EDISON

Biotie Therapies

In pivotal territory

Start of Phase III trial and H115 results

Pharma & biotech

H115 saw Biotie successfully complete an equity raise through the issue of convertible notes (€33m) and a US IPO (€50m), with net proceeds of €74.3m. The funds raised enabled the start of the pivotal Phase III study, TOZ-PD, for lead product candidate tozadenant in Parkinson's disease (PD). Biotie continues to receive a steady stream of royalties from Selincro, a novel treatment concept for alcohol dependence, which is partnered with Lundbeck across Europe. Two other products, SYN120 and BTT1023, are in Phase II trials. We value Biotie at €268m, or €0.27/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/13	27.7	3.7	0.01	0.0	22.4	N/A
12/14	14.9	(7.6)	(0.02)	0.0	N/A	N/A
12/15e	3.8	(32.6)	(0.05)	0.0	N/A	N/A
12/16e	6.4	(30.2)	(0.03)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items.

Tozadenant advances to Phase III

The start of the Phase III study of tozadenant in PD patients marked a significant milestone. The Special Protocol Assessment-agreed pivotal study, TOZ-PD, is divided into two phases: a 24-week placebo-controlled phase (n=450), followed by a 52-week open-label phase. Should the primary endpoint be met in the placebo-controlled phase, a second 52-week open-label study will be performed (n=450) to generate the requisite number of patient exposures for approval. TOZ-PD, along with the completed Phase IIb study, would form the basis of an NDA submission.

Funded through to key data readout

The financing in H115 secured sufficient funds to advance tozadenant into Phase III. Importantly, Biotie should now have a sufficient cash runway through to the next major milestone: the top-line data read-out from the initial phase of the TOZ-PD study, expected by end-2017. While we forecast additional funds will be required to complete the study, these data will inform further clinical and therefore financing requirements, with positive data providing a strong partnership negotiating position.

Pipeline offers nearer-term value inflection points

Biotie has two other product candidates in grant-funded proof-of-concept Phase IIa studies. Data from the SYNAPSE study investigating SYN120 for the treatment of Parkinson's disease dementia is due in H216. In Q115, recruitment began for the BUTEO study of BTT1023 for the treatment of primary sclerosing cholangitis; a pre-planned interim analysis is expected by end-2016.

Valuation: Risk-adjusted NPV of €268m

We value Biotie at €268m, or €0.27 per share, based on a risk-adjusted NPV of its key products – Selincro, tozadenant and SYN120 – and €94m gross cash at end-H115. Our model suggests Biotie should have sufficient cash to fund operations to at least end-2017, when initial data from the pivotal tozadenant study are expected.

1 September 2015

Price	**€0.19**
Market cap	**€186m**
Gross cash (€m) at 30 June 2015	94.2
Shares in issue	980.9m
Free float	91.4%
Code	BTH1V (OMX) BITI (NASDAQ)
Primary exchange	OMX, Helsinki
Secondary exchange	NASDAQ GM

Share price performance

%	1m	3m	12m
Abs	(8.7)	11.2	(6.0)
Rel (local)	(0.6)	20.6	(9.6)
52-week high/low		€0.26	€0.14

Business description

Biotie Therapies is a Finnish/US biotech company focused on CNS disorders. Selincro for alcohol dependence is partnered with Lundbeck and launched in Europe. Parkinson's therapy tozadenant has entered Phase III; two other programmes are in Phase II studies.

Next events

Q315 results	12 Nov 2015
Istradefylline (Kyowa Hakko Kirin) Phase III results (read across to tozadenant)	End-2015/ early-2016
SYN120: top-line data from Phase IIa study	H216
BTT1023: interim analysis of Phase IIa study	H216

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Edison profile page

Investment summary

Company description: CNS specialist

Biotie Therapies is a Finland-headquartered biotech firm with a focus on neurodegenerative and psychiatric CNS disorders. It was founded in 1992, listed in 2000 (now also on NASDAQ-OMX), and has 38 employees based mainly in Turku, Finland, and South San Francisco, US. Biotie has a strategic partnership with Lundbeck (which holds a c 2% stake) for the commercialisation of Selincro in Europe for alcohol dependency; Biotie receives milestones and royalties. The February 2011 purchase of Synosia for c €94m (all-share transaction) brought in tozadenant (Parkinson's disease) and SYN120 (PD dementia). A third product candidate, BTT1023 is in development for primary sclerosing cholangitis. In H115 Biotie underwent a refinancing, including a US IPO, to raise the funds required to progress tozadenant through to Phase III.

Valuation: €268m, or €0.27 per share

We value Biotie at €268m, or €0.27per share, based on a risk-adjusted NPV of its key products (Selincro, tozadenant and SYN120) and end-H115 gross cash of €94m, using a standard 12.5% cost of capital. We use the gross cash figure, excluding Biotie's long-term financial liabilities of €20.7m (and related interest), which mostly relate to loans from Tekes that are largely repayable only on sustainable profitability. We exclude BTT1023 from our valuation model, offering upside potential on positive clinical development.

We view the dilutive effects of the H115 refinancing as being offset by the greater economic return that could be generated if the tozadenant TOZ-PD Phase III study is successful. We assume Biotie will partner tozadenant following the top-line data readout from the placebo-controlled phase of the TOZ-PD study (end-2017). We assume a 25% royalty rate; we do not include potential upfronts or milestones. However, Biotie may decide to commercialise tozadenant alone; this may provide upside to our valuation. We maintain peak sales of $650m and a 65% probability of success. We estimate TOZ-PD data in 2018, with regulatory (EU/US) approvals, and initial launches, in 2020.

Sensitivities: Clinical execution risk

The key stock-specific sensitivities are connected to Lundbeck's success in commercialising Selincro in Europe and the outcome of the tozadenant pivotal study, TOZ-PD. As Selincro is a new treatment concept, our estimates could be significantly higher or lower depending on the extent to which the drug is adopted by European healthcare agencies; initial uptake is expected to be modest for a few years. The clinical risk profile for tozadenant is increased now that Biotie is conducting the TOZ-PD study alone. However, if the study is successful and regulatory approvals and commercial partnerships secured, Biotie stands to extract greater economic return from tozadenant.

Financials: Funded through to next key milestone

Gross cash at end H115 was €94m, which includes the €74m net proceeds raised from the total effective sale of 525m new shares: 220m from the convertible notes (€0.15/share) and 305m from the US IPO (€0.165/share; each ADS was priced at $14.9 with a ratio of 80:1). Our model suggests that current cash is sufficient to fund operations until at least the end of 2017. Importantly, this provides funds to complete the first phase of the TOZ-PD study (by end-2017), which will inform further clinical, and therefore financing, requirements. We have included €10m of illustrative financing in 2018 (nominally attributed to debt), though this may be reduced or removed by increased Selincro revenues or reduced R&D spend, depending on the timelines for the tozadenant trials. Forecast FY15 revenues of €3.8m mainly consist of royalties from Selincro sales, and the first commercial milestone of €0.5m received in Q215. Net loss in H115 of €14.9m (vs €7.6m in H114) is primarily due to increased R&D expenditure in support of the TOZ-PD study, in line with company guidance.

Outlook: Tozadenant enters pivotal territory

Tozadenant remains the focus, and key valuation driver, for Biotie. The start of the pivotal Phase III study in July 2015 marked a significant milestone for the company, having decided to conduct the study alone following UCB's decision to return rights to the compound in March 2014. Although this required additional finance to be raised, this could offer greater upside in the long run through an improved negotiating position with a Phase III asset. Biotie also benefits from receiving milestones and royalties from Lundbeck on Selincro's EU commercial roll-out. In addition, two other pipeline products, SYN120 and BTT1023, are currently in grant-funded proof-of-concept Phase IIa studies, with data due in 2016.

Biotie's product portfolio and anticipated key milestones are summarised in Exhibit 1.

Exhibit 1: Biotie's product portfolio

Product	Mechanism	Indication	Status	Partner	Next milestones	Notes
Selincro (nalmefene)	Opioid receptor antagonist	Alcohol dependence	Marketed (EU)	Lundbeck (EU; sub-licensed to Ostuka in Japan)	Ongoing commercial roll-out in EU	Biotie receives tiered, double-digit royalties (10-17%) and milestones (€22.5m of possible €94m received to date) from Lundbeck (H115 sales DKK 50m (€6.7m).
Tozadenant (SYN115)	Selective A2a antagonist	Parkinson's disease	Phase III	N/A	Top-line data from placebo-controlled phase of PIII study (end-2017)	Development for mild-to-mod PD patients experiencing motor fluctuations on levodopa. Pivotal PIII trial (TOZ-PD) commenced in July 2015 under SPA with the FDA. Positive Phase IIb (n=420) study regarded as pivotal. Compound licensed by Synosia from Roche in 2007.
SYN120	5-HT6/ 5HT2a dual antagonist	Parkinson's disease dementia	Phase IIa	The Michael J Fox Foundation ($2m grant)	Top-line data from PIIa study (H216)	MJFF $2m grant for 80-patient, placebo-controlled, 16-week treatment Phase IIa SYNAPSE study. Commenced December 2014. 20-40% of PD patients suffer dementia. Compound licensed by Synosia from Roche in 2009.
BTT1023	Anti-VAP-1 MAb	Primary sclerosing cholangitis	Phase IIa	National Institute for Health Research (NIHR)	Interim analysis of PIIa study (H216)	41-pt Phase IIa BUTEO study co-funded by €1m NIHR grant. Began in March 2015. Development now focused on niche liver inflammatory fibrotic diseases.

Source: Biotie reports, Edison Investment Research

Sufficient funds raised for initiation of pivotal study

To secure the funding required to advance tozadenant alone, Biotie underwent a convertible notes and warrants issue to certain US investors and certain existing shareholders, as well as a US IPO on the NASDAQ exchange in June 2015. Biotie raised €33m (gross) from the issue of 220m convertible notes (conversion price of €0.15 per share). This attracted a number of blue-chip US investors, including a number of specialist healthcare funds. 220m warrants were issued free of charge to the subscribers of the convertible notes. Each entitles its holder to subscribe for one new or treasury share at €0.17/share and may be exercised for a period of five years after their issue. The US IPO raised gross proceeds of c €50m (fixed ECB exchange rate) through the issue of 305m new shares at €0.165 per new share. Following the completion of the US IPO, the automatic conversion of the convertible notes was effected.

The net proceeds of €74m are slightly less than we had initially estimated when the financing was announced (€85m), and also less than the total potential raise of €95m (gross). However, these funds should still provide sufficient cash runway through to the next major milestone: the top-line data readout from the initial phase of the TOZ-PD study (by end-2017). This will inform further clinical, and therefore financing, requirements for the product. We view the dilutive effects of the refinancing as justified by the highly encouraging Phase IIb data, which suggests tozadenant is competitive with marketed PD therapies and others in development, thus meriting further development of tozadenant. In addition, as an asset in Phase III it enables an improved negotiating position for any future partnership discussions.

Tozadenant pivotal Phase III – flipping the 'ON' switch

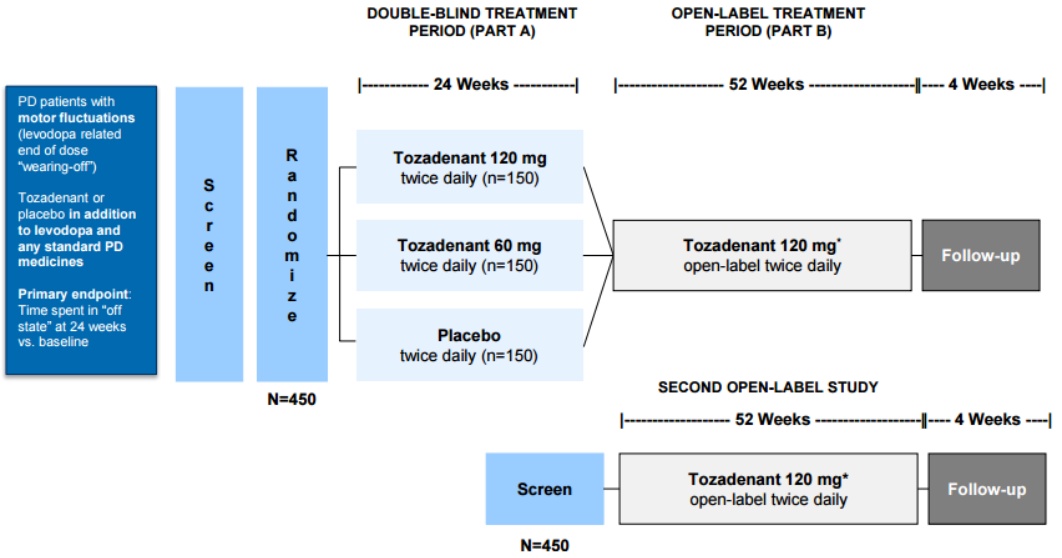
Tozadenant (SYN115), an oral, potent and selective adenosine A2a receptor antagonist, has displayed clinically relevant and statistically significant effects in a Phase IIb study in levodopa-treated Parkinson's disease (PD) patients experiencing end-of-dose 'wearing off' (motor fluctuations). Results of this study were published in *The Lancet Neurology* in August 2014.

Designed with approval in mind

Recruitment began for the pivotal Phase III study, TOZ-PD (Safety and Efficacy Study of SYN115 in Parkinson's Patients Using Levodopa to Treat End of Dose Wearing Off) in July 2015. The study, agreed under Special Protocol Assessment (SPA) with the FDA, is divided into two treatment periods (see Exhibit 2). The first (part A) is a 24-week randomised, double-blind, placebo-controlled trial in 450 levodopa-treated PD patients experiencing end-of-dose wearing-off episodes. In addition to their standard anti-PD medications, participants will be randomised to receive twice-daily (bid) doses of 60mg or 120mg of tozadenant or placebo. The primary endpoint will be reduction in time spent in the 'off' state (tozadenant vs placebo) between baseline and week 24. Secondary endpoints will include 'on' time without troublesome dyskinesia, the Unified Parkinson's Disease Rating Scale (UPDRS), Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC). The study will be conducted in the US, Canada and selected European countries. Top-line data from this phase of the study are expected in end-2017.

Following the placebo-controlled phase, a 52-week open-label treatment period (part B) will be used to collect additional safety and efficacy data. The expectation is that patients will be dosed with 120mg of tozadenant bid (the anticipated ideal dose based on current efficacy/safety profile), although this will likely depend on the outcome of the first Phase.

Exhibit 2: Tozadenant – pivotal Phase III study design



Source: Biotie Therapies

Should part A of TOZ-PD meet the primary endpoint, a second 52-week open-label study (n=450) will be started (running alongside part B of TOZ-PD) to generate the additional 900 unique patient exposures required for FDA approval. As an open-label study with evidence of efficacy, recruitment for this trial could be rapid.

Under the SPA agreement, a positive outcome of TOZ-PD, along with the results of the completed Phase IIb study, would satisfy the requirement of two pivotal studies supporting a claim of efficacy for tozadenant in this indication, forming the basis of a New Drug Application (NDA) submission.

Assuming part B starts in end-2017 as currently planned, data could be available by end-2018, allowing for a potential NDA filing by end-2018 or early 2019. With a standard 10-month FDA review process, approval could be granted by end-2019. We conservatively assume full commercialisation of tozadenant (in the US/EU) in 2020, leaving room for upside if the timeline is accelerated.

A high unmet clinical need

PD is a progressive, neurodegenerative movement disorder, affecting c 6.3m people worldwide, including 1.2 million in Europe. Initial treatment with levodopa and dopamine agonists improves and controls the hallmark symptoms of resting tremor, muscle stiffness, slowness of movement and impaired balance. However, over time PD patients start to develop motor fluctuations related to the use of levodopa; these include:

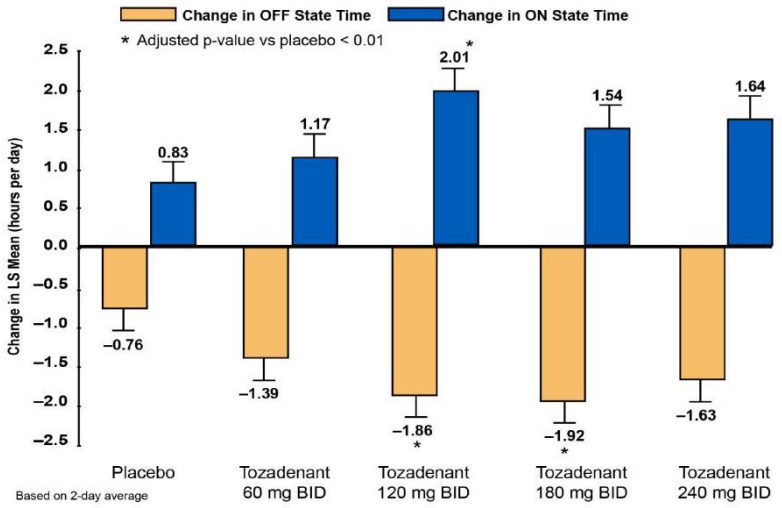
- The **wearing-off effect**. These periods occur when the effects of a single dose of levodopa do not last as long as they used to, resulting in increased time spent in the 'off' state.
- **Dyskinesias**. These are sudden, uncontrollable, often jerky or writhing movements.
- The **on-off response**. 'on' and 'off' periods occur without warning as a result of fluctuating dopamine levels in the brain. An 'off' period usually occurs suddenly, over seconds or minutes, causing a state of decreased mobility. During 'on' periods the medication is working and symptoms are controlled.

Within four to six years of onset, c 40% of PD patients will experience these debilitating motor fluctuations, and this figure increases by 10% per year thereafter (Parkinson's Disease Foundation). Therefore, by reducing the time spent in the 'off' state and increasing time in the 'on' state, tozadenant has the potential to significantly improve the quality of life for PD patients.

Building on significant Phase IIb data

The international Phase IIb study was a 12-week double-blind trial in which patients on stable dosages of levodopa with at least 2.5 hours of 'off' time per day were randomised to tozadenant 60mg, 120mg, 180mg or 240mg bid, or matching placebo. The primary outcome measure was the change from baseline to week 12 in hours per day spent in the 'off' state.

Exhibit 3: Mean change from baseline to week 12 in 'off' and unaffected 'on' time



Source: Olanow C, et al. AAN 2013 poster

Of the 420 patients randomised, 337 completed treatment (20% dropout). Significant reductions in mean, placebo-corrected, change from baseline in 'off' time were observed with tozadenant at 120mg bid (-1.1hr, p=0.0039) and 180mg bid (-1.2hr, p=0.0039) (Exhibit 3). Importantly, the amount of time patients spent in the 'on' time *with* troublesome dyskinesia was not significantly increased in

any tozadenant group, whereas *unaffected* 'on' time was significantly higher in the 120mg bid group (+2hr, p=<0.01). Multiple other assessments of Parkinson's disability/lifestyle impact (eg UPDRS) also showed encouraging treatment benefits with tozadenant, primarily with the 120mg bid dose.

A2a receptor competition

Istradefylline (Kyowa Hakko Kirin) is an A2a antagonist that has been marketed in Japan since May 2013. The FDA denied approval in 2008, due to concerns over mixed Phase III efficacy data and drug stability issues. In November 2013, Kyowa initiated a fresh 600-patient Phase III study, which is expected to complete by end-2015/early 2016. In 2013, Merck & Co abandoned the development of its A2a antagonist, preladenant, in 2013 following the failure of three Phase III studies, on the basis of lack of efficacy (not due to any adverse safety finding). We suggest that the tozadenant Phase IIb data indicate a more robust efficacy/safety profile in comparison (Exhibit 4).

Exhibit 4: Phase II studies with A2a receptor antagonists in Parkinson's disease

	Patients	Dropout	Dosing	Baseline	Primary endpoints	Secondary endpoints	Safety data
Preladenant	253	23%	1mg/2mg/ 5mg/10mg bid, placebo, 12 wks	Age: 62.4yrs; 'off' time: 5.7hrs/day	Off-time reduction: -1hr at 5mg (p=0.049); -1.2hr at 10mg (p=0.019)	No change in 'on' time with any dyskinesia. No significant improvements in UPDRS (except 5mg and 10mg on UPDRS part I).	Common adverse events in treatment groups vs placebo: worsening of Parkinson's (8-15% vs 9% placebo), somnolence (8-13% vs 6% placebo), dyskinesia (6-13% vs 13% placebo), nausea (4-13% vs 11% placebo), constipation and insomnia.
Tozadenant	420	20%	60mg/120mg/ 180mg/ 240mg bid, placebo, 12 wks	Age: 63.3yrs; 'off' time: 6.1hrs/day	Off-time reduction: -1.1hr at 120mg (p=0.004); -1.2hr at 180mg (p=0.004)	No change in 'on' time with any dyskinesia. Significant improvements in UPDRS parts I-III (all doses, p≤0.03) and part III (motor) score (at 120mg, -2.2 / p=0.033, and at 180mg, -2.5 / p=0.033).	Common adverse events in treatment groups vs placebo: dyskinesia (14-20% vs 8% placebo), nausea (6-12% vs 4% placebo), dizziness (5-13% vs 1% placebo), constipation, worsening of Parkinson's, insomnia and falls.
Istradefylline	363	10%	20mg/40mg od, placebo, 12 wks	Age: 65.9yrs; 'off' time: 6.3hrs/day	Off-time reduction: -0.65hr at 20mg (p=0.013); -0.92hr at 40mg (p=0.001)	Significant improvements in UPDRS part III (-2.0 for 20mg and 40mg, p=0.006).	Dyskinesia adverse events at 20mg (24% vs 14% placebo) and 40mg (30% vs 15%) reported.

Source: Edison Investment Research. Note: All trials were randomised, double-blind, placebo-controlled, multi-centre studies in Parkinson's disease patients receiving levodopa but experiencing end-of-dose wearing off.

Selincro – making steady progress

Selincro (nalmefene) is an EMA-approved drug for the reduction of alcohol consumption in adults with alcohol dependence who have a high drinking risk level, but without physical withdrawal symptoms and not requiring immediate detoxification. Global rights are licensed to Lundbeck, which has launched Selincro in 32 European markets.

Selincro is a dual-acting opioid system modulator. It is thought to counteract the reinforcing effects of alcohol consumption, possibly by modulating the mesolimbic release of dopamine in response to acute alcohol intake, the so-called 'reward pathway'. Results from three pivotal studies ESENSE1, ESENSE2 and SENSE showed that Selincro is safe, well tolerated and effective in reducing the monthly number of heavy drinking days (HDDs) and the monthly total alcohol consumption (TAC in g/day) by over 60% after six or 12 months in alcohol-dependent patients. Two-thirds of these patients had never previously received treatment for alcohol dependency.

Steady sales

The global rights for Selincro are licensed to Lundbeck, with Biotie receiving royalties on sales. As of 30 June 2015, Biotie had received €22.5m (of a possible €94m) of upfront and milestone payments. This includes the first commercial milestone of €0.5m, received in Q215. Biotie is eligible to receive further potential milestone payments on launches in certain ex-EU markets and if the product reaches certain predetermined sales. Biotie will continue to receive royalties on sales in all

markets and will make a contribution to Lundbeck towards post-approval commitment studies. Lundbeck is collaborating with Otsuka Pharmaceutical to develop and commercialise nalmefene in Japan. A 660-pt Phase III study in Japan began in Q115.

Lundbeck reports good progress with the European roll-out, with sales so far exceeding consensus estimates and our expectations. Sales in Q215 were DKK50m (vs DKK5m in Q214), with H115 sales of DKK91m (vs DKK8m in H114). Sales were primarily driven by France, and to a lesser extent Spain and Switzerland. Biotie does not anticipate any material impact to Selincro FY15 sales following Lundbeck's recently announced restructuring.

A much-needed alternative

Selincro tablets can be prescribed by specialists and general practitioners. The treatment should be used in conjunction with psycho-social support (counselling/support groups). Selincro is used on an 'as required' basis, whereby the patient takes a tablet when s/he perceives a risk of drinking alcohol (preferably one to two hours before drinking).

Unlike the long-established drug treatment options for alcohol dependency, such as Campral (acamprosate), Antabuse (disulfiram) and ReVia/Vivitrol (naltrexone), Selincro does not require complete abstinence on the part of the patient. Clearly, abstinence is the primary objective of treatment; however, it is often an unacceptable or unattainable treatment goal for these patients, which can affect the sustainability of treatment success. For example, although acamprosate (which reduces alcohol craving) has been shown to significantly improve the rate and duration of abstinence compared to placebo, <30% of patients are continuously abstinent after 12 months.

Even when abstinence cannot be achieved, reducing alcohol consumption has significant clinical benefits. Every HDD carries an increased risk of accidents, aggression, suicide and cardiac arrest,[1] and any reduction in alcohol consumption for a person who consumes more than 10g of alcohol per day will reduce the annual and lifetime risk of an alcohol-related death.[2] Furthermore, it has been suggested that increasing the drug-based treatment of alcohol dependency in Europe by 40% could potentially save 11,700 lives annually through reducing alcohol-attributable mortality by 9-13%.[3] Therefore, Selincro's ability to reduce HDDs by two days/month and reduce alcohol by 11g/day compared to placebo is highly clinically relevant, offering an alternative option to clinicians treating patients for whom abstinence is not a viable option.

SYN120 – targeting Parkinson's disease dementia

SYN120, an oral small molecule compound that blocks two serotonin receptors in the brain (5-HT6 and 5-HT2a) is being developed for the treatment of cognitive disorders, in particular, Parkinson's disease dementia (PDD). As c 20-40% of PD patients suffer from cognitive impairment, it is increasingly regarded as an important component of the disease. Cognition deficit is linked to an imbalance in neurotransmitters such as serotonin. Blockage of 5-HT6 receptors increases brain concentrations of pro-cognitive neurotransmitters, such as acetylcholine and glutamate, and has been found to improve cognition in studies. Psychotic symptoms are also relatively common in PD, and can often be as debilitating as the motor symptoms. Blockage of 5-HT2a receptors has demonstrated encouraging efficacy in psychosis associated with PD.[4]

[1] Rehm J, et al. (2010): The relation between different dimensions of alcohol consumption and burden of disease: An overview. Addiction 105: 817–843.

[2] Rehm J, et al. (2011): Epidemiology and alcohol policy in Europe. Addiction 106 (suppl 1): 11–19

[3] Rehm, J et al. (2013): Modelling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. European Neuropsychopharmacology; 23, 89-97.

[4] Friedman JH. (2013): Pimavenserin for the treatment of Parkinson's disease psychosis. Exert Opin Pharmacother. 14(14):1969-75.

SYNAPSE study: Evaluating safety, tolerability and efficacy

The 80-patient Phase IIa SYNAPSE study began in December 2014. The randomised, double-blind, placebo-controlled trial is in patients with PDD already treated with a cholinesterase inhibitor. The study includes a screening period of up to six weeks, a 16-week treatment period and a two-week safety follow-up. Patients are randomised 1:1 to placebo or SYN120 dosed once daily, with cognition assessments made at weeks four, eight and 16. Efficacy on cognition will be assessed by the change in Cognitive Drug Research (CDR) Computerized Cognition Battery from baseline. Safety and tolerability will also be assessed. The bulk of the cost of the study is covered by the $2m research contract with The Michael J Fox Foundation, with the Parkinson Study Group (PSG) conducting the study at c 12 sites in the US. Top-line data are expected in H216.

Potential not limited to Parkinson's disease dementia

Although Biotie's plans to evaluate SYN120 in Alzheimer's disease (AD) are currently on hold, this additional indication presents significant upside potential for SYN120. The huge appetite for investment in this notoriously risky indication was recently illustrated when Axovant Sciences, a single-product company, secured a >$2bn valuation when it listed on NYSE in June 2015. Axovant is developing RVT-101, an oral 5-HT6 receptor antagonist bought from GSK for $5m, for the treatment of mild-moderate AD. A Phase III study is due to start in Q415. Lundbeck, in collaboration with Otsuka, is also investigating an oral 5-HT6 receptor antagonist for the treatment of AD; LU AE58054 is currently in three Phase III trials reporting in H215/H116.

As in PD, psychotic symptoms are common in patients with AD. In also blocking the 5-HT2a receptor, SYN120 could have a unique therapeutic profile combining procognitive and antipsychotic activities, which could increase its appeal over drugs that inhibit only the 5-HT6 receptor. Additional funding and/or partnership would be required for Biotie to resume development in AD.

BTT1023 – proof-of-concept study underway

BTT1023 is being developed for the treatment of primary sclerosing cholangitis (PSC), a chronic and progressive liver disease characterised by bile duct inflammation and fibrosis. There are no approved therapies for PSC. BTT1023, a fully human monoclonal antibody, targets Vascular Adhesion Protein 1 (VAP-1), which plays an important role in mediating liver inflammation and fibrosis. BTT1023 was granted orphan drug designation in Europe for the treatment of PSC in H115; Biotie also intends to pursue orphan drug designation in the US.

Phase IIa BUTEO study

Using the €1m co-funding secured from the UK's National Institute for Health Research (NIHR), Biotie BEGAN the Phase IIa proof-of-concept study BUTEO in March 2015. The open-label, single-arm, multi-centre study will evaluate the efficacy, safety and pharmacokinetics of BTT1023 in 41 patients with PSC. Patients will receive an intravenous infusion of BTT1023 every two weeks over an 11-week treatment period. The primary efficacy endpoint is a reduction of elevated levels of alkaline phosphatase, a blood biomarker of bile duct inflammation; secondary endpoints include various measures of liver injury and fibrosis. The two-stage study design includes a pre-planned interim analysis, which is expected by end-2016.

Although we do not currently include BTT1023 in our valuation model, we note that it is a potentially lucrative orphan drug indication, with few other drugs in development. The total patient population across the US and Europe is approximately 50,000-130,000 (prevalence estimates for PSC at 6-16 per 100,000). With the potential for orphan drug pricing ($25,000-50,000 range), even relatively modest penetration rates would suggest peak potential sales of mid-$100m.

Valuation

We value Biotie at €268m, or €0.27 per share, based on a risk-adjusted NPV analysis and €94m gross cash at end-H115 (including the €74.3m from the recent financing). While our portfolio value has increased to €174m (vs €168m previously) as a result of changes to the near-term forecasts for Selincro (€3.8m in FY15 vs €3.4m previously), this is offset by the fact that cash raised was slightly less than our original estimate. Consequently, our valuation has reduced slightly (previous indicative valuation of €275m). We use the gross cash figure, excluding Biotie's long-term financial liabilities of €20.7m, which mostly relate to loans from Tekes (and €9.7m of related interest) that are largely repayable only on sustainable profitability. Our valuation includes only the key products – Selincro, tozadenant and SYN120; we exclude BTT1023 offering upside potential on positive clinical development. The breakdown of our valuation, which uses a standard 12.5% cost of capital, is shown in Exhibit 5.

Exhibit 5: Biotie valuation model and key assumptions

Product	Indication	Status	Launch	NPV ($m)	Peak sales ($m)	Probability of success	Royalty rate	rNPV (€m)	rNPV/ share (€)	Key assumptions
Selincro	Alcohol dependency	Marketed (EU)	2013	91	350	100-85% sliding scale	10-17%	72	0.07	2.4m diagnosed alcoholics in EU; 8-12% drug treatment rate; 35% peak Selincro penetration; €3.50-4.00/pill for 100 days/year = €375 average effective annual price.
Tozadenant (SYN115)	Parkinson's disease	Phase III	2020	172	650	65%	25%	92	0.09	Diagnosed PD population: 630,000 (US) + 1.2m (EU); mild-to-moderate PD (80%); combination therapy (45%); on levodopa (85%); motor fluctuations (55%); 30% (US)/ 25% (EU) peak tozadenant share; $5,500 (US)/$3,000 (EU) effective annual price.
SYN120	Parkinson's disease dementia	Phase IIa	2022	52	425	25%	12.5%	11	0.01	Diagnosed PD population: 630,000 (US) + 1.2m (EU); cognition deficit (35%); receiving cholinesterase inhibitors (75%); suitable for combination treatment (50%); 25% (US + EU) peak SYN120 share; $5,500 (US)/$3,000 (EU) effective annual price.
Portfolio total				**314**				**174**	**0.18**	
Gross cash								94	0.10	At 30 June 2015
Overall valuation								**268**	**0.27**	980.85m shares in issue at 30 June 2015

Source: Edison Investment Research

For Tozadenant, we assign a 65% probability of success and set the potential royalty rate at 25%, assuming a partner is secured on the back of positive headline results from the first phase of the TOZ-PD study (expected end-2017). However, Biotie is considering commercialising tozadenant independently, which may provide upside to our valuation. We estimate initial launch of the product by 2020, assuming regulatory approvals (US/EU) are secured by that time. As part of the transfer of rights to Biotie, UCB was required to contribute a portion of the outstanding short-term development costs. UCB may recover these from future revenues generated from tozadenant; we understand this is capped in the low single-digit €m. However, as we do not include any potential out-licensing deal terms in our model, we also exclude any potential future pay-away to UCB.

Our market assumptions for SYN120 relate exclusively to the potential to treat Parkinson's disease dementia, although the drug's mechanism of action would suggest further potential for use in similar settings in Alzheimer's disease patients and other psychosis disorders. We assign a probability of success of 25% and set the potential royalty rate at 12.5%, assuming a partner is secured on the back of encouraging Phase IIa data in 2016.

Despite the key regulatory approvals in the five major EU markets and being available in over 20 EU countries, Selincro's commercialisation in Europe remains at an early stage, partly as a result of it being a new treatment concept (requiring acceptance by specialists and patients), but also due to the ongoing requirement to secure widespread reimbursement from state healthcare systems. We

predict that uptake will significantly increase from 2018 onwards. Biotie reports that sales have exceeded consensus estimates in Q215, with sales of DKK50m (€6.7m), resulting in royalties to Biotie of €0.8m (vs €0.09m in Q214). Biotie also received its first commercial milestone of €0.5m in Q215 (details of the trigger are confidential).

We maintain our peak sales potential for Selincro at $420m (€325m) by 2023, although we apply a sliding scale of probability (100-85%) of achieving these peak sales, with higher probability on near-term sales gradually reducing to lower probabilities for long-term sales. Our peak sales estimate is in line with Lundbeck's peak sales estimate of DKK2.5bn (€330m). Our model excludes potential development of Selincro outside the EU. US commercialisation is unlikely for IP reasons, but development and commercialisation in other European countries (eg Russia) and Japan (partnered with Otsuka, Phase III in progress) would therefore represent upside.

We do not include BTT1023, which offers upside potential, dependent on the outcome of the BUTEO clinical trial and subsequent development/licensing strategies. A pre-planned interim analysis is expected by the end of 2016.

Sensitivities

Biotie is subject to the risks common to most biotech companies, including clinical development delays or failures, regulatory risks, competitor successes and commercialisation risks (launch, uptake, pricing, reimbursement). The key stock-specific sensitivities are connected to Lundbeck's success in commercialising Selincro in Europe and the outcome of the tozadenant pivotal study.

Although Biotie conducting the tozadenant Phase III programme alone increases its clinical risk profile, if the study is successful and regulatory approvals and commercial partnerships secured, Biotie stands to extract greater economic benefit from tozadenant. Our estimates for Selincro could be significantly higher or lower depending on the extent to which the drug is adopted by European healthcare agencies. As a new treatment concept, Selincro is likely to have slow initial uptake for a few years, although we predict a significant increase in uptake from 2018 onwards.

Financials

Gross cash as of end-H115 was €94m, which includes the €74m net proceeds raised from the total effective sale of 525m new shares (220m from the convertible notes priced at €0.15 per share and 305m from the US IPO priced at €0.165 per share; each ADS was priced at $14.9 with a ratio of 80:1). Our model suggests that current cash is at least sufficient to fund operations to completion of the first phase of the TOZ-PD study (by end-2017), which will inform further clinical, and therefore financing, requirements for the product. We have included illustrative financing of €10m in 2018 though this may be reduced or removed by increased Selincro revenues or reduced R&D spend depending on the timelines for the tozadenant trials. As mentioned previously, we use the gross cash figure, excluding Biotie's long-term financial liabilities of €20.7m (and related interest), which mostly relate to loans from Tekes that are largely repayable only on sustainable profitability. In addition to current cash, Biotie has the ability to raise up to €20m in additional capital under its standby equity distribution agreement (SEDA) with Yorkville. This is available until November 2015 (€1.1m drawn to date), though we do not expect any draw-down on this facility.

Net loss of €14.9m in H115 (vs €5.6m in H114) is primarily due to increased R&D expenditure in support of the TOZ-PD study, in line with company guidance. Biotie expects R&D expenditure to continue at these levels for H215; therefore we have increased our assumptions for R&D expenses in FY15 (€27m vs €24), though we maintain our FY16e forecast (€28m). Our forecasts for G&A are maintained (€8.8m in FY15e and €9.5m in FY16e). Following the strong sales of Selincro in Q215

and the commercial milestone received, we have increased our revenue estimate for FY15 to €3.8m (vs €3.4m previously). As a result of these revisions, our net loss for FY15e has increased to €33m (vs €29m previously; €35m in FY14). Our financial model is summarised in Exhibit 6.

Exhibit 6: Financial summary

Year end 31 December €'000s	2013	2014	2015e	2016e	2017e	2018e
Accounting basis	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	27,712	14,901	3,849	6,373	9,216	11,776
of which: Selincro milestones	4,000	6,000	500	800	1,500	0
Selincro royalties	155	923	3,136	5,573	7,712	11,768
UCB payments for tozadenant	23,457	7,853	213	0	0	0
Other	100	125	0	0	0	0
Cost of sales	0	0	0	0	0	0
Gross profit	27,712	14,901	3,849	6,373	9,216	11,776
R&D expenses (continuing operations, excludes write-downs)	(17,807)	(17,192)	(27,359)	(28,000)	(30,000)	(30,000)
G&A expenses (continuing operations, excludes exceptionals)	(8,971)	(7,326)	(8,791)	(9,451)	(9,734)	(10,026)
Other operating income (includes grants, e.g. MJFF)	565	1,132	1,000	1,400	1,500	1,500
EBITDA	1,499	(8,485)	(31,301)	(29,677)	(29,018)	(26,750)
Operating profit (before GW and except)	1,499	(8,485)	(31,301)	(29,677)	(29,018)	(26,750)
Intangible amortisation	0	0	0	0	0	0
Exceptionals (R&D write-downs)	0	(27,605)	0	0	0	0
Currency translation differences	0	0	0	0	0	0
Operating profit	1,499	(36,090)	(31,301)	(29,677)	(29,018)	(26,750)
Net interest	2,152	925	(1,300)	(500)	(500)	(500)
Profit before tax (norm)	3,651	(7,560)	(32,601)	(30,177)	(29,518)	(27,250)
Profit before tax (FRS 3)	3,651	(35,165)	(32,601)	(30,177)	(29,518)	(27,250)
Tax (credit)	2,195	0	0	0	0	0
Profit after tax (norm)	5,846	(7,560)	(32,601)	(30,177)	(29,518)	(27,250)
Profit after tax (FRS3)	5,846	(35,165)	(32,601)	(30,177)	(29,518)	(27,250)
Average number of shares outstanding (m)	446.2	450.7	718.4	980.9	980.9	980.9
EPS - normalised (€)	0.01	(0.02)	(0.05)	(0.03)	(0.03)	(0.03)
EPS - FRS 3 (€)	0.01	(0.08)	(0.05)	(0.03)	(0.03)	(0.03)
BALANCE SHEET						
Fixed assets	75,745	54,132	63,795	64,020	64,244	64,467
Intangible assets	74,059	53,155	59,060	59,110	59,160	59,210
Tangible assets	627	653	803	978	1,152	1,325
Other non-current assets	1,059	324	3,932	3,932	3,932	3,932
Current assets	44,253	34,199	82,749	52,847	23,604	6,631
Debtors	575	1,806	2,500	2,500	2,500	2,500
Cash	43,678	32,393	80,249	50,347	21,104	4,131
Other	0	0	0	0	0	0
Current liabilities	(6,483)	(2,677)	(7,000)	(7,000)	(7,000)	(7,000)
Creditors	(5,740)	(2,677)	(7,000)	(7,000)	(7,000)	(7,000)
Short-term borrowings	0	0	0	0	0	0
Deferred revenue	(743)	0	0	0	0	0
Long-term liabilities	(33,149)	(33,031)	(33,031)	(33,031)	(33,031)	(43,031)
Long-term borrowings	(20,690)	(20,690)	(20,690)	(20,690)	(20,690)	(30,690)
Provisions	(569)	(670)	(670)	(670)	(670)	(670)
Other long-term liabilities (includes loan interest)	(8,918)	(9,671)	(9,671)	(9,671)	(9,671)	(9,671)
Non-current deferred revenues	(2,972)	(2,000)	(2,000)	(2,000)	(2,000)	(2,000)
Net assets	80,366	52,623	106,513	76,836	47,817	21,067
CASH FLOW						
Operating cash flow	10,590	(14,065)	(26,209)	(29,627)	(28,968)	(26,700)
Net interest	(13)	(27)	(75)	(50)	(50)	(50)
Tax	0	0	0	0	0	0
Capex	(329)	(146)	(150)	(175)	(174)	(173)
Expenditure on intangibles	(52)	(50)	(50)	(50)	(50)	(50)
Acquisitions/disposals	0	1,350	0	0	0	0
Financing	370	126	74,340	0	0	0
Dividends	0	0	0	0	0	0
Other	(214)	323	0	0	0	0
Net cash flow	10,352	(12,489)	47,856	(29,902)	(29,242)	(26,973)
Opening net debt/(cash)	(1,866)	(14,070)	(2,032)	(49,888)	(19,986)	9,257
Other	1,852	451	0	0	0	0
Closing net debt/(cash)	(14,070)	(2,032)	(49,888)	(19,986)	9,257	36,230

Source: Biotie accounts; Edison Investment Research

Contact details	Revenue by geography
Joukahaisenkatu 6 FI-20520 Turku Finland +358 2 274 8900 www.biotie.com	N/A

Management team

Chief Executive Officer: Dr Timo Veromaa	Chief Financial Officer: David Cook
President and CEO since 2005; previously vice-president of R&D (1998-2005). Previous roles include medical director, Schering Oy, Finland (1996-98), research and programme manager, Collagen Corp, US (1994-96).	CFO since February 2013, also responsible for business development activities. Previous roles include: CFO, Jazz Pharmaceuticals International (2011-12); CFO, EUSA Pharma (2006-11); group financial controller, Zeneus Pharma (2004-06); and various roles at PriceWaterhouseCoopers (1992-2004).
Chief Operating Officer: Mehdi Paborji	**Chief Medical Officer: Stephen Bandak**
COO since January 2014. Previous roles include: founder and COO, TheraVida (2006-13); vice president, pharmaceutical development, Irvine Pharmaceutical Services (2004-06); senior director, pharmaceutical R&D, Theravance (2001-04); director, pharmaceutical R&D, Bristol-Myers Squibb (1986-2001).	CMO since February 2011. Previous roles include: CMO, Synosia Therapeutics (2007-11); vice president of medical and regulatory, Novavax (2004-06); a variety of leadership roles including executive director of the US Medical Organisation at Eli Lilly; and member of the Royal College of Physicians 1977.

Principal shareholders	(%)
Baupost Group	10.21
Vivo	9.95
Invesco	7.72
Fidelity	7.54
OrbiMed Advisors	7.49
Versant Ventures	5.97

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