hardman&co

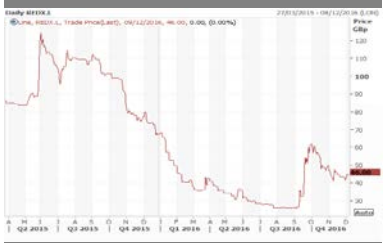
Redx Pharma

RXC005 BTK inhibitor – watch this space

Although Redx has only been in operation since late-2010, it has already created several valuable drug candidates that are about to begin clinical development. Progress into the clinic will enhance significantly the value of these drug candidates as well as providing further technical validation of the company's approach. Redx announced recently that its BTK inhibitor (RXC005) has a potential role in overcoming resistance occurring after Imbruvica treatment used in hematologic cancers. Redx aims to progress RXC005 into a first-in-man clinical study at the end of 2017.

- **Strategy**: To discover best and first-in-class drugs in therapeutic areas of significant commercial interest and, on a selective basis, to take those assets through early clinical development. Redx is focused on licensing out assets to drug major(s) for late-stage development and commercialisation to secure optimal returns.
- **RXC005 BTK inhibitor:** Redx is progressing RXC005, a reversible inhibitor of wild type and C481 mutant Bruton's tyrosine kinase (BTK) that has the potential to overcome sole C481 mediated resistance seen in roughly 65% of Chronic Lymphocytic Leukaemia (CLL) patients receiving Imbruvica treatment who have progressive CLL. The *in vitro* and *in vivo* profiles of RXC005 are very encouraging.
- **First-in-man trial:** In late 2017, Redx is planning to commence a first-in-man study with RXC005 for use in haematological cancers. This will also represent the second project that Redx has brought into the clinic since its creation in 2010, after its porcupine inhibitor RXC004, building up value adding momentum.
- **Valuation:** Redx has established itself as a well-run company, building a broad portfolio of pre-clinical assets. BTK programmes are increasingly being viewed as high value assets, with AbbVie paying $21bn to gain access Pharmacyclic's Imbruvica and AstraZeneca partnering with Acerta to develop acalabrutinib for potentially more than $4bn for 55% stake. Moreover, BTK inhibitors seem to be the right approach for use in combination therapies, increasing their value.
- **Risks:** Clearly not without financial risk, however, Redx's strategy and breadth of portfolio reduces the binary risk seen with single product companies. Also, timing of licensing deals is difficult to predict, but management has established already a track record of securing deals (including AstraZeneca, NHS, Horizon, Pierre Fabre). There is clear precedent that pharma/biotech is willing to pay high prices for assets, reflecting the level of de-risking undertaken by the developer.
- **Investment summary:** Redx offers investors access to a highly versatile and successful discovery engine, geared specifically towards clinically differentiating its assets to achieve potentially best-in-class and first-in-class status, which in turn should translate into highly valuable assets. Redx, which has two programmes that potentially could reach clinical studies in the next 12-15 months is gearing up the value and bringing Redx into the clinical stage arena.

Pharmaceuticals & Biotech



Source: Eikon Thomson Reuters

Market data

EPIC/TKR	REDX
Price (p)	45.0
12m High (p)	76.4
12m Low (p)	23.0
Shares (m)	93.6
Mkt Cap (£m)	42.2
EV (£m)	38.1
Free Float*	57%
Market	AIM

**As defined by AIM Rule 26*

Description

Redx Pharma is a drug discovery and development company, focused on creating best-in-class new drugs in the areas of cancer, infection and autoimmune disease. The company's work has been endorsed by partnerships with global pharma companies and the NHS

Company information

CEO	Neil Murray
CFO (interim)	Andrew Booth
Chairman	Frank Armstrong
	07491 651 406
	www.redxpharma.com

Key shareholders

Directors	11.7%
Seneca Partners	11.4%
Jon Moulton	10.7%
AXA Framlington	9.8%
Aviva	7.2%
Alderley Park Holdings	4.7%

Events

Aug-16	Hardman update
Jan-17	Finals
1H 2017	PORCN Phase I trial

Analysts

Martin Hall	020 7148 1433
	mh@hardmanandco.com
Dorothea Hill	020 7148 1433
	dmh @hardmanandco.com
Gregoire Pave	020 7148 1434
	gp @hardmanandco.com

BTK inhibitor RXC005

Redx recently identified the new drug development candidate from its cancer pipeline. RXC005 (REDX08608) is a selective and reversible inhibitor of Bruton's tyrosine kinase (BTK), potent against the wild-type and the mutant version C481S. RXC005 has the potential to overcome a resistance mechanism observed with Imbruvica. Redx aims to initiate a first-in-man clinical late in 2017.

RXC005

Presentation

RXC005 is a potent and selective reversible BTK inhibitor developed in Redx's labs, targeting chronic lymphocytic leukaemia (CLL) with the ability to overcome the resistance mechanism that builds up after treatment with Imbruvica (ibrutinib, J&J/AbbVie), used in haematological cancers, such as CLL. Unlike imbruvica, RXC005 does not interact with Cysteine 481 (C481) and is considered to be a reversible inhibitor. RXC005 inhibits BTK signalling and growth in cell lines dependent on the BTK pathway as well as CLL cells at very low, nanomolar, concentrations.

RXC005 shows a good selectivity against a panel of 468 kinases, providing the potential to exert minimal side effects. RXC005 has been thoroughly profiled in both *in vitro* and *in vivo* models and demonstrated as having good stability, exposure and bioavailability across species.

Overcoming resistance

Sole C481 resistance to Imbruvica appears in ~65% of patients who have progressive CLL. The mechanism of mutation is still unclear but it leads to a mutation of a specific cysteine residue within the binding site. C481 is a key binding partner for Imbruvica and mutations (C481S, C481Y, C481R, C481F) have been reported and associated to cases of resistance and progression of cancer. This key residue is also an important binding partner for other irreversible-binding clinical development products acalabrutinib (Acerta/AstraZeneca), GS-4059 (Ono/Gilead) and BGB-3111 (Beigene).

Unlike its competitors, RXC005 overcomes resistance mechanisms by targeting both wild type and the C481S mutation. By not interacting with the specific C481 amino acid, the BTK inhibitory activity of RXC005 is unaffected in C481 mutant cell-based assays.

Background

BTK is an important enzyme in the B-cell receptor (BCR) signalling pathway, which is required for the development, activation and survival of B-cells that are implicated in major market areas such as CLL and diffuse large B-cell lymphoma.

Imbruvica

Inhibition of BTK has been clinically validated through the commercial launch of Imbruvica. This first-in-class, orally bioavailable, small molecule BTK inhibitor was discovered originally by Celera Genomics to covalently bind to C481. At that time, it served as a research tool, being an irreversible kinase inhibitor and was not considered to be an ideal drug. In 2006, Pharmacyclics acquired the Celera's BTK programme for $3m to offset the failure of its own programme. After a successful Phase II clinical trial, Pharmacyclics entered into an Imbruvica co-development agreement with J&J for nearly $1bn. It was approved by the FDA in 2014 for the treatment of MCL, followed by CLL. Imbruvica was central to AbbVie's decision in March 2015 to acquire Pharmacyclics in a transaction valued at $21bn. This clearly shows the price that major Pharma are willing to pay for de-risked assets.

Sales of Imbruvica were reported to be $1,348m in 2015, the first full year on the market (shared between AbbVie ($659m) and J&J ($689m)), and this year it is expected to sell $2.85bn ($1.59bn by Abbvie and $1.26bn by J&J), representing growth of +111% despite the resistance issues.

Competitive landscape

Current clinical trials

As well as being used as a combination agent with existing therapies, Imbruvica is in trials for a number of cancer indications. In addition, there are more 40 clinical studies involving a BTK inhibitor currently running. Interestingly, BTK inhibitors also attract interest in the field of autoimmune disease, such as rheumatoid arthritis, as displayed by following table.

BTK inhibitors in clinical trial

Product	Company	Indication	Inhibition	Stage
Imbruvica	AbbVie	CLL, WM, MCL	Irreversible	Marketed
Acalabrutinib	Acerta/AstraZeneca	Multiple cancer indications	Irreversible	Phase I/II/III
Imbruvica	AbbVie	Multiple cancer indications	Irreversible	Phase II/III
BMS-986142	BMS	Rheumatoid arthritis/Sjögren's Syndrome	Reversible	Phase II
M2951/Evobrutinib	Merck Serono	Rheumatoid Arthritis / Systemic lupus erythematosus	Irreversible	Phase II
PRN1008	Principia Biopharma	Pemphigus vulgaris, other indication	Irreversible	Phase II, Phase I
CC-292/Spebrutinib	Celgene	CLL, B-cell lymphoma / Rheumatoid arthritis	Irreversible	Phase I and II
M7583	Merck Serono	Relapsed/Refractory B-Cell Malignancies	Not Reported	Phase I
AC0058TA	ACEA Biosciences	Rheumatoid arthritis and Systemic Lupus Erythematosus	Not Reported	Phase I
SNS062	Sunesis/Biogen	B Cell Malignancies	Reversible	Phase I
TAK-020	Takeda	Rheumatoid arthritis	Not Reported	Phase I
BIIB068	Biogen	Systemic Lupus Erythematosus	Not Reported	Phase I
HM71224	Lilly/Hanmi	Autoimmune diseases	Irreversible	Phase I
RG7845	Roche/Genentech	Autoimmune diseases	Reversible	Phase I
BGB-3111	BeiGene	B-cell malignancies	Irreversible	Phase I
GS4059/Tirabrutinib	Ono/Gilead	B-cell malignancies	Irreversible	Phase I
CT-1530	Centaurus Biopharma	Lymphoma, CLL, WM	Irreversible	Phase I

Source: www.clinicaltrials.gov, Companies' websites, Hardman & Co Life Sciences Research

Acalabrutinib

Acalabrutinib is a fast follower second generation BTK irreversible-inhibitor being developed by Acerta Pharma. In December 2015, AstraZeneca agreed to acquire 55% of the issued share capital of Acerta for an up-front payment of $2.5bn for access to acalabrutinib. A further payment of $1.5bn will be paid following regulatory approval or at the end of 2018, whichever is the earliest. The agreement also includes an option which, if exercised, provides Acerta shareholders the opportunity to sell the remaining 45% of shares. The options can be exercised conditional on the first approval of acalabrutinib in both the US and Europe for a consideration of approximately $3bn. AstraZeneca and Acerta are investing heavily in acalabrutinib with 12 clinical trials running, ranging from Phase I to Phase III in multiple cancer indications both as a single agent and in combination.

Potential for Redx

Small molecule BTK inhibitors clearly represent a new class of drugs and are attracting significant interest from the pharmaceutical majors which appear willing to enter multi-billion dollars deals to acquire de-risked assets. With RXC005, Redx is planning to commence first in man trials in end 2017. The fact that RXC005 appears to have considerable potency against C481 mutant BTKs will not go unnoticed. Watch this space!

Disclaimer

Hardman & Co provides professional independent research services. Whilst every reasonable effort has been made to ensure that the information in the research is correct, this cannot be guaranteed.

The research reflects the objective views of the analysts named on the front page. However, the companies or funds covered in this research may pay us a fee, commission or other remuneration in order for this research to be made available. A full list of companies or funds that have paid us for coverage within the past 12 months can be viewed at http://www.hardmanandco.com/

Hardman & Co has a personal dealing policy which debars staff and consultants from dealing in shares, bonds or other related instruments of companies which pay Hardman for any services, including research. They may be allowed to hold such securities if they were owned prior to joining Hardman or if they were held before the company appointed Hardman. In such cases sales will only be allowed in limited circumstances, generally in the two weeks following publication of figures.

Hardman & Co does not buy or sell shares, either for its own account or for other parties and neither does it undertake investment business. We may provide investment banking services to corporate clients.

Hardman & Co does not make recommendations. Accordingly, we do not publish records of our past recommendations. Where a Fair Value price is given in a research note this is the theoretical result of a study of a range of possible outcomes, and not a forecast of a likely share price. Hardman & Co may publish further notes on these securities/companies but has no scheduled commitment and may cease to follow these securities/companies without notice.

Nothing in this report should be construed as an offer, or the solicitation of an offer, to buy or sell securities by us.

This information is not tailored to your individual situation and the investment(s) covered may not be suitable for you. You should not make any investment decision without consulting a fully qualified financial adviser.

Hardman Research Ltd, trading as Hardman & Co, is an appointed representative of Capital Markets Strategy Ltd and is authorised and regulated by the Financial Conduct Authority (FCA) under registration number 600843. Hardman Research Ltd is registered at Companies House with number 8256259. However, the information in this research report is not FCA regulated because it does not constitute investment advice (as defined in the Financial Services and Markets Act 2000) and is provided for general information only.

Hardman & Co Research Limited (trading as Hardman & Co)
11/12 Tokenhouse Yard
London
EC2R 7AS
T +44 (0) 207 929 3399

Follow us on Twitter @HardmanandCo

(Disclaimer Version 2 – Effective from August 2015)

Hardman & Co

11/12 Tokenhouse Yard
London
EC2R 7AS
United Kingdom

Tel: +44(0)20 7929 3399
Fax: +44(0)20 7929 3377

www.hardmanandco.com