Edison investment research

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Phynova

Year End	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	PE (x)	Yield (%)
09/06	0.0	(1.6)	(13.6)	0.0	N/A	N/A
09/07	0.0	(2.9)	(14.9)	0.0	N/A	N/A
09/08e	0.0	(2.5)	(10.9)	0.0	N/A	N/A
09/09e	0.0	(4.6)	(19.0)	0.0	N/A	N/A

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

Investment Summary: Chinese expansion

After a management change, Phynova is to focus on commercialising its lead pipeline products while expanding its Chinese business. The company seeks to develop drugs derived from Chinese medicinal plants, a strategy that could offer advantages over NCEs, as well as developing single-molecule drugs derived from plant sources. The investment case rests on it obtaining additional funds, possibly through a licensing deal, to commercialise its lead project, PYN17.

Management reshuffle

Phynova has appointed a new executive chairman (John Pool) and CEO of its UK division (Dr Tony Mills), while its former CEO, Robert Miller, is now to head up operations in China. Merger and acquisition opportunities exist for Phynova, which already has a 45% stake in Botanic Century China Ltd (BCCL), a private drug R&D company.

Funding needed

Nevertheless, Phynova has a funding requirement to continue operations beyond January 2009, and management says a number of fund-raising possibilities are being investigated. In the meantime, we expect cash to be conserved and operating costs cut to a minimum.

Lead product development

Last year, PYN17 completed a multicentre Phase I/II study in 40 hepatitis C patients, and a Phase II proof-of-concept trial is planned. However, we do not expect Phynova to start this before it has either raised more cash or signed up a licensing partner prepared to fund most or all of late-stage development in return for milestone payments and royalties on future sales.

Valuation

Phynova's enterprise value of around £5m represents a significant opportunity if PYN17 can be licensed to a significant pharma partner. We had previously valued Phynova at around £45m, but we intend to carry out a detailed valuation of the company as part of an upcoming full initiation of coverage.

Phynova is a research client of Edison Investment Research Limited

Price	26p
Market Cap	£6m

Share price graph

Share details

Code	PYN
Listing	AIM
Sector	Pharmaceuticals and Biotechnology
Shares in issue	22.6m

Price

52 week	High	Low
	38.75p	14.75p

Balance Sheet as at 31 March 2008

Debt/equity (%)	N/A
NAV per share (p)	2.1
Net cash (£m)	0.5

Business

Phynova is a UK-based firm specialising in the development of prescription-only botanical drugs principally derived from the plants used in traditional Chinese medicines.

Valuation

	2007	2008e	2009e
P/E relative	N/A	N/A	N/A
P/CF	N/A	N/A	N/A
EV/sales	N/A	N/A	N/A
ROE	N/A	N/A	N/A

Revenues by geography

UK	Europe	US	Other
0%	0%	0%	0%

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Company description: Developer of botanical drugs

Phynova is a UK-based firm specialising in the development of prescription-only botanical drugs, as defined by relatively recent US FDA guidance. Its products are principally derived from Chinese medicinal plants, and include single-molecule agents derived from plant sources. Its strategy is to develop such drugs with supporting safety and efficacy data and to target conditions that are poorly served by Western medicine.

It expects these products to be treated as pharmaceuticals and will have to meet the same (or similar) standards of efficacy, safety and quality as new chemical entities. However, the existence of clinical data from the outset of each programme should mean that there is a better than average chance of success.

Strategic refocusing

Following a business review, Phynova's focus has been set on commercialising its lead pipeline products, presumably through licensing/development partners, and expanding its Chinese business through the licensing in of additional Chinese botanical-derived drug candidates as well as potential merger and acquisition activity. Phynova already holds a 45% equity stake in the private venture Botanic Century China, and has an option to increase this to over 50%.

Nevertheless, Phynova has a funding requirement to continue operating beyond January 2009, and in the meantime we expect it to run at minimal cost, conserving cash and trimming back non-essential activities, including some R&D. Phynova is investigating fund-raising possibilities to meet its medium-term development needs as well as possibly to fund acquisitions in China. Significant interest is understood to have been received from potential Chinese investors, and this could be resumed as part of future fund-raising activities.

Management reshuffle

Following Phynova's business review, its management team and directors have been changed, altering the roles of several individuals. The new management team is as follows (directors in bold):

Executive chairman: **John Pool** (formerly a non-executive director).

CEO of Phynova's UK division: **Dr Tony Mills** (formerly director of business development) is to lead efforts to commercialise Phynova's pipeline, most significantly PYN17.

CEO of Phynova China: **Robert Miller** (formerly CEO of Phynova) will head up operations in China, including managing Phynova's interest in Botanic Century China, and seeking new business there.

Chief financial officer: **Michael Martin** (formerly a non-executive director).

Non-executive directors: **Steve Harris** and **Dr Jin Li**. Joined in September 2008, replacing Karl Watkin (formerly chairman), Bill Doyle (formerly non-executive director) and Steve Marshall (formerly chief operating officer).

Chief scientific officer: Edward Blair (no longer a board member).

Finance director: Alan Brown (no longer a board member; reports to Michael Martin).

Prescription-only botanical drugs

Phynova specialises in the development of prescription-only botanical drugs (highly purified single and multiple plant fractions), which are principally derived from Chinese medicinal plants. The advantages of this approach versus the discovery of new chemical entities is that such botanicals have an existing record of extensive previous human use, along with efficacy and safety data.

In our view the near-term investment case for Phynova centres on the success of PYN17, its most advanced (and potentially most lucrative) R&D asset, which is being developed for hepatitis C (HCV) symptoms. A summary of Phynova's R&D pipeline is presented in Exhibit 1.

Key points:

- Phynova has a small head office in Oxfordshire in the UK, and has a presence in China through a 45%-owned affiliate, Botanic Century China Ltd, a private, plant-based drug development firm based in Beijing.
- Phynova also has a collaboration with the Hong Kong Jockey Club Institute of Chinese Medicine to screen for novel drugs for the treatment of cancer.
- Phynova has a number of Chinese national scientists who are skilled at interpretation of traditional Chinese medicine (TCM) in the context of the western approach to medicine.

Exhibit 1: Phynova's R&D pipeline

Note: *Botanic Century compound.

Product	Indication	Development stage/notes
PYN17	Liver inflammation as a result of chronic HCV infection.	Four-week, placebo-controlled Phase I/II study in 39 patients demonstrated safety and tolerability of PYN17, with levels of minor adverse events identical to that seen with placebo. Plans for a Phase II proof-of-concept study in 200 patients depend on securing additional funding.
PYN22	Obesity/fatty liver disease (non-alcoholic steatohepatitis).	A single-plant extract. *In vitro* studies in China and UK show lowering of expression of genes associated with obesity and fatty liver disease. Phase I/II trial is in preparation for H208.
PYN9	Post-operative ileus.	In development as a rectal suppository by BCCL, which has filed an IND to begin clinical studies in China. Clinical development expected to take two years. Phynova looking at developing PYN9 in markets outside China.
PYN6	Antibiotic-resistant bacterial infections/ acne.	Under option from BCCL. Activity against major classes of antibiotic-resistant strains of bacteria (including MRSA) and against *Propionobacterium acnes* established in *in vitro* models. Potential for topical use for acne. Phynova planning formulation studies.
PYN18	Treatment of HCV infection and dengue fever infection.	A single-plant extract. Anti-HCV activity established in industry-standard *in vitro* models. Collaborators at the Sirriraj Hospital in Bangkok have confirmed activity against the dengue virus.
PYN7	Solid tumours.	Series of molecules isolated from active fractions of a plant used in China. *In vitro* studies show activity against melanoma and oesophageal and lung cancer cell lines. Phynova is collaborating with the Institute of Cancer Studies at the University of Birmingham for further preclinical development. Mechanism of action studies and lead selection possible in 2008.
BCL-5*	Type 2 (adult onset) diabetes.	Preclinical development.

Source: Edison Investment Research

Licensing out after proof of principle

Phynova intends to license its drug candidates to pharmaceutical companies; it previously intended to do this after achieving clinical proof of principle, thus retaining a relatively high economic interest in projects. Given its funding requirement, we expect the company to consider a wider range of licensing agreements, including deals at a relatively early stage of product development.

Phynova expects to achieve an economic return in the form of up-front payments, development milestones and royalties on sales, and would expect any partners to complete the development of projects, apply for regulatory approvals and assume responsibility for sales, marketing and distribution of the drugs. However, Phynova has not yet concluded any such agreements with companies outside China. Phynova hopes to be able to take advantage of the US FDA's 2004 "Guidance for Industry – Botanical Drug Products" and, where possible, to seek approval of its drug candidates through the fast-track procedure.

PYN17

Phynova's near-term investment case is built around PYN17, a polymolecular botanical drug formulation based on highly purified extracts of four plants (Astragalus, Silymarin, Salvia and Schisandrin) that individually have been used to treat liver diseases in Asia and Europe. It is made by third parties, using pharmaceutical-grade raw material sourced from two manufacturers.

PYN17 may have potential as a treatment for inflammatory liver disease as a result of metabolic disorders, fatty diet or excessive alcohol intake. There are no drug treatments specifically for treating the symptoms associated with chronic hepatitis C infection (such as fatigue, muscle aches, anorexia and abdominal pain) and relatively few potentially competing therapies in development. Exhibit 2 lists therapies currently in development for the treatment of HCV symptomatology.

Exhibit 2: Developmental therapies for HCV symptoms

Company	Product	Development stage/notes
Intercept Pharmaceuticals	INT-747	Phase II for primary biliary cirrhosis and NASH.
ENZO Biochem	EGS-21	Phase II trial started in 2006 for NASH/fatty liver disease.
PYN17	Phynova	Phase I/II trial completed Nov 2007 for HCV symptoms; Phase II planned.
LG Life Sciences/Gilead	LB-84451	Phase IIa studies under way for HCV symptoms and NASH, with completion expected by the end of 2008.
Protemix	PX-811013 (glyponectin)	Preclinical. *In vitro* studies suggest reversal of alcohol-mediated and non-alcoholic liver disease.
Trophos	TRO-19622	Phase II trial in NASH patients in France.
Sucampo Pharmaceuticals	SPI-8811 (cobiprostone)	In a US Phase II trial in 30 patients with liver cirrhosis for the treatment of portal hypertension. The trial will assess safety, efficacy, change in hepatic venous pressure gradient after 28-days of treatment (primary endpoint), acute changes in HVPG, markers of liver disease and patient-reported quality-of-life measures (secondary endpoints).
Bennu Pharmaceuticals	ER Cysteamine	Enteric-coated, delayed-release formulation of cysteamine bitartrate in Phase IIa for NASH.

Source: Edison Investment Research

PYN17 has completed a one-month Phase I/II trial for the relief of inflammation and other symptoms suffered by patients with chronic hepatitis C infection, but full results of this have yet to be reported. Preliminary data showed no serious adverse events; 11/26 (42.3%) patients on PYN17 reported adverse events of some kind during treatment against 10/13 (76.9%) in the placebo group. For drug-related adverse events, the incidence was 6/26 (23.1%) on PYN17 compared with 3/13 (23.1%) on placebo. The trial is intended to provide support for a move into a three-month Phase II study, although this is dependent on additional financing, either through a fund-raising or a partnership.

The randomised, double-blind, placebo-controlled study was conducted at five centres in the US and evaluated safety and efficacy in 39 patients with chronic HCV infection, for whom approved treatments (such as pegylated interferon and ribavirin) had failed or were not appropriate. Patients were dosed for one month and symptoms monitored using quality-of-life scores and liver function tests to evaluate response and alleviation of disease symptoms.

An earlier, UK, 6-month, double-blind, placebo-controlled Phase II study in chronic hepatitis C patients refractory to (or unwilling/unable to take) interferon/ribavirin showed a downward trend in serum transaminase levels. In the SF-36 questionnaire, the vitality score improvement seen after PYN17 treatment was above that regarded as being clinically important.

Hepatitis C

Hepatitis C is a blood-borne disease caused by the hepatitis C virus. Infection with HCV is seen in a wide variety of people, including drug users, the recipients of unscreened blood, babies of HCV-infected mothers and patients who have undergone medical treatment abroad, although many are unaware that they have the disease.

More than 170m people worldwide are thought to be infected with HCV, with many more yet to be diagnosed (as many as 3-4m new cases per year are thought likely), and current treatments have severe drawbacks. The vast majority of infected patients are in the developing world, with around 32m infected people in Africa vs the 2.7m prevalence seen in the US. There is strong pharmaceutical industry interest in this competitive market.

The current treatment for HCV infection is a 24- to 48-week course of pegylated interferon (peg-IFN) and ribavirin. This treatment has significant side-effects (flu-like symptoms, suicidal ideation etc) and a poor sustained viral response rate in patients infected with genotype 1 HCV.

Around 70% of patients with HCV develop a chronic infection. HCV infection is associated with significant impairment in quality of life, including fatigue and pain and reduced mental health; many patients are unable to work. In the longer term, many develop cirrhosis (irreversible fibrosis of the liver), of which 3-8% are at risk of hepatic cancer, and 1-2% go on to develop liver failure. Each year, liver transplantation – a major healthcare cost – is needed in up to 10% of HCV patients, many of whom became infected decades ago; as this effect takes years to become apparent it looks set to be a drain on future healthcare spending.

Botanic Century deal

Phynova has in place a key long-term alliance with Botanic Century China Ltd, a private Chinese drug development company (focused on products from botanical sources) and contract research organisation. Under a deal signed in October 2006, Phynova acquired a 45% stake in Botanic Century for £531k (£465k in cash and the rest in Phynova stock), and this stake is held, for legal and commercial reasons, by Phynova China, a 100%-owned subsidiary based in Hong Kong that is the vehicle for Phynova's activities in China.

BCCL has therefore in effect become the vehicle for Phynova's R&D activities, in order to benefit from the company's experience in botanical drug development and its low-cost base. Phynova additionally has a current option to increase its holding in BCCL to a 51% stake.

The deal with BCCL gave Phynova rights to PYN9, a preclinical candidate for the treatment of post-operative ileus, and the option (which Phynova exercised) to license PYN6, BCCL's anti-bacterial drug candidate for the Western markets. Meanwhile, BCCL has licensed rights to Phynova's PYN18 for the treatment of hepatitis C virus for the Chinese market. The incidence of hepatitis C in China is among the highest in the world. The agreements provide Phynova with access to one of the world's fastest-growing pharmaceutical markets. According to IMS Health, pharmaceutical sales in China grew by 20% to $11.7bn in 2005 and China will become the world's seventh largest market by 2009. Other industry sources estimate the market size to be higher (using a broader definition of pharmaceuticals) and have put the figure at $32bn, rising to $70bn by 2010, by which time China would rank as the fifth largest market worldwide.

Plant-based medicines

Throughout history plants have been a key source of pharmacologically active compounds and were the prime source for the pharmaceutical industry up to the 1970s. Many of the pharmaceutical industry's top-selling drugs at various times have been derived from plants. Well-known plant-derived drugs include aspirin/ASA, first obtained from the bark of the willow tree; digoxin, a drug used to treat angina, derived from foxglove; artemether, an anti-malarial derived from the Chinese medicinal herb Artemesia; and morphine, derived from the opium poppy. Many anticancer drugs have been originally derived from plants, including irinotecan and topotecan, which were found in the bark of the Chinese *Camptotheca acuminate* tree; paclitaxel was originally derived from the bark of the Pacific yew tree; etoposide and teniposide, from the Mayapple plant family; and vincristine and vinblastine, from the rosy periwinkle.

Traditional Chinese medicine is one of a number of indigenous medical practices used in Asia, but it has a very long history (dating more than 2,000 years) and much of the practice has been well documented. There is also a high level of interest and state sponsorship of clinical research into this in China. Over 7,000 plants are used in the TCM pharmacopoeia, the text containing directions for the identification of samples and the preparation of compound medicines. There are also a number of areas where medicines are used in China in circumstances where there is an unmet need in the West.

US FDA botanicals guidance

It has often proved difficult to identify a single active agent (and to synthesise that agent) from botanical extracts. This is presumed to be because botanical extracts contain multiple pharmaceutical actives that contribute to the overall clinical effect. However, with the publication of the FDA guidance on botanical drugs (Guidance for Industry – Botanical Drug Products) in 2004 there has been a resurgence of interest.

The guidance puts the regulatory path for botanical products on a par with synthetics and biologicals; the first product to follow the new guidance has now been launched – Polyphenon E (Veregen), a topical ointment for the treatment of genital warts, developed by Epitome Pharmaceuticals/Medigene. The active substance in Polyphenon E is a green tea extract with a defined catechin composition.

There are believed to have been more than 240 botanical pre-IND enquiries made to the US FDA, and as of 1 June 2005 there were 192 INDs approved for botanical drugs, of which 128 were active (the remaining 64 are inactive, withdrawn, subject to a clinical hold or terminated).

Sensitivities

Phynova's business and strategy have a number of specific risk factors, including the following:

- The company's funding requirement to operate beyond January 2009 represents a key risk, especially given current market conditions and the company's share price. Phynova might not have sufficient funds to make meaningful progress in its R&D programmes to sign licensing deals on an attractive basis and may have to undertake additional share issues before it reaches breakeven.
- The regulatory regime, particularly in the US, for botanical pharmaceuticals is new and largely untested, notwithstanding the fact that the US FDA now has in place a formal registration regime for botanicals (Guidance for Industry Botanical Drug Products, issued by the CDER), making the approval pathway clearer.
- The ability to obtain robust intellectual property protection is unproven.
- Management might not be able to license its development products to partners on favourable terms, particularly as a result of the uncertainty with medical professionals over the commercial attractiveness of botanical pharmaceuticals.
- Phynova has a high degree of reliance on Chinese counterparties and might not be able to enforce its contracts or obtain remedies for breach of contract.
- No institutions hold substantial shareholdings (ie, above 3%).

Financials

Phynova raised £1.2m before expenses in a placing with current investors in April 2008. Its most recently reported financial results relate to the fiscal six months ended 31 March 2008, and these showed a net loss of £1.2m (£1.3m a year earlier) and a cash balance of £501k (this excluded the proceeds of the fund-raising).

Following its restructuring, Phynova committed to funding its current operations until the end of January 2009, but said it would need additional cash to continue beyond then. In the meantime we expect the company to run at minimal cost, conserving cash and trimming back non-essential activities, including some R&D. Our financial model, presented in Exhibit 3, illustrates the additional funding requirement for the remainder of 2009 as an increase in long-term debt.

Exhibit 3: Financials

£'000s	2006	2007	2008e	2009e
Year end 30 September				
PROFIT & LOSS				
Revenue	0	0	0	0
Cost of sales	0	0	0	0
Gross profit	0	0	0	0
EBITDA	(1,661)	(2,917)	(2,484)	(4,450)
Operating profit (before GW and except.)	(1,664)	(2,924)	(2,492)	(4,460)
Goodwill amortisation	0	0	0	0
Exceptionals	0	0	0	0
Share-based payments	0	(47)	0	(40)
Operating profit	(1,664)	(2,971)	(2,492)	(4,500)
Net interest	23	84	38	(100)
Profit before tax (norm)	(1,640)	(2,899)	(2,474)	(4,590)
Profit before tax (FRS 3)	(1,640)	(2,946)	(2,474)	(4,630)
Tax	0	93	170	300
Profit after tax (norm)	(1,640)	(2,806)	(2,304)	(4,290)
Profit after tax (FRS3)	(1,640)	(2,853)	(2,304)	(4,330)
Average number of shares outstanding (m)	12.0	18.9	21.1	22.6
EPS - normalised (p)	(13.6)	(14.9)	(10.9)	(19.0)
EPS - FRS 3 (p)	(13.6)	(15.1)	(10.9)	(19.2)
BALANCE SHEET				
Fixed assets	8	548	582	587
Intangible assets	0	0	0	0
Tangible assets	8	16	23	28
Investment in associates	0	531	559	559
Current assets	2,232	1,845	664	629
Stocks	0	0	0	0
Debtors	254	419	300	450
Cash	1,978	1,427	364	179
Other	0	0	0	0
Current liabilities	(207)	(375)	(168)	(238)
Creditors	(207)	(375)	(168)	(238)
Short-term borrowings	0	0	0	0
Long-term liabilities	(371)	(343)	(343)	(4,343)
Long-term borrowings	0	0	0	(4,000)
Other long-term liabilities	(371)	(343)	(343)	(343)
Net assets	1,662	1,675	735	(3,365)
CASH FLOW				
Operating cash flow	(1,586)	(2,847)	(2,396)	(4,370)
Net interest	23	84	38	(100)
Tax	0	0	170	300
Capex	(8)	(16)	(15)	(15)
Acquisitions/disposals	0	(593)	0	0
Financing	3,520	2,821	1,140	0
Dividends	0	0	0	0
Other	0	0	0	0
Net cash flow	1,949	(551)	(1,063)	(4,185)
Opening net debt/(cash)	(29)	(1,978)	(1,427)	(364)
HP finance leases initiated	0	0	0	0
Other	0	0	0	0
Closing net debt/(cash)	(1,978)	(1,427)	(364)	3,821

Source: Edison Investment Research