certain points existing therapies lose all effectiveness. The bypassing of the blood brain barrier, through use of NsGene’s Brain Repair Device, could allow for a number of molecules that previously could not reach the brain to target PD related tissue. PD is a systemic, degenerative disorder that affects one in every 500 people, or approximately 14mn people worldwide.

**Takeda Seeking Partnerships To Fuel Long Term Prospects**

For Takeda the collaboration is a natural fit with its established CNS and PD pipeline and marks continued attempts to diversify its product base. It joins an established move towards partnership as a means of generating new research and opposes a current trend in pharmaceuticals towards late stage and developed acquisition. Takeda saw its net income turn negative in 2015 (measured in either USD or JPY) and partnerships such as with NsGene will be key to the recovery of the company.

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Despite the gloomy outlook for 2015, Takeda saw growth in revenues in JPY, which was obscured by the strong USD. Consistent revenue growth is a strong sign that a recovery in income is still very likely. Takeda is making shifts towards ‘agility’ and seeks to become best in class, with a focus on streamlining its processes and investing in discovery and development partnerships to provide future products and maintain its portfolio through research. Overall, the company retains a high level of confidence and the income situation will, if not recover to previous levels, normalise at a consistently positive value.

**Neurodegenerative Disorders**

**Zambon Launches Xadago For PD In Switzerland**

Zambon and its partner, Newron Pharmaceuticals, have reported the launch of Xadago (safinamide) in Switzerland, the second market after Germany. Swissmedic approved Xadago on November 12 2015 as add-on therapy to levodopa alone or in combination with other therapies for patients with Parkinson's disease (PD) in mid-to late-stage and motor fluctuations.

Xadago is a new chemical entity. Clinical trials have established its efficacy in controlling motor symptoms and motor complications in the short term, maintaining this effect also in the long term (over two years). Results from long-term (24 months) double-blind controlled studies suggest that Xadago shows significant effects on motor fluctuations without increasing the risk of developing troublesome dyskinesia. Xadago is well tolerated with a favourable side-effect profile.

Marketing authorisation in the EU for Xadago for the treatment of PD was granted by the EC in February 2015, followed by the launch by Zambon in the first key EU country, Germany, in May 2015. The NDA has been accepted for review by the FDA, as reported in March 2015. Zambon has the rights to develop and commercialise Xadago globally, excluding Japan and other key Asian territories, where Meiji Seika has the rights to develop and commercialise the compound.

**Biotie Acquisition Underscores Acorda’s Focus On Parkinson’s Need**

**BMI View:** The heavy investment Acorda has made into its Parkinson’s pipeline by the acquisition of Biotie will raise concerns over the additional risk borne by the company. Tozadenant has broad potential in Parkinson’s management and will be pursued aggressively by Acorda as it attempts to break into a market that has a high need for new therapeutics.

**Acorda Therapeutics and Biotie Therapies** have announced an agreement under which Acorda will acquire Biotie for approximately USD363mn in cash. The acquisition has been driven by Biotie’s development pipeline, notably the company’s Phase III candidate for Parkinson’s disease (PD), tozadenant.

**Biotie Purchase Adds Parkinson’s Synergy**

Under the terms of the agreement Acorda has pledged to pay USD25.60 per share, at a premium of 94% over the closing share price of USD13.20 on January 15, and an excess over even Biotie’s all time share maximum which stood at USD24.00. The cash transition in the deal is valued at USD363mn and Acorda has entered agreements for financing the purchase with an equity private placement and asset-based loan facility valued at USD135mn. The high valuation comes mostly from Biotie’s research into PD. Biotie has two compounds under investigation for PD, tozadenant, which has shown efficacy in a Phase Ib trial and SYN120, which is anticipated to provide Phase II data by the end of 2016.

The PD specialisation has synergies with Acorda’s existing experience with development of CNS-based treatments and with its own PD development programme. While Acorda’s own potential therapeutic, CVT-301, is somewhat more developed and already in Phase III trials, the addition of Biotie’s pipeline greatly strengthens Acorda’s ability to bring a PD therapeutic to market. The deal also included other drug candidates and double-digit royalty payments, double-digit royalties from sales of Selincro (nalmefene) and an EMA approved therapy for reduction in alcohol consumption.

**Large Potential Remains For Parkinson’s Therapies**

Tozadenant is an orally administered antagonist of the adenosine A2a receptor. This receptor is expressed particularly in the motor control part of the brain that is affected in people with PD. Blocking of A2a receptors with tozadenant serves to dampen the antagonistic effect of adenosine on dopamine...
PD affects an estimated 10mn people worldwide and of those, 1mn live in the US. The condition is costly and requires constant medication for the remainder of the patients’ lives, but current drug regimens still leave significant room for improvement. While the demand for new therapeutics is high, new PD therapeutics have proven difficult to produce and, as such, late-stage therapeutics with strong efficacy in Phase Iib trials such as tozadenant represents an appealing investment.

**Biotie Agreement Increases Investor Concerns**

Acorda is a neuroscience focused company with a pipeline focused on CNS based conditions including MS, pain and PD. The company’s primary revenue is from Ampyra (dalfampridine) sales and in FY14 this earned the company USD366mn in revenue, an increase of 21% over the previous year; this growth is anticipated to continue into FY15. In Q315, the company declared it had USD323.4mn in cash and cash equivalents and has indicated that it will soon be in a positive cashflow position. The company has previously made a very similar purchase to the Biotie acquisition. In September 2014, Acorda purchased Civitas Therapeutics for USD525mn and acquired its lead PD drug, CVT-301. On both occasions, Acorda acquired a late-stage, high profile PD therapeutic.

**Acorda Recovered From 2015 Losses In Stock Price**

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Acorda’s share price has dropped by 6% from USD39.90 on January 15 to USD37.55 on January 19. PD therapeutics, and even more specifically, A2a targeted drugs, have seen late-stage failures before and large pharma companies such as Merck and Biogen have had to scrap promising programmes. While the potential pay-offs for a PD therapeutic are high, there is no small amount of risk attached to development, especially as Acorda has already invested so significantly into tozadenant.

**Alzheimer’s Disease**

**Neurotrope Initiates Phase Iib Study Of Bryostatin For Alzheimer’s Disease**

Neurotrope has announced the initiation of a Phase Iib clinical trial of lead candidate bryostatin 1 for the treatment of Alzheimer’s disease (AD). The Phase Iib trial is a randomised, double-blind, placebo-controlled study designed to evaluate the safety, tolerability and efficacy of bryostatin 1 in the treatment of moderately severe to severe AD. The study, which plans to enrol 150 patients, is currently recruiting subjects at five trial sites in Florida, New Jersey, New York and Ohio. Neurotrope is engaging additional sites for the trial with a goal of over 30 participating sites.

The clinical trial will evaluate two different doses of bryostatin (20 or 40 micro-grams) versus placebo, with a total of seven doses administered over 12 weeks. The primary efficacy endpoint is based on Severe Impairment Battery Scale, a benchmark assessment used extensively in severe Alzheimer’s drug trials. Secondary efficacy endpoints include Activities of Daily Living, Neuropsychiatric Inventory and Mini-Mental State Exam. The Company expects to complete enrolment and report interim data from the study in H116, with the complete data set expected in H117.

**Probiodrug’s pGlu-Abeta For AD Granted Japanese/US Patents**

Probiodrug received key patents for its antibody programme targeting pyroglutamate amyloid beta (pGlu-Abeta, also N3pG Abeta) in Q415. US Patent No 9,156,907 and Japanese Patent No. 5,828,762, were granted and cover method as well as composition of matter claims.

A variant of amyloid beta, pGlu-Abeta has been shown to form hyper-neurotoxic Abeta oligomers, which are supposed to be a key component leading to neurodegeneration and cognitive impairment. Probiodrug focuses on two pGlu-Abeta targeting approaches for the treatment of Alzheimer’s disease: PQ912, a small molecule inhibitor of glutaminyl cyclase, which prevents pGlu-Abeta formation and is currently in a Phase II trial; and PBD-C06, a monoclonal antibody, binding specifically to pGlu-Abeta, is currently in preclinical development.

**Alector Closes USD29.5mn Series D Financing**

Alector has announced that it has raised USD29.5mn in a Series D financing. After completing a Series C financing of USD32mn in 2015, this financing brings the total amount of capital raised in 2015 to USD62mn. The financing was led by the Dementia Discovery Fund, with new investors Amgen Ventures and AbbVie joining the syndicate.
Alector is a neurology-focused startup that is developing first-in-class, immuno-modulatory therapies for Alzheimer’s disease and other neurodegenerative disorders. Its strategy is to efficiently generate and validate antibody drugs that engage key targets. Alector’s approach is enabled by a strategic alliance with Adimab, the technology leader in the discovery of fully human antibodies and bispecifics.

**Multiple Sclerosis**

**EMD Serono Takes Exclusive Promotion Of Rebif In US**

**EMD Serono** (Merck KGaA) has taken the sole rights to Rebif (interferon beta-1a) in the US as of January 1. Rebif, the number one prescribed interferon for relapsing MS in patients new to therapy in the US, is now the exclusive interferon beta-1a on **CVS Caremark** National Formulary and will also continue to be covered on most major national formulary plans.

Rebif is used to treat relapsing forms of MS to decrease the frequency of relapses and delay the occurrence of some of the physical disability that is common in people with MS. The efficacy and safety of Rebif in controlled clinical trials beyond two years has not been established.

**Other Neurodegenerative Disorders**

**Focus On Partnership Securing Results For Ionis**

**BMI View:** Ionis’ IONIS-HTTRx’s second orphan drug designation will greatly speed development and raises the potential for Roche to licence the drug candidate for its own development. Another development milestone reached is a strong sign for Ionis, which relies heavily on the success of development in partnership to fund its diverse pipeline, and the ODD will reduce the risk associated with development.

**Ionis Pharmaceuticals** (formerly Isis Pharmaceuticals) has received orphan drug designation (ODD) for its Huntington’s disease (HD) therapeutic candidate, IONIS-HTTRx, from the FDA. IONIS-HTTRx is the first therapy to enter clinical development that is designed to directly target the cause of the disease by reducing the production of the protein responsible for HD. The development is being pursued in collaboration with **Roche** combining Ionis’ antisense expertise with Roche’s expertise in neurodegenerative therapeutics.

**Ionis Partnership Development Encourages Broad Pipeline**

With a firm focus on genetic causes of disease, Ionis has a large and varied pipeline of therapeutics under development, including therapeutics for treatment of cancers and a number of rare diseases with underlying genetic causes. These include HD, but also under development are therapeutics for familial amyloidosis, juvenile muscular atrophy and familial hypercholesterolaemia. Ionis uses its expertise in antisense therapeutics to deliver RNA-targeted therapeutics to disrupt the formation of faulty proteins and so suppress the expression of genetic diseases. This technique has a range of potential targets including a huge number of inheritable disorders that currently lack medication.

Ionis has an extremely broad pipeline and the scope of research has lead Ionis to adopt a partnership strategy to pursue its developments. In 2014, Ionis received over USD200mn in milestone payments as part of this strategy and, with only two products commercialised, this represents the majority of the company’s income. Overall, the partnerships act to reduce the risk of development. The large number of different partners Ionis is working with reduces it further. Ionis’ strong support from a range of established companies demonstrates a high level of confidence in its pipeline, and the company is well placed to further its research goals as the existing projects mature.

**Huntington’s Disease Therapeutics Have High Potential**

Worldwide, HD prevalence is approximately five to 10 in 100,000, suggesting approximately 500,000 patients with the disease. There is no known cure and current therapeutics focus around slowing disease progression and eventual long-term care. Like Alzheimer’s disease, HD imposes a high social cost as it does not kill, but disable, and care costs can be extremely high.

The ODD for IONIS-HTTRx from the FDA joins an announcement of ODD from the EMA, and the designation will accelerate development of the drug. There are a number of techniques under investigation for control of HD, but Ionis’ approach is unique in exploiting gene silencing which may, if effective at switching off the aberrant genes, stop or greatly reduce disease progression.

The ongoing Phase I/IIa study will be critical for determining the long-term future of IONIS-HTTRx. Ionis has earned USD52mn in upfront and milestone payments from its relationship with Roche for the development of IONIS-HTTRx so far, and is eligible to earn additional milestone payments, as well as royalties for the commercialised product. Roche has the option to license IONIS-HTTRx from Ionis after the completion of the Phase I/IIa study, however, and the ODD from the FDA will weigh heavily on this decision. Positive results in the ongoing trial would make it very that Roche will take over development for the final stages of IONIS-HTTRx.

**BrainStorm Building On Strong Results In ALS**

**BMI View:** The development of key therapeutics for amyotrophic lateral sclerosis will continue, due to the high burden the disease imposes. **BrainStorm Cell Therapeutics’ NurOwn has shown extremely strong early results and this new Phase II trial will place the company on a firm footing to assess its effectiveness before moving onto Phase III.**

**BrainStorm Cell Therapeutics** has announced that it has entered into an agreement with Hadassha Medical Center in Jerusalem, Israel, to conduct planned Phase II trials into amyotrophic lateral sclerosis (ALS). The trial will test Brainstorm’s...
NurOwn based stem cell therapy as the company prepares to move into Phase III research. ALS represents a major unmet need in neurological therapy, however, has seen little success in later trials.

**Strong Evidence For NurOwn Success**

NurOwn is a proprietary technique practiced by BrainStorm, wherein the patient's own mesenchymal stem cells are extracted and modified to enhance the secretion of neurotrophic factors (NTF). These modified cells are then re-injected into the patient's spinal cord or muscle and secret NTF, promoting neuron health and survival. In October 2014 it was granted an orphan drug designation by the FDA for treatment of ALS. In total, 26 patients have so far been treated with NurOwn and, in a Phase II cohort consisting of 12 patients, 92% experienced a decrease in disease progression. While this was a strong result that gathered significant interest at the time, the limited cohort number greatly reduces the predictive power.

The new study is designed to provide guidance for an upcoming Phase III study in order to explore the safety and efficacy of a multi-dose treatment. A total of 24 patients will be recruited and will receive three consecutive stem cell transplantations in order to explore the safety and efficacy of a multi-dose treatment. Commencement of the trial is subject to approval by both Hadassah’s Helsinki Committee and the Israeli Ministry of Health.

**ALS Carries High Cost**

Treatment for ALS began in 1995 with the release of Riluzole (rilutek) by Sanofi, however, like many neurological disorders, the condition has proven extremely difficult to treat and Riluzole only prolongs patient survival by a few months. The disease has a two to five year survival time untreated. While development of improved treatments has attracted significant attention, the disease has not seen significant breakthrough in many years and care is mostly palliative.

This represents a large unmet need, as the disorder is one of the most common neuromuscular diseases worldwide, affecting two in every 100,000 people. In the US alone it is estimated that 5,600 people a year are diagnosed with ALS and approximately 30,000 Americans have the condition at any given time. As is true of a great many degenerative diseases, ALS is an extremely expensive condition, requiring extensive medical and social care at a cost estimated to be USD50,000 a year by the Muscular Dystrophy Association. There is large potential in a drug that slows progression, extending the patient’s life, or eases the symptoms, reducing the requirement for care.
J&J was found guilty by a number of US State Courts and settled with many others. The South Carolina case is notable for being an extremely large payment to a single state, though commensurate with an USD158mn settlement with the state of Texas in 2012, other states, like the state of Arkansas (which initially required a fine of USD1.2bn) settled out of court for million dollar sums. In 2013, J&J paid the Department of Justice USD2.2bn to resolve criminal and civil liability regarding promotion of drugs including Risperdal for purposes not approved by the FDA, on the proviso that J&J does not admit improper conduct. J&J has also settled with large number of patients who experienced gynecomastia as a result of Risperdal for emotional distress caused and these have tended to be multi-million sums.

**Legal Costs Continue To Rise**

The total cost of J&J's actions has yet to be calculated. At least USD2bn has been paid to states alone and the current total is in excess of USD5bn. With over 1,000 lawsuits concerning gynecomastia still pending, and settlements reaching USD2mn per case, a significant amount may still be lost due to settlements and legal fees. There remains an open a discussion as to whether the penalties imposed on J&J have been commensurate.

J&J had total revenue of USD74bn in FY14 and has shown a steady upward trend in its profit margin, despite these issues. The legal costs of its marketing decisions are significant when compared to revenues estimates from Risperdal. At almost one sixth of the drug's total revenues the total costs are considerable, and could be argued as out of proportion to the benefits provided by marketing off-label. These punitive measures are a strong sign that off-label marketing will not be tolerated in the US.

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**Tribute Granted Canadian Patent Allowance Expanding Cambia Use**

The Canadian Intellectual Property Office has issued a Notice of Allowance to **Tribute Pharmaceuticals Canada** for Canadian patent No. 2,632,375, entitled: ‘Diclofenac Formulations and Method of Use.’ This patent, which was developed by **Applied Pharma Research** (APR), is licensed exclusively to Tribute in Canada through a sublicense agreement with **Depomed**.

Depomed has the exclusive North American rights to **Cambia** (diclofenac potassium, oral solution) licensed with APR. The issuance of the new patent will expand Tribute's intellectual property protection for Cambia, currently indicated in Canada for the treatment of acute migraine in adults over 18 years of age. According to Tribute, this new patent extends its intellectual property rights to June 6 2026.

**Ipsen/Galderma Expand Dysport Distribution Deal**

**Ipsen** and **Galderma** have expanded the geographical scope of their neurotoxin partnership, with Galderma acquiring the exclusive rights to develop, promote and distribute **Dysport** (abobotulinumtoxinA) for aesthetic indications in Asia-Pacific territory.

Ipsen and Galderma initiated their partnership in 2007 for the commercialisation of **Azzalure** (botulinum toxin) in the aesthetic and dermatology indications in Europe, further extended for Dysport to Mexico, Brazil, Argentina and Australia. In 2014, the companies significantly strengthened their collaboration by prolonging their partnership until 2036, expanding the geographical coverage to the US and Canada, and by increasing the scope of their R&D collaboration.

Further to the distribution agreement, Ipsen and Galderma have extended their R&D collaboration. Ipsen is running a Phase III trial for Dysport in glabellar lines in China, for which a launch is expected beyond 2020. The clinical study will be funded by Galderma in exchange for the right to use the results of such study to support regulatory filing and commercialise the product in China. In addition, Ipsen acquires the intellectual property for Galderma's liquid toxin in Asia-Pacific territory.

**Dysport**, Ipsen's botulinum toxin type A, is a neuromuscular blocking toxin which acts to block acetylcholine release at motor nerve ends and reduces muscular spasm. It was initially developed for the treatment of movement disorders such as cervical dystonia, blepharospasm, haemifacial spasm and various forms of muscle spasticity, including post-stroke arm spasticity, spasticity of the lower limbs in adults and children with cerebral palsy. The product is currently referred to as **Dysport** for medical and aesthetic markets and as **Azzalure** for aesthetic indications in the EU.

**BioQ And Cipla Enter Ropivacaine Agreement**

San Francisco, CA-based **BioQ Pharma** and **Cipla** have entered into a strategic distribution, supply and development agreement for the registration and commercialisation of BioQ's ropivacaine infusion in India. BioQ commented that it was excited to expand its worldwide commercial footprint into India.

BioQ's unit-dose infusion pharmaceuticals have been developed as ready-to-use presentations in which the drugs and administration systems are self-contained and delivered at the point of care. The ropivacaine infusion system is pre-filled, ready to use at the point of care, and intended to provide a safer, more efficient continuous-infusion post-operative pain solution.
AcelRx Plans Additional Zalviso Phase III Trial

AcelRx Pharmaceuticals has received comments from the Division of Anesthesia, Analgesia, and Addiction Products of the FDA on the company’s proposed protocol for a Phase III study (IAP312) designed to assess the overall performance of Zalviso (sufentanil sublingual tablet system). In response to the comments, the protocol has been amended and AcelRx plans to initiate the study in Q116.

The IAP312 study will include approximately 310 postoperative patients and collect information requested by the division to supplement the three positive Phase III trials already completed. Zalviso is being developed for the management of moderate-to-severe acute pain in adult patients in the hospital setting. Zalviso delivers 15mcg sufentanil sublingually through a non-invasive delivery route via a pre-programmed, patient-controlled analgesia device.

In response to the NDA AcelRx submitted to the FDA seeking approval for Zalviso, the company received a complete response letter on July 25 2014. The NDA resubmission will include, in addition to the results of bench testing and human factors studies conducted with the modified Zalviso design, the results from the IAP312 study. Prior Phase III trials include two placebo-controlled Phase III studies (IAP310 and IAP311) in which Zalviso demonstrated superiority over placebo in the management of moderate-to-severe acute postoperative pain. In IAP309, an active-controlled Phase III study, Zalviso was statistically significantly superior in comparison with intravenous PCA morphine. The most common adverse events experienced by patients using Zalviso were nausea, pyrexia and vomiting.

Positive PDAC Opinion Puts Probuphine On Track For FDA Approval

BMI View: A positive opinion from the FDA’s PDAC is a strong sign that Titan and Braeburn Pharmaceuticals’ Probuphine is on track for FDA approval. Despite a previous rejection, demonstrated non-inferiority and a narrowed indication will ease concerns over Probuphine’s application. The therapy, however, has failed to prove itself superior to sublingual alternatives and raises questions as to the extent of uptake it will see.

The FDA’s Psychopharmacologic Drugs Advisory Committee (PDAC) has voted in favor of approving Titan Pharmaceuticals’ and partner Braeburn Pharmaceuticals’ Probuphine (buprenorphine) 12 to five after discussion of Probuphine’s efficacy, safety and risk-benefit profile. Probuphine is under consideration for the second time by the FDA, after it was initially rejected in April 2013 and has an Agency action target date of February 27 2016. Probuphine, if approved, would represent the longest acting therapy for treatment of opioid addiction, allowing patients to be continually medicated for up to six months.

Opioid Epidemic Underscores Probuphine’s Appeal

The Probuphine system is a subdermal implant that is designed to maintain a continuous level of buprenorphine in the patient for as much as six months. The therapy is intended for those recovering from addiction to opioids, both prescription and illicit, and intended for those already on a maintenance therapy of buprenorphine of 8mg a day or less. The indication was narrowed significantly for the most recent FDA NDA due to issues in the original study requiring rescue doses of sublingual buprenorphine as a rescue drug. While the narrower indication will limit the potential of Probuphine, the positive recommendation speaks well of the efficacy of the drug, and its proven non-inferiority to competitors in trials.

Probuphine utilises Titan’s ProNeura delivery system, small non-bio-degradable rods (26mm x 2.5mm) infused with buprenorphine hydrochloride that are implanted beneath the skin. The system provides protection against withdrawal effects and deadens the highs of opiates if they are taken. Probuphine, unlike classical capsule based therapies, avoids the peaks and troughs of a daily regimen and the patients’ lack of access to self medication drastically cuts the chance of an incorrect dosage.

US Opioid Abuse Burden Soaring

Opioid addiction is becoming an increasing burden to the US healthcare system. In 2014 alone 28,647 died in the US due to opioid overdose and it estimated that more than 2mn people are currently abusing or dependent on opioid-based drugs. The highly addictive nature of these drugs and the tendency for patients seeking to overcome addiction to fall back into old habits makes extended release and depot formulations such as Probuphine highly attractive. Probuphine’s long-period infusion is a critical distinguishing point in a market that is rapidly gaining competitors and it compares well against other depot techniques, which tend to only be effective for just a few months.

Efficacy Questions Still To Be Answered

The development of Probuphine has not been a simple process and it has already seen one FDA rejection in 2013 over concerns that rescue buprenorphine was required by some patients.
The FDA required an additional study, which was completed in June 2015 and demonstrated statistical superiority of a 96.4% response rate versus 87.6% for sublingual buprenorphine. This statistic was, however, questioned by the FDA’s PDAC whose own statistical review found the response rate to be a far lower 69% versus 64%. While this still showed some level of superiority, it was not a statistical demonstration of superiority and instead Probuphine proved itself non-inferior to sublingual methods.

Overall, while the FDA PDAC advice was positive, issues were highlighted that could negatively affect the chances of approval. Members of the advisory panel directly raised concerns that the implantable device may produce more harm than benefit and that data was missing from the submitted study. For Probuphine, the key point to demonstrate was that the invasive therapy was a benefit to the patient, despite the additional risks, but the evidence as provided was not able to do so. If approved, doctors would have to use their own judgement as to whether the potential benefits of Probuphine out way the risks compared to current medication.

Probuphine To Find Extended Release Niche

At this stage, FDA approval seems likely for Probuphine. If successful, Probuphine will be entering the market of buprenorphine-based opioid addiction drugs which has been estimated to be worth USD1.75bn in 2014. Distinguishing itself will prove difficult, buprenorphine has been available in other forms for many years and the narrow indication greatly reduces the patient pool available. The large demand for opioid abuse drugs, brought about by the worsening opioid epidemic, suggests however that it will find a niche in the market.

Drugs used in Nausea & Vertigo

Positive Results Raise Acacia IPO Potential

**BMI View:** Strong trial results indicate a viable niche for Acacia Pharma’s lead product candidate, Baremsis in the control of PONV. The company delayed an IPO in October 2015 but with these results, Acacia can pursue investment with high confidence of eventual approval. The PONV sector is significant and Baremsis has the potential to replace established therapeutics with a reduced side-effect profile.

Acacia Pharma has announced positive results from a second pivotal Phase III study of APD421 in the prevention of post-operative nausea and vomiting (PONV). The trial represents a pivotal step for Acacia, confirming the results of an earlier Phase III trial and showing that the company has a strong potential drug candidate as their first commercial drug. Acacia delayed an initial public offering (IPO) in October of 2015 due to market uncertainty and these results will greatly increase the company’s IPO potential.

**Strong Results Confirm Potential**

Acacia’s lead candidate, Baremsis (amisulpride injection), formerly referred to as APD421, was studied in one of the largest PONV studies ever undertaken. Conducted at multiple sites in Europe and the US, the trial evaluated 1,147 patients with three or four risk factors for PONV (the "Apfel risk factors"). The Phase III combination trial compared the prophylactic use of Baremsis plus a standard antiemetic (ondansetron or dexamethasone) against placebo plus a standard antiemetic. The primary endpoint was complete response, defined as no vomiting or retching, and no requirement for antiemetic rescue medication in the first 24 hours after surgery.

The study showed statistically significant improvement in comparison (57.7% to 46.6%). In addition, all secondary efficacy endpoints, including the rate of vomiting, nausea and use of rescue medication, were also met. No toxicities were seen and the profile of adverse events was as good as placebo.

Overall, a 22% risk reduction over traditional therapy modes was observed and this represents a very strong potential offering for the suppression of PONV. It mirrors the results of monotherapy trials and represents an opportunity for Acacia to carve out a niche in the PONV sector.

**PONV Management Has Room For Improvement**

PONV is a common side-effect of surgery and can effect between 10%-30% of patients depending on a number of factors including patient risk factors, surgical techniques and the use of anaesthetics. With more than 100mn patients undergoing surgery a year worldwide the management of post-operative symptoms is critical to speed recovery, prevent complications and lower overall healthcare costs. PONV drugs have an uncommon profile of strong additive effects and Baremsis has now been shown to contribute positively to the standard combinations of therapeutics. Additionally, some of the stronger antiemetics, such as droperidol, can have severe side effects and Baremsis may be able to find a niche as a lower risk alternative.

**Solid Candidate Raises Hopes Of Financing**

Acacia is a late-stage pharmaceutical development company with a modest pipeline focused on the control of vomiting, post-operatively and in cancer therapy, and cancer-related therapeutics. The company has no approved products at this time and is currently operating privately after an IPO announced in September 2015 was delayed due to market volatility. The IPO was estimated to be valued at GBP150mn (USD220mn), which would have represented a highpoint on the trend of life-sciences IPOs in recent years. Acacia announced the delay of the IPO on October 16 as the pharmaceutical industry came under increasing scrutiny due to concerns over drug pricing.

The successful trial is a strong sign for Acacia and raises the question of when an IPO will be considered again. While it has
been made clear by the delay that Acacia's existing investors have the resources to pursue an independent strategy in the short-term, the company is entering the registration and distribution phase of development. An IPO after the results of the Phase III Baremsis trial is significantly more likely. There no seems little doubt that Acacia will receive approval given the results and safety profile, though there may be concerns over its ability to break into the established market. Acacia have announced plans to submit and NDA for Baremsis in H216.

General Development News

Serious Side-Effects In Bial Trial Will Raise Development Scrutiny

**BMI View:** The results of the BIA 10-2474 trial will see a huge investigation as the companies involved and independent authorities attempt to assess what went wrong and whether it could have been prevented. The severe side-effects seen will cast doubt on the safety of the entire class of fatty acid amide hydrolase inhibitor therapeutics, raise doubts over the safety of current procedures and will make recruitment for EU trials more difficult in the short term.

A Phase I trial in France has lead to one death and five cases of hospitalisation in the trial participants. The event is by far the most serious case of a trial failure on European soil in the last ten years and will raise many questions as to culpability, the safety of drug testing and potential dangers of the drug candidate. The trial was run by Biotrial, a clinical research organisation with decades of experience running clinical trials, and was performed on behalf of Bial. Three separate investigations have begun to discover what went wrong during the trial.

**Full Investigation Due After Major Side-Effects**

The drug candidate under investigation was BIA 10-2474, a fatty acid amide hydrolase (FAAH) inhibitor, which had potential links to pain, mood and coordination diseases via the endocannabinoid system. BIA 10-2474 in particular was being investigated for the effect on pain relief, of which there is currently a very large demand due to the dangerously addictive profile of opioid based drugs. The trial recruited 128 healthy volunteers, men and women aged between 18-55, and tested a range of doses of BIA 10-2474 in accordance with standard practice, beginning with low doses. In the final highest dose stage of the trial, six male volunteers received the compound simultaneously and all but one became critically ill.

Due to the extremely serious nature of this result, the trial has been suspended and a full investigation is underway. At this point it is unclear what went wrong with the trial and, while no evidence has so far arisen to suggest that errors or contamination were responsible, all aspects of the trial will be under extreme scrutiny. If misconduct is found, it will be extremely damaging for Biotrial and would have large implications for drug trials across France and Europe. The media attention on trial risks will drive down applications in the immediate future and as such, the appeal of European drug trials will be reduced in the short term and remuneration costs may have to be increased to attract sufficient participants.

Careful investigation will be required to assess just why the trial went as badly wrong as it did and whether there is any potential for the molecule. Phase I trials frequently treat at significantly higher doses than are necessary for therapeutic effect and if the problem was dosage related, which seems likely given only the highest dose group experienced significant side effects, the molecule may still have medical applications.

**FAAH Inhibitors Will See High Levels Of Scrutiny**

Bial has a CNS focus and a single product available, marketed for epilepsy. Its pipeline addresses epilepsy, Parkinson's, pulmonary arterial hypertension and features a number of other candidates without a specific development goal. BIA 10-2474 was under investigation for neurological pathologies and acts as a FAAH inhibitor, where it was predicted to produce similar activation on the cannabinoid receptors without the psychoactive effects. The results of the BIA 10-2474 study may represent an expensive loss of a promising candidate, but whether this is damaging to the company's long-term prospects, will depend heavily on the final conclusions as to what went wrong.

FAAH-targeting drugs have seen increased interest as novel candidates to address pain and other neurological conditions, and a number of large pharmaceuticals have similar candidate molecules under investigation. These include: Johnson & Johnson's JNJ-42165279; Merck & Co's MK-4409; Vernalis' V158866 and Kadmus Pharmaceuticals' KDS-4103. Both Pfizer and Eli Lilly also had FAAH drug candidates, but these were discontinued for being ineffective at controlling osteoarthritis and having low specificity respectively. All of these drugs will be under additional scrutiny after the BIA 10-2474 trial failure despite no evidence of serious side effects in published research.

**Avoiding Future Failures**

The outcomes of the BIA 10-2474 study are unlikely to have a large effect on the drug trial industry as a whole. One point to highlight, however, is the simultaneous dosage of all six men in the trial, which was linked to similar disastrous results in a trial in 2006, assessing injections of TGN1412, which caused multiple organ failure in six participants. At the time, it was strongly recommended that dosing patients should be done sequentially, reducing the odds of the whole cohort succumbing to the same side effect. Sequential dosing is not currently required by international practice guidelines, but this will see renewed interest in light of recent events.
**Corporate Activity**

**Lilly Stabilising After Patent Slump**

*BMI View*: Eli Lilly’s revenue will stabilise after the severe downturn in 2014 due to generic competition, however, growth will be slow. The company has seen large reductions in its core CNS sector revenues and there is little to suggest that a blockbuster drug will revitalise this, barring a surprise breakthrough in Alzheimer’s disease. The company has begun a shift away from CNS medication, giving Eli Lilly a broad base on which to build future growth.

Eli Lilly has announced its estimated revenue for FY2016 will be between USD20.2bn and USD20.7bn, a reduction over industry consensus which anticipated revenues to be USD21bn or more. Despite this news, Eli Lilly’s stock price rose after the announcement from USD82.87 on January 4 to USD84.11 on January 5. The company is showing signs of recovery after the loss of patent protection for a number of key products between January 5. The company is showing signs of recovery after the loss of patent protection for a number of key products between 2010 and 2014.

**Sales Stabilising After Severe Headwinds**

In 2014, Eli Lilly saw its sales drop precipitously, with total revenues falling from USD23.1bn in 2013 to USD19.6bn in 2014. This fall was the result of a number of factors, but a large portion of these lost revenues were due to the loss of patent protection on leading attention deficit hyperactivity disorder (ADHD) medication, Cymbalta ( duloxetine), which fell from a peak of USD5bn in sales in 2013 to USD1.6bn in 2014; this declining trend of Cymbalta sales is anticipated to continue. While this drop was considerable, Eli Lilly’s sales have survived the loss of patent protection and are now showing signs of recovery. FY2015 sales are anticipated to rise to USD19.9bn, approximately 1.5% growth overall, although, this is closer to stabilisation rather than a full recovery. The FY2016 sales prediction was that this growth rate would be at least met and most likely exceeded, which would be a far stronger signal of new sustained growth.

**Slow Recovery Predicted For Eli Lilly**

Eli Lilly Revenue By Subsector (USDmn)

Lilly’s recovery can be put down to growth in established medicines, such as: Humalog (insulin lispro) for diabetes, Cialis (tadalafil) for erectile dysfunction, or Forteo (teriparatide) for osteoporosis. A growing portfolio specialising in endocrinology, oncology and cardiovascular health has allowed Lilly to buffer the losses in its CNS portfolio. Eli Lilly downgraded the rate of growth expected from industry estimates of approximately USD21bn in FY16 for a number of reasons, including the threat of generic Alimta (pemetrexed) in Europe and the strong US dollar hurting export profits.

**CNS Falloff Shifts Focus Of Development**

Prior to 2014, Eli Lilly’s predominant source of revenue growth was located in CNS medication, but this came under fire twice in recent years. Generic competition for both Cymbalta in 2014 and Zyprexa (olanzapine) in 2012 slashed revenues from the sector, falling from a peak of USD9.7bn in FY11 to USD3.6bn FY14 and it is questionable as to how relevant CNS medication will become to Lilly’s core business as the company attempts to recover from the patent slump.

In 2015, Eli Lilly announced another failure of a Phase III trial of solanezumab, investigating Alzheimer’s disease (AD) in patients with a mild form of the condition. Solanezumab had failed in two additional Phase III trials for reducing disease progression in general AD patients prior to this announcement and so expectations were not high. While investigation is still ongoing, this is more indicative of the attractiveness of a viable AD therapy, rather than the efficacy of solanezumab, as AD could represent a mega-blockbuster. Eli Lilly is also currently in collaboration with AstraZeneca investigating a Phase II/III AD therapy, AZD3293/LY3314814.

The reduction of research into CNS medication is somewhat surprising given Lilly’s long focus on disorders of the central nervous system. Previously, Lilly’s blockbuster CNS drugs addressed the symptoms of ADHD or schizophrenia, but beyond AD-related drugs, there seems little in Lilly’s immediate pipeline to suggest a potential blockbuster in this area. The two therapeutics other than solanezumab currently in Phase III development are: LY2951742 for the treatment of cluster headaches and tanezumab for a number of pain indications. While these may have strong niches, they lack the blockbuster potential of AD medication.

Compared to Eli Lilly’s full pipeline, CNS still represents a healthy proportion of drugs under development, but is clearly no longer the only focus of the company. The earnings projections suggest that this diversification strategy is working, with Eli Lilly predicting a steady recovery from the FY14 slump. The addition of other key areas of speciality will provide access to new markets and a greater level of security against failures in any one area.

**Source**: Bloomberg
Shire To Combine With Baxalta

The Boards of Directors of Shire and Baxalta have reached an agreement under which Shire will combine with Baxalta. Under the agreement, Baxalta shareholders will receive USD18 in cash and 0.1482 Shire ADS per Baxalta share. The value of the offer, as of Shire’s January 8 2016 closing ADS price, represents a premium of approximately 37.5% to Baxalta’s unaffected share price on August 3 2015, the day prior to the public announcement of Shire’s initial offer for Baxalta. This will provide Baxalta shareholders with approximately 34% ownership in the combined company. The parties expect the transaction to close mid-2016.

The combination of Baxalta and Shire will create the number one rare diseases platform in revenue and pipeline depth, with best-in-class products in the following franchises: haematology; immunology; neuroscience; lysosomal storage diseases; gastrointestinal/endocrine; and hereditary angioedema. The combined portfolio will have an expanded range of therapeutic areas with more than 60 programmes in development, including over 50 that will address rare diseases and the newly-approved Baxalta products Adynovate (antihemophilic factor [recombinant]), Vonvendi (von willebrand factor [recombinant]) and Obizur (antihemophilic factor [recombinant [porcine sequence]]). Shire anticipates more than 30 recent and planned product launches from the combined pipeline, contributing approximately USD6bn in annual revenues by 2020.

Shire anticipates that it will realise more than USD500mn in annual cost synergies. Further, Shire expects to generate additional revenue synergies and a combined non-GAAP effective tax rate of 16-17% by 2017. Growth is expected to be accelerated by combining capabilities and establishing a global infrastructure that will include a 'best of both' commercial model and a presence in over 100 global markets.

The transaction is expected to be accretive to non-GAAP diluted EPS in 2017, the first calendar year of ownership, and beyond. The combined company is expected to generate annual operating cash flow of USD6bn beginning in 2018, underpinning an attractive ROIC that will exceed Shire’s cost of capital in 2020. Shire has secured an USD18bn fully written bank facility to finance the combination.

Collaboration Key To Arena And BI's Neuroscience Research

BMI View: Boehringer Ingelheim and Arena’s collaboration is indicative of the high demand for novel neurological drugs due to an increasing burden of disease. The deal will go a long way to support Arena’s development of new compounds after its debut product, Belviq, disappointed. It also marks a shift towards a more open research model from Boehringer Ingelheim, as it attempts to overcome a loss of revenues.

Boehringer Ingelheim has announced it has signed an exclusive agreement with Arena Pharmaceuticals to conduct joint research into identifying drug candidates. The candidates will target ‘orphan’ G protein-coupled receptors (GPCR) with strong ties to CNS disorders. The companies will jointly conduct research to identify additional drug candidates that are suitable for continued research and development as therapeutic compounds for various disease indications.

Agreement To Explore Novel Targets

Under the terms of the agreement Arena will provide Boehringer Ingelheim exclusive rights to its internally discovered novel compounds and intellectual property for a specific orphan CNS receptor. BI will receive exclusive worldwide rights to develop, manufacture and commercialise products resulting from the collaboration. GPCR therapies represent a new angle for treatment of neurological disease, potentially allowing regulation of cell processes and signalling that has not previously been accessible. These systems may provide novel therapeutics for the treatment of conditions such as Alzheimer’s disease, schizophrenia, and depression.

Arena is eligible to receive payments up to USD262mn in milestones in the case of full commercial success of multiple drug products, including an upfront payment and research funding. In addition, Arena is eligible to receive tiered royalties on future sales of products that arise from the collaboration. Further details of the agreement were not disclosed.

Neurological disease is a growing concern for public health, brought about by an aging population and a better understanding of mental health. The World Health Organization estimates that mental health disorders affect approximately 450mn people worldwide and this poses a high economic burden. GPCR therapeutics are a hot topic in research; Pfizer reached a similar deal with Heptares Therapeutics in December 2015.

Arena Recovering From Belviq Slump

With a GPCR speciality Arena is a drug discovery and development company with a strong focus on neurological disorders and treatment of conditions through receptor coupled agonists. The company has a single commercialised product, Belviq (lorcaserin), which is indicated for weight loss and was produced in collaboration with Eisai. While obesity is a serious threat to public health and has a large potential market - USD60bn is spent on weight loss techniques in the US yearly - Belviq has seen poor uptake. As a weight loss drug it has low efficacy and has failed to penetrate a market flooded with lifestyle alternatives. As such, Arena has seen a large fall in its stock price over the course of 2015 and the announcement of the agreement with BI has produced only a modest rise.
The deal between Johnson & Johnson and DiamiR BMI View: Precision Medicine Focus To Increase CNS Pipeline

wider range of therapeutic candidates. The protectionism seen in the industry traditionally, more open agreement. While this model of research and development due to trial failures, investment is curtailed as by the original agreement. Under the agreement, DiamiR receives research funding based on upfront and specified milestone payments and Janssen has an option to negotiate a license to a companion diagnostic test to be used with certain Janssen proprietary therapeutic products. Financial terms of the collaboration were not disclosed.

J&J's neurology pipeline focuses on pain and psychiatric disorders, and neurodegenerative diseases appear to be lacking from the late-stage. DiamiR has developed a proprietary targeted approach for early detection and monitoring of neurodegenerative diseases based on quantitative analysis of brain-enriched microRNA pairs in plasma. In this collaboration, DiamiR and Janssen Neuroscience teams will jointly investigate how DiamiR technology can be used in the context of clinical development of a therapeutic agent for treatment of neurodegenerative disease indications. If J&J can successfully develop a therapeutic agent from this agreement, it will be placed on trajectory to target a lucrative segment of the pharmaceutical market.

Neurodegenerative Disease Represents High Burden

As populations age, neurodegenerative diseases are becoming increasingly prevalent. Conditions such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) are expected to rise by between 30-50% by 2030. Ageing populations are the greatest contributing factor to the rise in neurodegenerative conditions. The number of people over the age of 60 in the world is expected to triple to 22% of the population in 2050, compared to 8% in 1950.

The financial burden of this class of disease is also high. In the US alone, the direct costs of Alzheimer's disease are estimated to be USD200bn annually, and across the world, 1% of global GDP is consumed by the impact of dementia. Alzheimer's disease and other dementias are the greatest burden, with disability adjusted life years (DALYs) lost in 2015 totalling 2.3mn according to BMI, and this is expected to increase to 2.9mn by 2025.
The high burden highlights the potential for any successful drug to become a mega blockbuster. Furthermore, the likelihood that future treatments will require a companion diagnostic will reduce the cost of unnecessary or ineffective treatments.

High Failure Rates Drive High Development Costs

A study examined Clinicaltrials.gov and found that during the 2002-2012 observation period, 413 AD trials were performed: 124 Phase I trials, 206 Phase II trials, and 83 Phase III trials. A very high attrition rate was found, with an overall success rate during the 2002-2012 period of 0.4% (99.6% failure)\(^1\). Compared with other therapy areas, such as oncology, the Clinicaltrials.gov database demonstrates that relatively few clinical trials are undertaken for Alzheimer’s disease therapeutics. This is despite the high burden of the disease. The success rate for advancing from one phase to another is low, and the number of compounds progressing to regulatory review is among the lowest found in any therapeutic area.

According to the National Institute of Health’s ‘2014-2015 Alzheimer’s Disease Progress Report: Advancing Research Toward a Cure’, the process of discovering and developing drugs for neurodegenerative disorders is extremely expensive and time-consuming. It takes 10-15 years from the discovery of a new therapeutic target until a new drug reaches the market, with an average cost of about USD1.8bn. Of note, cancer drugs have a much faster development rate since the widespread use of precision method. AstraZeneca’s Tagrisso (osimertinib) reached the market 2.5 years after entering clinical trials. While this does not include preclinical development time, it does highlight the effect of development in combination with a companion diagnostic.

A lengthy list of costly clinical trial failures exists in Alzheimer’s; Eli Lilly, Roche, J&J and Pfizer have all experienced disappointment in this area. Despite the lack of success, Alzheimer’s will remain a large focus for these companies.

Targeted Medicine May Ensure Success

Any drug that can successfully treat a neurodegenerative disorder, and not just treat symptoms, has the potential to be a mega blockbuster. This has kept interest in the field high despite many failures. Genomic data has piqued the interest of many pharmaceutical companies, with the potential to unveil therapeutic targets. The large datasets being gathered from genomic analyses, partly coming from direct-to-consumer tests, yield an opportunity to develop further insights into the underlying disease drivers of neurodegenerative conditions. This data will enable developers to identify treatment targets, and enhance the ability to treat an underserved patient population. Partnerships to secure human genome data to enhance drug development capabilities have become increasingly common. Roche has been at the forefront of this with numerous deals.

Investment in the CNS genomic data field could create a boom in new neurology drugs. Companies that gather data from genomic tests will provide an abundance of research material that will enable unprecedented insight into the underlying mechanisms of disease. With the high number of genomic data and biomarker deals occurring in the neurological field, targeted treatments for Alzheimer’s disease will enter pipelines in the mid-term.

April

2-3

23rd Annual Anaesthesia Symposium & Colorado Society Of Anaesthesiologists Annual Meeting, Colorado Springs, CO, USA

Contact: CSA

Tel: 1-303-770-6048 Fax: 1-303-771-2550 Email: info@csa-online.org

15-17

American Society of International Pain Physicians, Dallas, TX, USA

Contact: ASIPP

Tel: 1-270-554-9412 Fax: 1-270-554-5394 Email: asipp@asipp.org

15-21

2016 American Academy of Neurology (Annual Meeting), Vancouver, Canada

Contact: Member Services, AAN

Tel: 1-612-928-6000 Fax: 1-612-454-2746 Email: memberservices@aan.com

20-23

7th World Anaesthesia Convention, New York, NY, USA

Contact: NWAC

Tel: 44-14-6248-3466 Email: registration@nwac.org

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