Medigene

Seeking RhuDex proof-of-concept

Edison investment research

Nice niche for RhuDex

Pharma & biotech

Medigene's selection of primary biliary cirrhosis (PBC) as a niche indication to determine RhuDex's proof-of-concept could prove to be a shrewd move. While rheumatoid arthritis remains RhuDex's main target in the long run, conducting a Phase II study in PBC presents a market opportunity in itself and offers a reduced timeframe to generate clinical data by end-2013 to influence future development and/or partnering decisions. We raise our valuation by €15m to €96m.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/10	2.3	(17.2)	(0.47)	0.0	N/A	N/A
12/11	4.7	(15.5)	(0.26)	0.0	N/A	N/A
12/12e	6.7	(10.3)	(0.28)	0.0	N/A	N/A
12/13e	8.0	(11.1)	(0.30)	0.0	N/A	N/A

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

Phase II to start by year-end

PBC, an autoimmune disorder of the liver, has been selected primarily because it will allow Medigene to generate clinical data on clearly defined endpoints within just three months of treatment. Efficacy and safety outcomes from the trial should also be 'clean' as PBC patients do not normally receive other immunomodulatory drugs. Assuming the trial starts by year-end we estimate headline data will be available by the end of 2013, allowing Medigene time to assess next best steps before existing cash starts to run low in H214, according to our estimates.

PBC offers unique opportunity

Aside from generating the required proof-of-concept data for RhuDex, PBC offers an orphan drug indication that could be attractive to potential partners or to Medigene as a viable go-it-alone opportunity. We estimate the potential global PBC market at $800m, with limited, symptomatic treatments available and a thin pipeline.

Successful RapidFACT study

The RapidFACT formulation study in 10 healthy volunteers was successfully completed. An optimised oral capsule formulation of RhuDex has been identified and is based on gelucire, a commonly used excipient in many marketed drugs, such as bisphosphonates (risedronate). This positive outcome, coupled with Medigene's recent €14.1m monetisation of Eligard 2% EU royalties, paves the way for the proof-of-concept trial in PBC.

Valuation: Increased by €15m to €96m

We increase our valuation of Medigene by €15m to €96m, which now includes the PBC opportunity for RhuDex. This includes our net cash estimate of €26m at end of June 2012 and shows clear upside to the company's €40m market capitalisation. We have increased our R&D expense estimates for 2012 and 2013, to €8.0m and €8.8m respectively, such that Medigene is likely to have a funding requirement in H214.

Medigene is a research client of Edison Investment Research Limited

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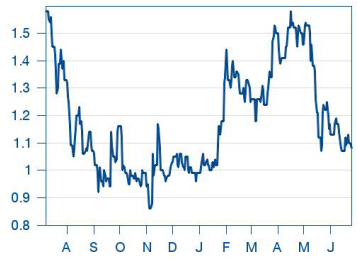
Price	€1.08
Market cap	€40m

Shares in issue	37.1m
Free float	94%
Code	MDG
Primary exchange	Frankfurt Prime Standard
Other exchanges	Xetra

Share price performance



%	1m	3m	12m
Abs	(11.4)	(19.2)	(35.9)
Rel (local)	(8.4)	(7.8)	(25.5)
52-week high/low	€1.65		€0.86

Business description

Medigene is a German biotech company with a focus on cancer and autoimmune diseases. It has brought two products to the market - Eligard for treating prostate cancer and Veregen for genital warts - and research efforts are currently focused on anti-rheumatic agent RhuDex.

Next events

Start RhuDex Phase II in PBC	Q412
H112 results	3 August 12

Analysts

Christian Glennie +44(0)20 3077 5727

Robin Davison +44(0)20 3077 5737

healthcare@edisoninvestmentresearch.co.uk

Edison profile page

Update: PBC for PoC with RhuDex

RhuDex is a small-molecule CD80 inhibitor, under development as an orally available disease-modifying anti-rheumatic agent (DMARD). Although its biggest commercial potential clearly lies in the rheumatoid arthritis (RA) setting – a Phase IIa trial in 2008 in 29 RA patients showed signs of activity – Medigene has opted for the primary biliary cirrhosis (PBC) setting in which to try and generate the first proof-of-concept (PoC) data for RhuDex. We believe this could prove to be a shrewd move, not only in terms of the short clinical timelines involved, but also from the potential market opportunity in PBC.

Orphan drug indication

PBC is an autoimmune disease of the liver, a chronic disorder in which the bile ducts are progressively destroyed by inflammatory processes. Excess bile causes liver tissue damage, which leads to fibrosis and cirrhosis of the liver. The activation of T-cells – via a CD28-CD80 interaction between antigen-presenting cells and T-cells, the process specifically inhibited by RhuDex – is thought to be involved in the pathogenesis of PBC.

PBC affects an estimated 200,000 people, across the developed countries of North America, Europe and Japan. Diagnosis is relatively straightforward and well-defined, but few treatment options exist and those that are available are more symptomatic in nature. A summary of PBC is displayed in Exhibit 1.

Exhibit 1: Primary biliary cirrhosis (PBC)

What is primary biliary cirrhosis (PBC)?	PBC is an autoimmune disease of the liver, a chronic disorder in which the bile ducts are progressively destroyed by inflammatory processes. As the flow of bile becomes restricted or blocked, liver tissue is gradually destroyed and replaced by connective tissue, causing scarring, fibrosis and cirrhosis.
What causes PBC?	The precise cause of PBC is unknown but evidence suggests it is autoimmune in origin. The disorder is associated with: elevated serum levels of immunoglobulins (mainly IgM), multiple circulating autoantibodies (particularly anti-mitochondrial antibodies – AMAs), granulomas in the liver and regional lymph nodes, and impaired regulation of B and T lymphocytes.
What are the symptoms?	Early stage PBC is characterised by chronic fatigue, itchy skin (pruritus) and dry eyes/mouth. Advanced PBC from more serious liver damage results in jaundice, fluid retention (oedema/ascites), hepatomegaly and splenomegaly.
How is PBC diagnosed?	Blood tests to detect elevated levels of anti-mitochondrial antibodies (AMAs), bilirubin and liver function tests for gamma-glutamyl transferase/alkaline phosphatase. Abdominal ultrasound or CT scan performed to determine blockage of bile ducts and ultimately a liver biopsy to determine the stage of disease and extent of liver damage.
Who suffers the most?	PBC mainly affects women (90% of all cases) and usually occurs in people aged 30-65 years. Genetics is thought to be a factor, so a family history of PBC increases the risk.
How widespread is PBC?	Prevalence estimates vary. Of the few epidemiology studies conducted, a prevalence rate of 15-25 per 100,000 is indicated, equating to 150,000-250,000 sufferers in developed countries. Reported prevalence rates are slightly higher in the UK and Scandinavia.
How is PBC treated?	No known curative therapy and current treatments are symptomatic in nature: **Ursodeoxycholic acid** (UDCA) is widely used, with evidence it helps to prevent liver damage by reducing levels of bilirubin, liver enzymes and the need for a liver transplant. **Cholestyramine** can be used to relieve the severe itching caused by increased bile acids in circulation. **Provigil** (modafinil) is sometimes used to treat the chronic fatigue associated with PBC. **Liver transplant** may ultimately be required in cases of severe liver damage which threatens life expectancy.

Source: Edison Investment Research

A disease-modifying agent for PBC would be of huge benefit to patients, which presents RhuDex with an attractive opportunity. Taking the mid-prevalence range of 20 cases of PBC per 100,000, across the almost 1bn population in developed countries, equates to approximately 200,000 sufferers from PBC.

With the most widely used treatment, ursodeoxycholic acid (UDCA), costing $2,500 annually[1], prior to patent expiry, and the higher price potential for drugs offering disease-modifying potential, we assume a potential annual cost for RhuDex in PBC at $4,000. However, we note that developing RhuDex purely for PBC could attract a significantly higher orphan drug price point (c $10,000-30,000), which is probably closer to the target price range for the two antibodies in development (NI-0801 and ustekinumab). At an annual cost of $4,000, the global market opportunity for PBC could be worth $800m. Given RhuDex's novel mode of action and limited pipeline competition, we estimate the drug could capture a 20% share of the market.

The listed therapeutic agents in active clinical development for PBC, according to clinicaltrials.gov, are shown in Exhibit 2.

Exhibit 2: Pipeline of treatment candidates for PBC

Product	Company	Status	Target date*	Notes
Obeticholic acid (INT-747)	Intercept Pharmaceuticals	Phase III	Jan-14	FXR agonist. 180-pt Phase III, with ursodeoxycholic acid (UDCA) or placebo, started Jan 12 and results expected in 2014. Primary endpoints targets significant reductions in alkaline phosphatase (AP) and total bilirubin levels. 2x Phase II (n=59 / n=165) studies produced significant reductions (40% and 20%) reductions in AP and substantial reductions in gamma-glutamyl transferase (GGT).
Budesonide	Dr. Falk Pharma	Phase III	Dec-13	Corticosteroid. 183-pt Phase III started in 2009 and ongoing with budesonide added to UDCA to decrease the number of patients with treatment failure after three years.
NI-0801	NovImmune	Phase II	Aug-12	Anti-CXCL10 MAb (targets neutralising the CXCL10/Interferon-gamma-inducible protein-10 (IP-10) chemokine). Phase II PIANO study started September 2011. Data available in Q312.
Ustekinumab (Stelara)	Johnson & Johnson	Phase II	Oct-13	Anti-IL-12 & IL-23 MAb. 128-pt Phase II initiated August 2011 and ongoing in patients with inadequate response to UDCA. Approved US and EU for plaque psoriasis.

Source: Edison Investment Research, clinicaltrials.gov (* target date refers to primary completion date)

Intercept Pharmaceuticals' obeticholic acid (a modified version of bile acid chenodeoxycholic acid – CDCA) is most advanced, currently undergoing a Phase III trial that completes in 2014. The drug is primarily targeting significant reductions in alkaline phosphatase (AP) and bilirubin levels.

The antibodies in development by NovImmune (NI-0801) and Johnson & Johnson (ustekinumab) likely represent the most direct potential competition to RhuDex, as agents that offer disease-modifying potential. Both candidates are being tested in patients with inadequate response to UDCA, with reductions in AP the primary outcome measures. Imminent results from the Phase II study with NI-0801 should provide insight into its potential and the validity of its specific target.

PoC trial – short and sweet

The size and scope of these ongoing trials, with clearly defined endpoints such as reductions in AP enzyme and bilirubin, offer insight into the potential design of Medigene's Phase II study with RhuDex. The company has not yet provided any specifics on the trial, but expects the endpoints to be clearly defined and easily measured such that a disease modification effect should be determined after just three months of treatment. The fact that most PBC patients are not receiving immunomodulatory drugs, such as methotrexate, is important as it should allow the study to prove that RhuDex does not impair the body's natural ability to mount a spontaneous inflammatory reaction. In contrast, a similar PoC trial in RA would require at least six months of treatment and underlying use of methotrexate in RA patients could cloud any assessment of RhuDex's safety profile.

1 Pasha T, et al. Cost-effectiveness of ursodeoxycholic acid therapy in primary biliary cirrhosis. Hepatology. 1999 Jan;29 (1): 21-6.

Assuming the trial, which we estimate will enrol 50-100 PBC patients, starts by the end of 2012, headline results should be available towards the end of 2013.

Assuming a positive outcome – clean safety profile and encouraging efficacy signal – Medigene could seek a partner or possibly go it alone with further development in PBC.

Securing a partner for RA, and other larger indications such as Crohn's disease, while retaining rights in niche indications such as PBC, could be an ideal situation, although a major pharma company may prefer to take full rights to the programme. Medigene remains flexible on its development strategy for RhuDex but has stated it "intends to outlicense RhuDex once proof of concept has been established, if not earlier".

Importantly, the recent €14.1m cash injection from transferring Eligard 2% EU royalties to Cowen Royalty provides Medigene with the flexibility and breathing space to secure the best terms possible for RhuDex, assuming the Phase II study is positive.

Valuation and sensitivities

We have added the PBC opportunity for RhuDex to our valuation model, and following successful completion of the RapidFACT study, which has produced a clinically and commercially viable oral capsule formulation, increased RhuDex's probability of success to 20% (previously 15%). Our combined rNPV for Medigene's product portfolio has therefore increased by €15m to €70m. Adding in our estimated 31 June 2012 net cash of €26m, we value Medigene at €96m, showing upside compared with its €40m market capitalisation.

A summary of our valuation inputs for RhuDex in RA and PBC, as well as Medigene's other products – marketed genital warts ointment Veregen and breast cancer agent EndoTAG-1 – are displayed in Exhibit 3.

Exhibit 3: Medigene valuation model inputs

Product	Status	Probability of success	Est. launch year	Est. peak market share	Current market value	Est. max. royalty	Patent expiry	Est. peak sales
Veregen	Marketed	100%	2004	13%	$500m	12%	2022	$105m
EndoTAG-1	Phase II	35%	2017	14%	$2,500m	14%	2029	$630m
RhuDex – RA	Phase IIa	20%	2019	10%	$5,000m	12%	2029	$960m
RhuDex – PBC	Phase II-ready	20%	2017	20%	$800m	12%	2029	$200m
Total rNPV		**€70m**						
Jun 2012 net cash (est)		€26m						
Total valuation		**€96m**						

Source: Edison Investment Research. Note: Assumes EndoTAG-1 use for triple-negative breast cancer only.

RhuDex was acquired by Medigene in 2006 through the purchase of Avidex. In 2001 Avidex licensed Active Biotech's CD80 antagonists for the potential treatment of autoimmune diseases, a deal that includes royalties (at an undisclosed rate) on product sales. Given the early stage of the deal between Avidex and Active Biotech, we have assumed that the original deal terms have not changed and that Medigene will pay just 2% royalties on RhuDex sales to Active Biotech. Our 12% estimated royalty rate for RhuDex is therefore net of the royalties owing to Active Biotech. Generating positive Phase II data in PBC would help to de-risk the programme, particularly from a safety perspective, and lead to increasing our probability of success and therefore valuation.

Key sensitivities associated with this valuation centre on the progress of RhuDex – in the near-term there is particular sensitivity linked to the outcome of the Phase II trial in PBC. Clinical trial recruitment for orphan drug indications can be slower than larger indications like RA, which could delay our current estimate for generating headline data by the end of 2013. We await further details of the clinical trial design, particularly the selection criteria, to re-assess the likely timescale of the study.

In comparison to RA, the underlying disease mechanisms behind PBC are not so extensively defined, particularly the extent to which the CD28-CD80 interaction is involved in PBC pathogenesis, which could affect the outcome of the Phase II study.

The procurement of Veregen and currency exchange fluctuations are also important sensitivities. A failure to secure a development partner for EndoTAG-1 would negatively impact our overall valuation of Medigene.

Financials

For 2012 and 2013 we forecast modest increases in selling and general and administrative spending, but we have increased our R&D expense estimates, to €8.0m and €8.8m, respectively, compared to prior estimates of €7.5m and €7.9m. This reflects the cost of conducting the Phase II study for RhuDex in PBC and additional non-clinical work required.

With cash reserves estimated at €10m by the end of 2013, Medigene is mostly funded through to the end of 2014, but in reality is likely to require fresh funds during 2014. This coincides with a potential licensing deal over RhuDex, but as is standard practice we do not include revenue from as-yet unsigned licensing deals.

A summary of our financial model is displayed in Exhibit 4.

Exhibit 4: Financial summary

€'000s	2010	2011	2012e	2013e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	**2,292**	**4,656**	**6,675**	**7,973**
Cost of sales	(781)	(953)	(1,627)	(2,092)
Gross profit	**1,511**	**3,703**	**5,048**	**5,881**
Selling, general & administrative spending	(9,399)	(8,103)	(7,386)	(7,755)
R&D expenditure	(13,494)	(11,254)	(8,000)	(8,800)
Operating profit	**(27,594)**	**(15,654)**	**(10,338)**	**(10,674)**
Goodwill & intangible amortisation	(9,672)	(4,273)	(800)	(850)
Share-based payment	(264)	(144)	(64)	(150)
EBITDA	**(17,269)**	**(16,648)**	**(9,024)**	**(9,224)**
Operating profit (before GW and except.)	(17,658)	(11,237)	(9,474)	(9,674)
Net interest	25	131	(869)	(1,442)
Other	392	49	0	0
Profit before tax (norm)	**(17,241)**	**(15,474)**	**(10,343)**	**(11,116)**
Profit before tax (FRS 3)	**(27,177)**	**(15,474)**	**(11,207)**	**(12,116)**
Tax	0	1,241	0	0
Profit/(loss) from discontinued operations	9,308	20,514	4,997	0
Profit after tax (norm)	**(17,241)**	**(9,816)**	**(10,343)**	**(11,116)**
Profit after tax (FRS 3)	**(17,869)**	**6,281**	**(6,210)**	**(12,116)**
Average number of shares outstanding (m)	36.6	37.1	37.1	37.1
EPS - normalised (€)	(0.47)	(0.26)	(0.28)	(0.30)
EPS - FRS 3 (€)	(0.49)	0.17	(0.17)	(0.33)
Dividend per share (€)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed assets	**40,274**	**35,212**	**34,482**	**33,775**
Intangible assets & goodwill	34,098	29,937	29,137	28,287
Tangible assets	960	829	972	1,115
Other non-current assets	5,216	4,446	4,373	4,373
Current assets	**17,927**	**18,080**	**24,923**	**15,356**
Stocks	1,693	2,203	2,800	3,200
Debtors	4,516	1,897	1,150	1,150
Cash	4,770	12,811	19,868	9,901
Other	6,948	1,169	1,105	1,105
Current liabilities	**(17,156)**	**(4,824)**	**(3,451)**	**(3,376)**
Trade accounts payable	(2,354)	(1,773)	(1,800)	(1,800)
Short-term borrowings	0	0	0	0
Deferred income	(5,088)	(77)	(75)	0
Other	(9,714)	(2,974)	(1,576)	(1,576)
Long-term liabilities	**(247)**	**(536)**	**(13,577)**	**(12,167)**
Pension provisions	(245)	(255)	(255)	(255)
Long-term borrowings	(2)	0	0	0
Deferred taxes	0	(281)	(280)	(280)
Deferred revenues	0	0	(13,042)	(11,632)
Net assets	40,798	47,932	42,377	33,588
CASH FLOW				
Operating cash flow	**(11,436)**	**6,737**	**(6,850)**	**(9,624)**
Net interest	25	133	400	250
Tax	0	0	0	0
Capex	(321)	(351)	(593)	(593)
Acquisitions/disposals	0	1,774	0	0
Equity financing	4,478	0	0	0
Other	(218)	(246)	14,100	0
Net cash flow	(7,472)	8,047	7,057	(9,967)
Opening net debt/(cash)	**(12,242)**	**(4,768)**	**(12,811)**	**(19,868)**
Closing net debt/(cash)	**(4,768)**	**(12,811)**	**(19,868)**	**(9,901)**

Source: Edison Investment Research. Notes: Excludes potential licensing deals that have yet to be signed. €14.1m from Cowen Royalty in 2012 for 2% EU Eligard royalties is accounted for as a financial liability (deferred revenue), which will be amortised, pro rata, over 10 years. EBITDA does not include €5m profit from discontinued operations in 2012 (company's EBITDA guidance of mid-single digit €million loss in 2012 includes the €5m discontinued profit).