Phytopharm

Looking ahead to February 2013

Edison investment research

Binary vision

Pharma & Biotech

Phytopharm's investment case centres on a binary event in February 2013 when top-line results are expected from its Confident-PD Phase II trial of Cogane in early-stage Parkinson's disease. Positive data could allow Phytopharm to secure a development and commercialisation partner for Cogane, milestones that would significantly increase our rNPV of £48m to £83m. A failure of Cogane in the Confident-PD study could reduce the company's market value to cash or lower, although encouraging data in amyotrophic lateral sclerosis may offer an alternative route to market.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
09/10	0.7	(4.1)	(1.3)	0.0	N/A	N/A
09/11	0.1	(8.0)	(2.2)	0.0	N/A	N/A
09/12e	0.0	(10.4)	(2.7)	0.0	N/A	N/A
09/13e	0.0	(8.2)	(2.2)	0.0	N/A	N/A

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

Confidence required

The Confident-PD study has enrolled 408 patients with newly diagnosed, treatment-naive Parkinson's disease at multiple centres across the US and Europe. Dosing should complete by the end of 2012 and, allowing for a four-week follow-up period, Phytopharm expects to announce top-line results in February 2013. Cogane has the potential to become the first small-molecule, disease-modifying therapy for Parkinson's, and therefore could attract a lucrative licensing deal.

ALS back-up

Positive and confirmatory data from the gold-standard pre-clinical mouse model for amyotrophic lateral sclerosis (ALS) provides Cogane with an important second line of development. Depending on the outcome of Confident-PD, ALS could offer an additional valuation parameter in any licensing discussions or may provide a fall-back avenue of development for Cogane should the drug fail in the Parkinson's trial.

Myogane on hold in glaucoma

A recent pre-clinical study of Myogane proved inconclusive due to a failure of the animal model of glaucoma to induce sufficient neuronal cell death in both the treatment and control groups. Phytopharm continues to assess next steps but we assume further development is on hold until the outcome of the Confident-PD study.

Valuation: rNPV of £48m with significant uplift potential

We have revised our risk-adjusted NPV to £48m (previously £53m) due to removal of Myogane. This compares favourably with Phytopharm's £8.7m enterprise value, based on net cash of £13.3m as of 31 March 2012. Over 50% of our valuation is assigned to Cogane's potential in Parkinson's. Ahead of data from the Confident-PD trial, we assign a 25% probability of success – positive results and securing a partner would raise that probability to 50% and therefore our rNPV to £83m.

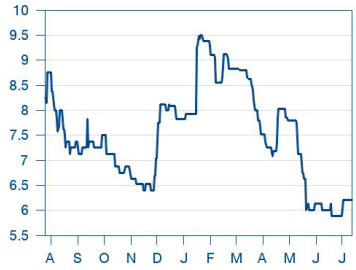
Phytopharm is a research client of Edison Investment Research Limited

13 July 2012

Price	6.2p
Market cap	£22m

Shares in issue	346.8m
Free float	39%
Code	PYM
Primary exchange	LSE

Share price performance



%	1m	3m	12m
Abs	3.3	(12.4)	(18.7)
Rel (local)	(0.7	(10.4)	(14.5)
52-week high/low		9.5p	5.9p

Business description

Phytopharm is a UK biotech company principally focused on the development of drugs for neurodegenerative disease. Lead candidate Cogane is undergoing a Phase II study in Parkinson's disease, with results due in February 2013.

Next events

Confident-PD data	February 2013

Analysts

Christian Glennie +44(0)20 3077 5727

Robin Davison +44(0)20 3077 5737

healthcare@edisoninvestmentresearch.co.uk

Edison profile page

Investment summary: Cogane Phase II data in February 2013

Company description: Focus on neurodegenerative disorders

Phytopharm is a UK company focused on the development of small-molecule drugs, principally in neurodegenerative disease. Phytopharm's products are sapogenins, derived from botanical sources (often sourced from Chinese research organisations), but are single chemical entities and the company operates as a small-molecule drug development business. Phytopharm has raised a total of £78.3m since its flotation in April 1996, and obtained c £12m in funding under three now-discontinued licensing agreements. It has 14 employees.

Exhibit 1: Phytopharm's R&D programme summary

Programme	Indication	Development stage/notes
Cogane	Parkinson's disease	Phase II. Headline efficacy/safety results expected in Feb 2013.
Cogane	ALS	Pre-clinical. Positive results from *in vivo* pre-clinical models.
Myogane (eyedrop)	Glaucoma	On hold. Inconclusive *in vivo* pre-clinical model.
P61 programme	Inflammatory diseases	Pre-clinical. Lead optimisation.

Source: Edison Investment Research

Valuation

Phytopharm's near-term investment proposition centres on the value uplift that would be expected if the Phase II (Confident-PD) study of Cogane proves successful, and on potential partnering of the project with a pharmaceutical group soon after. Top-line results from Confident-PD are expected in February 2013 and Phytopharm's current cash runway extends to the end of 2013. Our risk-adjusted NPV methodology, using industry-standard probabilities and a 12.5% cost of capital, indicates a value of £48m, which compares favourably with Phytopharm's enterprise value of £8.7m, based on reported net cash of £13.3m at 31 March 2012. Positive Confident-PD data and successful partnering would significantly raise our rNPV to £83m.

Sensitivities

The key sensitivity to the investment proposition for Phytopharm is the company's almost complete reliance on the Phase II study (Confident-PD) of Cogane and, if successful, its ability to secure an economically attractive licensing deal with a major pharmaceutical group. Aside from a complete failure to meet key efficacy and safety endpoints, there is a risk that Confident-PD produces ambiguous or contradictory results, which could hinder further development and/or licensing negotiations. Failure to secure a development partner for Cogane by the end of 2013 would force Phytopharm into seeking fresh finance, implying a likely dilution for current holders if raised through a new equity issue. Development projects outside those specifically considered in the rNPV model represent upside. Phytopharm has one substantial shareholder in the form of Invesco (56.4% holding).

Financials

Phytopharm ended its six months to 31 March 2012 with a balance of cash and equivalents of £13.3m, and no debt, sufficient to last until December 2013. R&D expenses increased significantly to £4.8m (vs £3.6m in fiscal H111) due to the Confident-PD study. We have assumed the same R&D expense run rate for fiscal H212, indicating an annual R&D expense of £9.6m for the year-ended September 2012, which declines to £7.2m in fiscal 2013 with completion of the Confident-PD study.

Outlook: Date with destiny

Phytopharm's investment case centres on the timely execution and success of its Confident-PD Phase II study of Cogane, its orally active neurodegenerative/neuroprotective agent for early-stage Parkinson's disease (PD). The 408-patient study is fully recruited, and should render top-line results in February 2013.

Data from Confident-PD, if positive, could provide the basis for securing a corporate partnership to exploit Cogane in PD and potentially various other neurodegenerative conditions, which might include amyotrophic lateral sclerosis (ALS) and Alzheimer's disease. Such a partnership would be expected to generate a significant economic return to Phytopharm in the form of up-front and milestone payments and royalties on sales, and is therefore central to the investment case.

Phytopharm has conducted pre-clinical research with Cogane in ALS and now has a solid and encouraging data package following positive results in a SOD-1 mouse model of this disease. The structurally related sapogenin molecule, Myogane, has been studied in glaucoma, although a recent pre-clinical study of Myogane was inconclusive due to a failure of the animal model of glaucoma to induce sufficient neuronal cell death in both the treatment and control groups. Phytopharm says it saw indications of a neuroprotective effect after Myogane treatment, but was unable to draw definitive conclusions. Phytopharm continues to analyse the results of the study, although in reality further development is on hold until the outcome of Confident-PD.

Phytopharm has also previously studied Cogane in Alzheimer's disease (a Phase IIa study was completed in 2005), and development in this indication could be resumed by a potential future partner.

Phytopharm continues to research its P61 programme (PYM60001), a series of molecules with anti-inflammatory/anti-spasmodic/anti-remodelling activities and some modulation of the TRPV1 receptor. The current status of Phytopharm's R&D programmes are summarised in Exhibit 2.

Exhibit 2: Phytopharm's R&D pipeline

Product	Indication	Development status/notes
Cogane (smilagenin/ PYM50028)	Early-stage Parkinson's disease	408-pt, six-month Phase II Confident-PD study in early-stage, treatment-naive PD examining three doses of Cogane and placebo. Primary endpoint: change from baseline in UPDRS Parts II (activities of daily living) and III (motor function). Secondary endpoints: Cognition, sleep and quality of life. Safety assessments (including standard ECG, blood pressure and pulse, and haematology and clinical chemistry). Status: First patient enrolled Nov 2010. Recruitment complete Apr 2012. Dosing to be completed Dec 2012. Headline results should be available in Feb 2013.
Cogane	Amyotrophic lateral sclerosis (ALS)	Pre-clinical. In the gold-standard SOD1 mouse model of ALS, showed improvements in muscle strength and functional motor neurons vs placebo and riluzole. Potential Phase II to start H212.
Cogane	Alzheimer's disease	On hold. Three-month Phase II study of Cogane (120mg qd) in 256 mild to moderate AD was completed in 2005 and confirmed safety in elderly patients and showed trends towards efficacy in moderate sub-group. Development could be resumed in this indication by a partner.
Myogane	Glaucoma	On-hold. Pre-clinical study proved inconclusive because of a failure to induce sufficient neuronal cell death in both the treatment and control groups. Phytopharm analysing data and assessing next steps.
P61 programme	Inflammatory diseases	Pre-clinical. Programme to investigate the known pharmacological properties of curcumin and gingerol. Lead optimisation of small molecules with anti-inflammatory, anti-spasmodic and anti-remodelling activity. Some have TRPV1 (transient receptor potential cation channel subfamily V) – or vanilloid / capsaicin receptor - modulatory activity. Multiple pre-clinical models, including asthma, COPD, dermatitis, psoriasis, GI conditions and pain.

Source: Edison Investment Research, company reports

Confident-PD study

Recruitment into the Confident-PD study was completed in April 2012. The study examines the efficacy, safety and tolerability of Cogane given over 28 weeks, as a first-line therapy for treatment-naïve PD patients. The primary endpoint is change as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III.[1] Other efficacy endpoints include assessment of cognitive function, sleep and quality of life.

Exhibit 3: Confident-PD study design

Study design	408-pt Phase IIb study with three doses of Cogane or placebo (given once-daily as an oral solution) over 28 wks, with a 4-week follow-up period.
Population	Diagnosis of early-stage idiopathic Parkinson's disease <2 years before screening.
Primary endpoint	Change from baseline in UPDRS Parts II and III. UPDRS scores are assessed at baseline and over the treatment period.
Secondary endpoints	Cognition, sleep and quality of life. Safety assessments (including standard ECG, blood pressure and pulse, and haematology and clinical chemistry).
Recruitment status	Over 80 centres, across the US, Canada and Europe. First patient enrolled Nov 2010, recruitment completed Apr 2012, dosing to complete Dec 2012, and headline efficacy/safety results due to be released in Feb 2013.

Source: Edison Investment Research, clinicaltrials.gov

The study enrolled patients with a recent diagnosis (<2 years prior to screening) of early-stage idiopathic PD, who were not receiving any other treatment, suggesting there should not be any confounding factor in the study. Typically such patients would normally have started symptomatic treatment with a monoamine oxidase B inhibitor[2] or a dopamine agonist[3], as a strategy to delay the start of levodopa-based treatment.

Phytopharm is looking for the study to demonstrate a clinically relevant difference over placebo in the primary and various secondary efficacy endpoints. The study is powered to detect a clinically significant difference in UPDRS at the end of the treatment period. Patients' UPDRS scores are assessed at baseline and over the treatment period. Baseline UPDRS scores for these early-stage PD patients are expected to be 10-15 points – a decline of 3 points or more is considered clinically meaningful and the Confident-PD study is powered to detect this level of change from baseline. There is no interim efficacy or futility analysis.

The study is examining three different doses of Cogane (as an oral solution) and placebo, given once-daily. Phytopharm is developing a solid dosage formulation, which is likely to be required for further development and to make Cogane commercially viable.

Prior studies in healthy volunteers examined Cogane at 150mg/day and 450mg/day in 18 (m/f) volunteers and 150mg/day in older patients (aged 40-80 years). The prior Phase IIa study in Alzheimer's disease examined 120mg/day in c 130 patients for three months.

Parkinson's disease

Parkinson's disease is neurodegenerative disorder caused by loss, for unknown reasons, of dopaminergic neurones in the substantia nigra region of the brain. This leads to insufficient formation of dopamine and initially causes movement-related symptoms, such as shaking, rigidity, slowness and difficulty in initiation of movement (bradykinesia) and gait problems. Later on, cognitive and behavioural symptoms develop. Drug treatment is usually effective for a period at managing motor symptoms, however, as the disease progresses and there is a greater loss of dopamine producing neurones, this becomes ineffective, while at the same time, patients develop dyskinesia (a jerky, dance-like movement of the arms and/or head) from long-term treatment with standard therapy levodopa (known as levodopa-induced dyskinesia, or PD-LID).

[1] UPDRS Part II measures activities of daily living and Part III measures motor function
[2] Eg rasagline (Azilect, Teva Pharmaceuticals).
[3] Eg ropinirole (Requip, GSK) or pramipexole (Mirapex, Roche).

Neuroprotective mechanism

Cogane is has been shown in *in vitro* models to stimulate expression of neurotrophic factors, including glial cell-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), although the exact mechanism by which it does this has not yet been established. These neurotrophic factors are known to promote the survival and viability of neurones as well as the out-growth of neurites. However, as proteins, these neurotrophic factors cannot easily be delivered to the brain. Direct injection of GDNF into the brain has shown some restoration of the control of movement in PD patients.[4] However, this requires complex and difficult surgical procedures. Since Cogane is an orally-available small molecule, it should readily cross the blood brain barrier, providing a viable route of administration.

Cogane significantly reduced Parkinsonian disability activity in the gold-standard macaque MPTP[5] model of PD, at similar plasma levels to those being tested in the Confident-PD study. In this model, Cogane was dosed at 20mg/kg/day and showed a 43% ($p<0.001$) reduction in median overall parkinsonian disability score after 18 weeks.

In this study a statistically significant reduction in parkinsonian symptoms was reached after nine weeks of administration with Cogane. The magnitude of the effect increased over the subsequent nine weeks of administration and was still increasing at the end of the study (week 18). Data from this study suggests that the mechanism underlying these effects is considerably more complex than originally envisaged. This study was supported by the Michael J Fox Foundation and further work in this area is ongoing. Pre-clinical studies with Cogane when given in conjunction with levodopa showed improved control of symptoms compared to levodopa alone. Cogane has also shown evidence of efficacy in pre-clinical models of cognitive impairment, in connection with earlier development in Alzheimer's disease.

Earlier pre-clinical studies of Cogane have also shown efficacy in cellular (MPP+ induced neuronal damage in mesencephalic neurons) and rodent (MPTP-treated mice) models of PD. Oral administration of PYM50028 (10mg/kg/day for 60 days) to MPTP-lesioned mice resulted in a significant elevation of striatal GDNF (+297%) and BDNF (+511%) and attenuated the loss of striatal dopaminergic transporter levels and dopaminergic neurons in the substantia nigra.[6]

Seeking an early-stage niche

The overall market for PD is valued at around $4.5bn, dominated by symptomatic treatments, the majority of which are now generically available. Cogane is one of a relatively small number of novel small molecule therapies in development for PD, and one of a few with disease modifying potential. This places Cogane in a small group with gene therapies (CERE-120/ProSavin), other GDNF-based products (MedGenesis) and Parkinson's disease vaccines (AFFiRiS). The current status of the overall pipeline of candidates for the treatment of Parkinson's disease, including related disorders such as PD-LID, is shown in Exhibit 4.

[4] Promising results have been seen in small Phase I trials (Gill *et al.*, 2003 and Slevin *et al.*, 2005). However, a larger Amgen sponsored 34-pt trial of intraputamental GDNF did not show superiority to placebo (Lang *et al.*, 2006).
[5] MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP = 1-methyl-4-phenylpyridinium.
[6] Visanji NP *et al.* FASEB J. 2008 Jul; 22(7): 2,488-97

Exhibit 4: Pipeline candidates for Parkinson's disease

Product	Company (s)	Target date	Notes
IPX066 (carbidopa-levodopa ER)	IMPAX Laboratories / GlaxoSmithKline	21-Oct-12	Dopamine precursor & dopa decarboxylase inhibitor. 3x Phase III studies – APEX-PD (LD-naïve, early-stage PD), ADVANCE-PD (advanced PD) and ASCEND-PD (advanced PD) – with significant reductions in "off time". NDA filed 21 Dec 11, PDUFA 21 Oct 12. Dec 10 GSK licensed WW ex. US rights for $11.5m upfront, $175m milestones and double-digit royalties.
Istradefylline (KW-6002)	Kyowa Hakko Kirin	Q1 2013	A2A antagonist. Mar 12 Filed in Japan. Feb 08 FDA non-approvable letter.
Safinamide	Newron Pharmaceuticals / Zambon	May-12	Monoamine oxidase B inhibitor. May 14 positive results from 549-pt Phase III (SETTLE) in advanced PD as add-on to L-dopa and 679-pt Phase III (MOTION) in early-PD (results: March 2012); details not released but 'consistent' with previous phase II/III studies. Zambon licensed WW rights (previously partnered with Merck Serono).
Preladenant (MK-3814)	Merck & Co	Sep-12	A2A antagonist. 3x Phase III studies: 1,000-pt in early PD (complete: Mar 13), 750-pt (Dec 12) and 450-pt (Sep 12), both in moderate to severe PD. 12-wk, 253-pt Phase II study showed improvement in off/on time. NDA due 2014.
Opicapone (BIA 9-1067)	Bial	Oct-12	COMT inhibitor. In development with standard therapy to treat "wearing-off" phenomenon. 405-pt Phase III (BIPARKII) to complete Oct 12 and 550-pt Phase III to complete Jan 13.
Tozadenant (SYN115)	UCB / Biotie Therapies	Dec-12	A2A antagonist. 400-pt Phase II/III in PD using levodopa to treat end of dose "wearing off". Jul12 Enrolment complete and headline data due end-2012.
ADS-5102 (amantadine ER)	Adamas Pharmaceuticals	Dec-12	NMDA antagonist. 80-pt Phase II/III (EASED study), recruitment ongoing, to treat PD-LID.
Mavoglurant (AFQ056)	Novartis	Jul-12	mGluR5 allosteric modulator. Phase III programme for PD-LID planned for end 2012, filing possible in 2014. 92-pt Phase II (150/200mg bid; results: Mar 13); 63-pt Phase II (results: Jul 12). Also in development for Fragile X syndrome (160-pt Phase II/III study; results: Aug 12).
Cogane (smilagenin/ PYM50028)	Phytopharm	Feb-13	Neurotrophic factor accelerator. 408-pt (Confident-PD), 6-month Phase II in early-stage treatment-naive PD examining three doses of Cogane vs. placebo.
CERE-120	Ceregene	Mar-13	Neurturin gene therapy. 51-pt Phase IIb recruitment complete.
Accordion-Pill-Carbi/Levodopa	Intec Pharma	-	Phase IIb. Different doses of carbidopa and levodopa for the treatment of different stages of PD.
Dipraglurant	Addex Therapeutics	Mar-12	mGluR5 allosteric modulator. Mar 12: statistically significant reduction in PD-LID severity with 50mg and 100mg doses in 76-pt Phase II.
AZD3241	AstraZeneca	Jun-13	Myeloperoxidase (MPO) inhibitor. 50-pt Phase IIa to start Jul 12. studies completed. Phase II PET study started Apr 12.
AQW051	Novartis	Oct-12	α-7 nAChR inhibitor. 72-pt Phase II to treat mod-to-severe PD-LID.
HP-3000 (ropinirole patch)	Hisamitsu Pharmaceutical	-	Dopamine agonist. Phase II ongoing in Japan, Phase III expected to start in 2015.
GDNF	MedGenesis Therapeutix	-	Glial cell-derived neurotrophic factor (GDNF) protein. Jan 2012 Phase II ongoing, MedGenesis raised $5m to complete trial.
DM-1992 (levodopa+ carbidopa)	Depomed	Sep-12	Dopamine precursor & dopa decarboxylase inhibitor. Gastric-retentive ER formulation of levodopa and carbidopa. 45-pt Phase II compared to IR carbidopa, in advanced PD.
CVT-301	Civitas Therapeutics	-	Dopamine agonist – inhalable levodopa. Jun 2012 Phase II initiated.
ProSavin	Oxford BioMedica	Jul-12	Dopamine gene therapy. 27-pt Phase I/II in advanced PD and failing to respond to L-dopa, results due H2 2012.
Neu-120	Neurim	Aug-12	MAO-B inhibitor/GSK-3 beta inhibitor. 20-pt Phase I/II in PD-LID.
sNN0031	NeuroNova (Newron)	-	Platelet-derived growth factor (PDGF). 12-pt Phase I/II complete. Jun 2012 Newron acquired NeuroNova for €15.4m and planning Phase II.
ND0611	NeuroDerm	-	Dopamine agonist. Carbidopa patch. 24-pt Phase I/II complete.
PD01A	AFFiRiS	Dec-13	Parkinson's disease vaccine. 32-pt Phase I in early-stage PD.

Source: Edison Investment Research, clinicaltrials.gov. Note: Target date refers to primary completion date on clinicaltrials.gov.

Cogane also has relatively few competitors as a potential treatment for early-stage Parkinson's disease. Although Impax/GSK's IPX066 (an extended-release formulation of carbidopa-levodopa) and Newron's safinamide have been studied in levodopa-naïve, early-stage PD, the trial patients may also have received prior therapy with a MAO-B inhibitor or dopamine agonist.

Only Merck & Co's preladenant (an A2A antagonist) is undergoing a Phase III trial for early-stage PD patients of a similar profile as the Confident-PD study. The trial will recruit 1,000 patients with a diagnosis of idiopathic PD less than five years prior to screening, who must have a UPDRS Part III score of ≥10, with the primary endpoint being the change from baseline in UPDRS Parts II and III

scores. Three doses of preladenant will be tested against placebo and an active comparator in rasagiline. The trial started in 2010, recruitment is ongoing and headline results should be available in H213.

Results from this study of preladenant in early-stage PD are likely to be significant for Cogane, both in terms of helping to define Cogane's potential competition, as well as providing insight into the size and scope of a pivotal trial required for Cogane.

Partnership to be sought in 2013

Phytopharm intends to seek a partnership, most likely a global development and commercialisation deal, with a major pharmaceutical company for Cogane on the back of the Confident-PD data. It is difficult to speculate on the economic terms of any such agreement, but assuming the Confident-PD data is positive and unambiguous, a deal would be expected to include a substantial upfront fee, development and regulatory milestones and double-digit royalties on sales.

Precedent deals for Parkinson's disease or ALS pipeline candidates include: Biogen Idec's licensing deal for Knopp Neurosciences' dexpramipexole ($60m in stock, $20m upfront and $265m in milestones, plus double-digit royalties on worldwide sales); Actelion's option agreement to acquire Trophos (€10m upfront and between €125-195m, depending on the outcome of the Phase III study of olesoxime for ALS[7]); and UCB's licensing of global rights to Synosia's Parkinson's disease candidates (tozadenant/SYN115 and SYN-118) in 2010 for $20m upfront and a further $725m in regulatory and commercial milestones.

Amyotrophic lateral sclerosis

With the support of the Motor Neurone Disease Association, Phytopharm recently examined Cogane in the gold standard SOD-1 animal model of ALS to establish a second, niche indication which offers an alternative path forward should the Confident-PD trial fail to deliver positive results. Cogane has received US and EU orphan drug status for ALS.

Phytopharm now has a solid and encouraging data package in ALS, the SOD-1 data confirming positive outcomes from other models of ALS. With Cogane already undergoing a large Phase II study, there is scope for development in ALS to proceed straight into a Phase II or Phase II/III trial.

Orphan drug

ALS is a rare condition (incidence well below the 200,000-patient threshold to qualify for orphan drug status). A disease profile and competing development candidates are shown in Exhibits 5 and 6.

Exhibit 5: Amyotrophic lateral sclerosis background

Description	A form of motor neuron disease caused by the degeneration of neurons located in the ventral horn of the spinal cord and the cortical neurons that provide their afferent input. Known as Lou Gehrig's disease in the US.
Symptoms	Rapidly progressive weakness, muscle atrophy and fasciculations, spasticity, dysarthria, dysphagia and respiratory compromise. Sensory, autonomic and oculomotor function is generally spared.
Incidence/prevalence	~15,000 people have ALS in the US, with an incidence rate of 2/100,000 and a prevalence rate of 5/100,000. Typically affects people between 40-60 years, higher proportion of male sufferers. ~50% of ALS patients die within 18 months and 80% within five years of diagnosis.
Current treatment	Riluzole (glutamate inhibitor). Cochrane Review (2005) of four clinical trials shows 2-3 months' survival benefit.
Market size	Currently small (~$200m) but with potential to grow to $1bn-$2bn with disease-modifying therapies.
Developmental symptomatic therapies	Neuroprotectant (dexpramiopexole, arimoclolomol). Protective against glutamate toxicity (ceftriaxone, mecobalamin). Free-radical scavenger (edaravone).

Source: Edison Investment Research

[7] The Phase III study of olesoxime failed in December 2011 and Actelion has decided not to exercise its option.

Exhibit 6: Pipeline candidates for amyotrophic lateral sclerosis (ALS)

Product	Company(s)	Target date	Notes
Dexpramipexole (KNS-760704 / BIIB050)	Biogen Idec / Knopp Neurosciences	Feb-13	Dopamine D3 agonist. 804-pt Phase III (EMPOWER) of 150mg bid vs placebo for <18 mths; recruitment complete and primary endpoint assessing joint rank of functional outcomes adjusted for mortality. 102-pt Phase II showed dependent trend in slowing rate of disease progression using ALS Functional Rating Scale-Revised (ALSFRS-R). FDA fast track status and orphan drug designation in US and EU.
Ceftriaxone	National Institute of Neurological Disorders & Stroke	Dec-12	Cephalosporin antibiotic (aimed at decreasing glutamate levels near nerves). 600-pt, 12-mth Phase III study, recruitment complete with survival and ALSFRS-R scores the primary endpoints.
MCI-186 (Radicut / edaravone)	Mitsubishi Tanabe Pharma	Mar-15	Free radical scavenger. 128-pt Phase III recruitment ongoing; IV admin o.d. with ALSFRS-R score the primary endpoint. Three Phase III studies completed; 140-pt, 36-week, 200-pt, 24-week and 20-pt in severe pts (no results published). Approved in Japan as a cerebral neuroprotectant for acute ischaemic stroke.
E0302 (Nabolin / mecobalamin)	Eisai	Mar-14	Vitamin B12. 360-pt Phase II/III recruitment complete; IM injection twice a week for 3.5 yrs, with survival and ALSFRS-R scores the primary endpoints. 300-pt long-term safety study to complete 2016. Approved in Japan for peripheral neuropathy.
Arimoclomol	University of Miami (Orphazyme)	Dec-12	Molecular chaperone activator. 80-pt Phase II/III trial in SOD1-positive familial ALS, recruitment complete and rate of decline in ALSFRS-R is the primary endpoint.
CK-2017357	Cytokinetics	-	Fast skeletal muscle troponin activator. Extensive Phase II programme successfully completed and discussions with EU and US regulators ongoing for pivotal programme. Dose titration (n=28) and multi-dose (n=50) studies showed encouraging trends in ALSFRS-R. US fast track / orphan drug status in EU.
sNN0029	NeuroNova (Newron)	Dec-13	VEGF165. 18-pt Phase I/II with intra-CSF dosing complete. 18-pt open-label safety/tolerability study ongoing. Jun12 Newron acquired NeuroNova for €15.4m.
NP-001	Neuraltus Pharmaceuticals	Oct-12	Macrophage activation regulator. 105-pt Phase II, two IV dose levels, recruitment complete.
NurOwn	BrainStorm Cell Therapeutics	Dec-12	Mesenchymal bone marrow stromal cell therapy. 24-pt Phase I/II, single centre study, recruitment ongoing.
HYNR-CS	Corestem	Jul-12	Bone marrow-derived stem cells. 71-pt Phase I/II, recruitment ongoing.
AEN-100	Synthetic Biologics	-	High-dose zinc. 10-pt Phase I/II completed Nov 2011. Plans underway for a PII (n=65) / PIII (n=114) study.
GSK1223249	GlaxoSmithKline	-	Anti-neurite outgrowth alpha (nogo-A) MAb. 76-pt Phase I completed Sep 2011.
NSI-566RSC	Neuralstem	Dec-12	Neural stem cells (spinal cord derived). 18-pt Phase I enrolling by invitation.
TCA-CT for ALS	TCA Cellular Therapy	-	Autologous bone marrow-derived stem cells. 6-pt Phase I, under partial clinical hold.
ISIS-SOD1Rx	Isis Pharmaceuticals	-	Superoxide dismutase (SOD1) RNAi therapeutic. 33-pt Phase I complete.

Source: Edison Investment Research, clinicaltrials.gov. Note: Target date refers to primary completion date on clinicaltrials.gov.

Preliminary ALS data positive

Phytopharm has reported positive preliminary data with Cogane in the SOD1 mouse model, which involves a mutation of the SOD1 gene (a known cause of ALS in humans) and is thus considered to be the gold-standard model of ALS. The trial included groups testing the administration of Cogane and riluzole (the only marketed product for ALS), as well as an untreated control. Among the key findings:

- In one muscle type, administering Cogane gave a 30-50% improvement in muscle strength vs the untreated group and vs riluzole alone. In a second muscle type, which was more severely damaged in the model, treatment effects were less clear, although the Cogane group showed a numerical improvement in strength vs riluzole.
- Administering Cogane resulted in an increase in the number of motor units (a measure of the number of functional motor neurons) vs the untreated and riluzole groups.

Cogane was previously shown to prevent motor impairment in an environmental mouse neurotoxin model of ALS, which provided useful initial validation of Phytopharm's strategy of targeting ALS with Cogane. Depending on the outcome of Confident-PD and subsequent partnering activities, a Phase II study of Cogane in ALS could be initiated by Phytopharm (subject to funding) or a future partner in 2013.

Glaucoma development on hold

Phytopharm had aimed to differentiate Cogane and Myogane by positioning the latter for ophthalmic indications. However, a pre-clinical study aimed to show Myogane's neuroprotective effect in an established animal model of glaucoma failed because insufficient neuronal cell death was induced in the treatment and control arms. The aim of the model is to raise intraocular pressure to induce neuronal cell loss in the retina (characteristic in glaucoma), and the endpoint was a comparative measurement of neuronal cell loss.

Phytopharm says it saw indications of a neuroprotective effect after Myogane treatment, but was unable to draw definitive conclusions because of the limited neurodegeneration in the control arm. Pharmacokinetic evaluation indicated that levels of Myogane in the plasma were broadly in line with that expected from previous studies and that Myogane was present in the retina. Previous in vitro studies demonstrated that Myogane is protective of retinal ganglion cells. Phytopharm is still analysing the data from this study, but in reality further development is on hold until the outcome of the Confident-PD study.

Valuation

Our risk-adjusted NPV for Cogane is £48m, derived from its potential development for Parkinson's disease, ALS and Alzheimer's. This compares favourably with Phytopharm's enterprise value of £8.7m (based on a reported cash balance of £13.3m as of 31 March 2012). We have removed Myogane (glaucoma) from our valuation model due to uncertainty over further development and have pushed back Cogane's potential launch date by one year to 2016 (our previous rNPV was £53m). We apply a 12.5% cost of capital, include a base cost of business and make various assumptions of development probabilities, launch date, market share and royalty rate – these are summarised in Exhibit 7.

Exhibit 7: Risk-adjusted NPV valuation parameters

Product	Indication	Status	Probability of success	Estimated launch year	Estimated peak market share	Current market value	Estimated peak sales	Estimated max royalty	Patent expiry
Cogane	Parkinson's	Phase II	25%	2016	10%	$4,500m	$790m	17%	2024
Cogane	ALS	Pre-Phase II	15%	2016	20%	$825m	$200m	17%	2027
Cogane	Alzheimer's	Phase II	15%	2016	3%	$7,400m	$635m	17%	2024

Source: Edison Investment Research

Over 50% of our valuation is currently assigned to Cogane's potential in Parkinson's. We estimate a total Parkinson's disease patient population across North America and Europe of 3.7m, of which around 30% are estimated to be less than four years from diagnosis, the early-to-mid stage setting that is Cogane's initial target. This indicates a potential patient population of 1.1m, of which we have assumed a 10% market share for Cogane, at a base annual price of $5,000. This is comparable with the annual treatment cost for Azilect, a drug also used as an early-stage therapy. Global Azilect sales in 2011 were $393m, and on current run rates and assuming generics do not enter the market, should exceed $500m in 2013. However, should Cogane succeed in becoming a disease-modifying therapy, a premium price should be achievable (potentially in excess of $10,000), which would significantly raise our peak sale and valuation estimates.

In ALS, we estimate a total patient population across North America and Europe of 55,000, and assume an orphan drug price of $15,000 per year and for Cogane to capture 20% of the market.

Given the binary nature of Phytopharm's investment case, it is worth highlighting the potential upside upon reporting positive, and unambiguous, results from Confident-PD and securing a big pharma partner to take over Phase III development and commercialisation duties.

Based on successfully meeting these key milestones, Cogane's probability of success would increase, such that our rNPV could rise to £83m (see Exhibit 8).

Exhibit 8: rNPV sensitivity analysis

	Base case scenario	Positive Phase II data	Securing Phase III partner	Start full Phase III programme
Cogane's probability of success in Parkinson's	25%	35%	45%	50%
Company valuation	£48m	£62m	£76m	£83m
Valuation per share	14p	18p	22p	24p

Source: Edison Investment Research

Sensitivities

The key sensitivity to the investment proposition for Phytopharm is the company's almost complete reliance on the Phase II study (Confident-PD) of Cogane and, if successful, its ability to secure an economically attractive licensing deal with a major pharmaceutical group. Aside from a complete failure to meet key efficacy and safety endpoints, there is a risk that Confident-PD produces ambiguous or contradictory results, which could hinder further development and/or licensing negotiations. Failure to secure a development partner for Cogane by the end of 2013 would force Phytopharm into seeking fresh finance, implying a likely dilution for current holders if raised through a new equity issue.

Although Cogane's mechanism of action, the stimulation of neuroprotective factors in GDNF and BDNF, may produce some significant long-term benefits, there is a risk that the six-month treatment duration in Confident-PD may not be long enough to observe the clinical efficacy required to meet the trial's endpoints. As for the discrepancy between the oral liquid formulation of Cogane used in Confident-PD and the requirement for a solid dosage form for Parkinson's, there is a risk that a potential partner may want to conduct further dose-ranging/pharmacokinetic studies with the solid dose formulation, prior to launching the pivotal trial programme, which would likely impact our current estimate for a Cogane launch in 2016.

Although Cogane has potential in both Parkinson's and ALS, and we have assumed differential pricing in the separate indications, in commercial reality this may not be achievable, even if the product is available in different dosages or formulations (solid dose for Parkinson's and oral liquid for ALS).

Development projects outside the ones specifically considered in the NPV model offer upside, such as Myogane in glaucoma. Phytopharm has a large single investor in the form of Invesco (56.4% holding) and the free-float across its 347m shares in issue is just 39%.

Financials

Phytopharm ended its six months to 31 March 2012 with a balance of cash and equivalents of £13.3m, and no debt. R&D expenses increased significantly to £4.8m (vs £3.6m in fiscal H111) due to the Confident-PD study. We have assumed the same R&D expense run rate for fiscal H212, indicating an annual R&D expense of £9.6m for the year-ended September 2012, which declines to £7.2m in fiscal 2013 with completion of the Confident-PD study. We expect annual SG&A expenses to remain flat at around £1.2m and therefore forecast net operating losses in fiscal 2012 and 2013 of £10.7m and £8.4m, respectively.

We estimate Phytopharm's cash balance at the end of September 2013 to be around £1.5m, which matches the company's guidance that current cash will last until the end of calendar 2013. As per Edison's standard policy, we do not include potential up-front payments under licensing deal(s) that have not yet been signed. Our financial model is summarised in Exhibit 9.

Edison investment research

Exhibit 9: Financial summary

Year end 30 September	£'000s	2009	2010	2011	2012e	2013e
Accounting basis		IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue		**867**	**697**	**67**	**17**	**0**
Cost of sales		(187)	(87)	0	0	0
Gross profit		681	609	67	17	0
Other income		245	17	0	66	0
Selling, general & administrative spending		(1,393)	(1,116)	(1,153)	(1,200)	(1,237)
R&D expenditure		(3,914)	(4,013)	(7,461)	(9,600)	(7,200)
Operating profit		**(4,381)**	**(4,503)**	**(8,547)**	**(10,717)**	**(8,437)**
Goodwill amortisation		0	(99)	0	0	0
Exceptionals		(406)	0	0	0	0
Stock option charge		148	(56)	(138)	(165)	(150)
EBITDA		**(4,021)**	**(4,280)**	**(8,360)**	**(10,532)**	**(8,267)**
Operating profit (before GW and except.)		(4,122)	(4,347)	(8,410)	(10,552)	(8,287)
Net interest		176	290	376	200	110
Profit before tax (norm)		**(3,946)**	**(4,057)**	**(8,034)**	**(10,352)**	**(8,177)**
Profit before tax (reported)		(4,205)	(4,213)	(8,171)	(10,517)	(8,327)
Tax		294	411	513	864	648
Profit after tax (norm)		**(3,652)**	**(3,646)**	**(7,521)**	**(9,488)**	**(7,529)**
Profit after tax (reported)		(3,911)	(3,802)	(7,658)	(9,653)	(7,679)
Average number of shares outstanding (m)		94.5	284.2	346.6	346.8	346.8
EPS - normalised (p)		(3.9)	(1.3)	(2.2)	(2.7)	(2.2)
EPS - reported (p)		(4.1)	(1.3)	(2.2)	(2.8)	(2.2)
Gross margin (%)		78.5%	87.5%	N/A	N/A	N/A
EBITDA margin (%)		N/A	N/A	N/A	N/A	N/A
Operating margin (before GW and except.) (%)		N/A	N/A	N/A	N/A	N/A
BALANCE SHEET						
Fixed assets		**202**	**113**	**84**	**79**	**69**
Intangible assets		99	0	0	0	0
Tangible assets		102	113	84	79	69
Investment in associates		0	0	0	0	0
Current assets		**4,682**	**24,500**	**18,514**	**8,677**	**2,578**
Stocks		249	0	0	0	0
Debtors		522	892	939	1,339	1,104
Cash		3,910	23,608	17,574	7,340	1,475
Current liabilities		**(1,741)**	**(1,123)**	**(2,595)**	**(2,984)**	**(1,527)**
Creditors		(1,747)	(1,135)	(2,633)	(3,023)	(1,566)
Short-term borrowings		0	0	0	0	0
Long-term liabilities		**0**	**0**	**0**	**0**	**0**
Long-term borrowings		0	0	0	0	0
Other long-term liabilities		0	0	0	0	0
Net Assets		**3,143**	**23,490**	**16,002**	**5,772**	**1,120**
CASH FLOW						
Operating cash flow		**(3,599)**	**(4,637)**	**(6,869)**	**(10,933)**	**(6,829)**
Net interest		176	127	380	200	110
Tax		199	295	445	513	864
Capex		(8)	(74)	4	(15)	(10)
Acquisitions/disposals		0	0	0	0	0
Financing		35	23,986	6	0	0
Dividends		0	0	0	0	0
Net cash flow		(3,197)	19,697	(6,034)	(10,237)	(5,865)
Opening net debt/(cash)		**(7,107)**	**(3,910)**	**(23,608)**	**(17,574)**	**(7,340)**
Other		0	0	0	0	0
Closing net debt/(cash)		**(3,910)**	**(23,608)**	**(17,574)**	**(7,340)**	**(1,475)**

Source: Edison Investment Research, company reports

Contact details	Revenue by geography
2 Lakeview Court, Ermine Business Park, Huntingdon, PE29 6UA, UK +44 (0)1480 437697 www.phytopharm.com	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS CAGR 2009-13	N/A	ROCE 2012e	N/A	Gearing 2012e	N/A	Litigation/regulatory	●
EPS CAGR 2011-13	N/A	Avg ROCE 2009-13	N/A	Interest cover 2012e	52.8	Pensions	○
EBITDA CAGR 2009-13	N/A	ROE 2012e	N/A	CA/CL 2012e	N/A	Currency	○
EBITDA CAGR 2011-13	N/A	Gross margin 2012e	N/A	Stock turn 2012e	N/A	Stock overhang	○
Sales CAGR 2009-13	N/A	Operating margin 2012e	N/A	Debtor days 2012e	N/A	Interest rates	○
Sales CAGR 2011-13	N/A	Gross mgn/Op mgn	N/A	Creditor days 2012e	N/A	Oil/commodity prices	○

Management team

CEO: Tim Sharpington

Appointed June 2010. Previously founder/CEO of Serentis (2006-2010), development director at Arakis (2002-06), VP European operations at ICON, and director of clinical operations at Sequus (now part of J&J).

R&D Director: Roger Hickling

Appointed January 2010. Previously director of R&D at Alizyme (2002-09, initially as head of development operations, and subsequently as director of R&D, 2006-09). He had previously spent 22 years at SmithKline Beecham in various R&D roles.

Chairman (non-exec): Alistair Taylor

Appointed June 2007. Formerly executive chairman of Lombard Medical Technologies (2000-07) and CEO of Biocompatibles International (1994-98). Has extensive management experience in the healthcare/medical device industry. Also non-executive director of Vascular Concepts.

Principal shareholders	(%)
Invesco Perpetual	56.4
Henderson Investment	11.02
Mr Klaus Hebben	4.28

Companies named in this report

Merck & Co, UCB, Biotie Therapies, Ceregene, MedGenesis Therapeutix, Oxford BioMedica, Newron Pharmaceuticals, Cytokinetics, Biogen Idec