Pharmaceuticals & Biotechnology

Source: Eikon Thomson Reuters

Market data

EPIC/TKR	**REDX**
Price (p)	7.3
12m High (p)	23.5
12m Low (p)	3.5
Shares (m)	126.5
Mkt Cap (£m)	9.2
EV (£m)	2.7
Free Float*	81%
Market	AIM

**As defined by AIM Rule 26*

Description

Redx Pharma (REDX) is focused on the discovery and development of proprietary, small molecule therapeutics to address areas of high unmet medical need, in cancer and fibrosis. The aim is to develop putative drugs through early trials and then to partner them for late-stage development and commercialisation.

Company information

CEO	Lisa Anson
CFO	Dominic Jackson
Chairman	Iain Ross
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	www.redxpharma.com

Key shareholders

Directors	0.5%
Jon Moulton	18.2%
Seneca Partners	12.6%
AXA	9.7%
Aviva	8.2%

Diary

29 Nov	RXC006 data
1H'19	Resume Ph. I with RXC004
1H'19	Dev candidate for NASH
1H'19	Dev candidate for Crohn's

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REDX PHARMA

RXC006: first anti-fibrosis development candidate

REDX is a clinical-stage biotechnology company focused on drugs targeting oncology and fibrotic diseases. An extensive review, led by the new CEO, has reinforced the vision of a streamlined pipeline in these two disease areas, with the aim of progressing drug candidates to deliver clinical proof-of-concept. Progress in the fibrotic programme is going apace, with the recent announcement that RXC006 has been nominated as REDX's first anti-fibrosis development candidate. The strong pre-clinical evidence behind this decision was presented for the first time on 29 November at the 2nd anti-fibrotic drug development summit in Cambridge, MA.

- **Strategy:** REDX is focused on the discovery and early clinical development of small molecule therapeutics in oncology and fibrotic disease. It is also focused on taking assets through proof-of-concept clinical trials and then partnering them for late-stage development and commercialisation.

- **Idiopathic pulmonary fibrosis (IPF):** IPF is a chronic and progressive fibrotic disorder of the lung that typically affects adults over the age of 40, with median survival in the US estimated at three to four years after diagnosis. There is a real medical need, as no treatments are available to stop or reverse the disease.

- **RXC006:** In its oral and poster presentations, REDX disclosed for the first time its drug development candidate RXC006, an orally bioavailable porcupine inhibitor that had demonstrated encouraging results in suppressing Wnt pathway involvement in fibrosis in different *in vivo* disease models, of the lung, kidney and liver. REDX aims to enter the clinic during 2020.

- **Risks:** REDX has emerged from fiscal 2018 in a clean position, with a focused strategy. The company has cash runway into 2Q'19 and will therefore require investment for clinical trials for its pipeline of porcupine and ROCK inhibitor development programmes.

- **Investment summary:** New management is moving forward with a revised business plan that focuses cash resources on progressing its drug leads in oncology and fibrotic disease to proof-of-concept studies. Big pharma has been shown to pay substantial prices for good science and novel and/or de-risked assets with such clinical data, reinforcing REDX's strategy, potentially generating good returns and enhancing shareholder value.

Financial summary and valuation

Year-end Sept (£m)	2016	2017	2018	2019E	2020E	2021E
Other income	2.38	1.29	1.32	1.00	1.00	1.00
R&D investment	-14.32	-13.00	-7.42	-11.06	-11.29	-13.54
SG&A (corp. cost)	-2.21	-5.70	-2.81	-2.59	-2.74	-2.88
Underlying EBIT	-14.15	-17.41	-8.92	-12.65	-13.03	-15.42
Underlying PBT	-14.61	-17.74	-8.90	-12.64	-13.02	-15.42
Statutory PBT	-15.41	1.65	-10.15	-12.94	-13.35	-15.76
R&D tax credit	0.64	-0.12	1.30	1.94	1.98	2.37
Underlying EPS (p)	-17.83	-15.80	-6.01	-6.70	-5.72	-3.06
Statutory EPS (p)	-19.81	1.35	-6.99	-6.89	-5.89	-3.22
Disposals	0.00	30.47	0.00	0.00	0.00	0.00
Net (debt)/cash	3.76	23.81	6.47	8.95	-2.56	-16.73
Capital increase	9.30	11.07	0.00	14.10	0.00	0.00

Source: Hardman & Co Life Sciences Research

Development candidate in IPF

Designation of RXC006 as a potential clinical candidate, an important milestone for REDX

The first development candidate for its anti-fibrotic programmes, RXC006 was nominated recently by REDX in an announcement (14 November) that was ahead of schedule (originally expected in 1H'19). This represents a key step in progressing the candidate that will be taken into the clinic, now expected in 2020.

RXC006 is an orally bioavailable and once/twice daily administered small molecule porcupine inhibitor and a potential first-in-class treatment for IPF. RXC006 acts upstream on the Wnt pathway, which is known to be involved in the fibrosis process in the lung, liver and kidney.

It is the first time REDX disclosed the profile of its development candidate RXC006

Pre-clinical data were presented for the first time by Dr Peter Bunyard, REDX's Head of Fibrosis, at the 2nd anti-fibrotic drug development summit in Cambridge, MA. on Thursday 29 November 2018. The presentation highlighted that porcupine inhibition with RXC006 is effective in several *in vivo* fibrotic models, and in different organs (lung, liver and kidney), with the potential to reverse the fibrotic condition.

RDXC006 porcupine inhibitor

REDX's lead anti-fibrotic programme

RXC006 is an orally bioavailable porcupine inhibitor with a different PK profile to RXC004…

For fibrotic disease, REDX is developing a new series of porcupine inhibitor compounds that are distinct from the company's RXC004 series, which is currently in Phase I for cancer and protected by a different patent family. The lead fibrosis compound, RXC006, was selected because it is orally bioavailable, has a different pharmacokinetic (PK) profile to RXC004, and has shown encouraging results in suppressing the Wnt pathway involved in fibrosis in different *in vivo* disease models.

… that has the potential to be first-in-class in IPF

RXC006 has the potential to be first-in-class with the aim of treating IPF, a progressive and life-threatening condition with a very poor prognosis. Animal studies have demonstrated RXC006 to be safe and well tolerated and to possess a PK profile that will allow flexibility in dosing. REDX believes that its porcupine inhibitor may be effective in more severe IPF patients, where current therapy is ineffective. The company is aiming to enter a first-in-man clinical trial during 2020.

What is a development candidate?

A development candidate is a molecule that has been selected with the view to being optimised through further pre-clinical testing and then to progress into a Phase I clinical study. REDX is entering a period in which it will evaluate the likelihood of completing successfully the investigational new drug (IND)-enabling work that will be required as part of its regulatory application for first-in-human testing. This work is expected to last around a year, during which time formulation, dosing, and ultimately, safety margins will be confirmed. Typically, most pharma and biotech companies will select a single development candidate with one designated back-up. In many cases, a pre-IND meeting with the regulatory agency might be considered. The development candidate molecule should possess the following six criteria:

- acceptable PK (with a validated bioanalytical method);
- demonstrated *in vivo* efficacy and activity;
- acceptable safety and toxicity margin in different animal species;
- Good Manufacturing Practice (GMP) feasibility;
- acceptable drug interaction profile; and
- well-developed clinical endpoints and potential to address an unmet clinical need(s).

Porcupine and fibrotic diseases

Rationale

The initial focus is on lung fibrosis, with the potential to be extended to other fibrotic conditions

Fibrosis is the formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process. This can be in a reactive, benign, or pathological state. The porcupine protein acts upstream in the Wnt pathway. Inhibition of porcupine can, therefore, influence the development of fibrotic conditions through its role in controlling the level of several pro-fibrotic proteins. The influence of Wnt activation of β-catenin signalling in fibroblasts is believed to trigger the fibrotic pathology in various organs such as the lung, liver and kidney. This new approach is strongly supported by Dr Jörg Distler, whose group focuses on discovery of causes, mechanisms and the effects of pathological activation of fibroblasts, as well as the development of new therapeutic approaches. He has commented that "*Wnt pathway inhibition presents a novel and exciting opportunity to treat fibrotic diseases. I truly support the idea of targeting the porcupine enzyme*."

Wnt signaling is essential for lung development, but in healthy adult lungs, Wnt signalling is inactivated. However, in the lungs of IPF patients, overexpression of Wnt proteins and activated Wnt signaling have been found in the alveolar epithelium and fibroblasts[1]. RXC006 is a potent inhibitor of the secretion of Wnt3a that acts upstream of the β-catenin pathway critically involved in fibroblast formation.

With RXC006, REDX will focus initially on lung fibrosis, where a vast body of scientific papers have demonstrated the influence of the Wnt pathway in the establishment and progression of the disease[2]. Due to the aberrant activation of the Wnt signalling in kidney and liver fibrosis, we anticipate that REDX will extend the use of RXC006 into other fibrotic conditions.

RXC006 in lung fibrosis

RXC006 supresses fibrosis in a lung model

RXC006 has a strong anti-fibrotic effect

In a fibrotic animal model generated by the administration of bleomycin, both porcupine inhibitors, RXC006 and RXC004, were shown to have strong anti-fibrotic effects in the murine lung fibrosis model. These were demonstrated through:

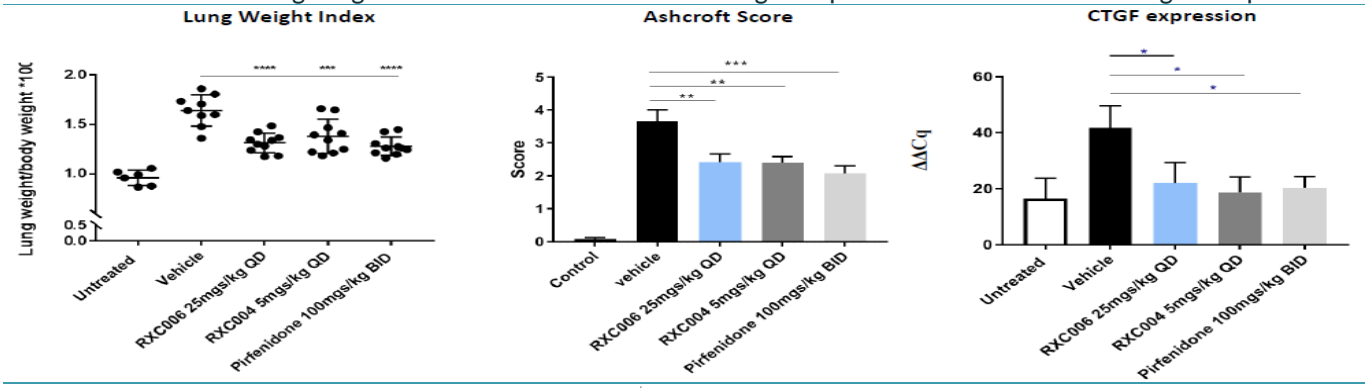
- significant reductions in lung weight;
- significant reductions in collagen deposition; and
- significant reductions in pro-fibrotic genes as exemplified by CTGF, as well as Axin-2 and TGFβ gene expression (data not shown).

More importantly, the anti-fibrotic effect was seen in a therapeutic context when the compound was administered from day 7, when the initial injury and inflammatory phases had subsided.

[1] King TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. *Lancet*. **2011**;378(9087):1949-61
[2] Baarsma et al 'WNT-er is coming': WNT signalling in chronic lung diseases, *Thorax*, **2017**, 72, 746-759.

Wnt inhibition with RXC006 and RXC004 in a lung fibrosis model

Reduction in lung weight | Reduction in Collagen deposition | Pro-fibrotic gene expression



Source: REDX, 2nd anti-fibrotic drug development summit in Cambridge, MA, Thursday 29 November

Commercial opportunity

With RXC006, REDX is targeting a patient population in high unmet medical needs...

IPF is a chronic, progressive, fibrotic disorder of the lower respiratory tract that typically affects adults over the age of 40. It is the most common interstitial lung disease seen by pulmonologists. The National Institute of Health (NIH) indicates that IPF has an estimated prevalence of 13 to 20 per 100,000 people worldwide. About 100,000 people are affected in the US, and 30,000 to 40,000 new cases are diagnosed each year. Because age is a major risk factor and predictor of IPF, the disease prevalence is expected to rise with the ageing population, and because there is no medication that stops or reverses the scaring of the lung tissue, there is clearly a high unmet medical need. There are currently several companies that are progressing treatment for IPF but, to our knowledge, REDX is in the forefront with respect to the porcupine inhibitor approach.

... with no real treatment option

There is currently no cure for IPF, and the five-year survival rate is around 20% according to the UK's National Health Service (NHS), while the median survival in the US is estimated at three to four years after diagnosis (sources: National Institutes og Health, NIH). The standard-of-care is just to relieve the symptoms as much as possible (oxygen mask) and slow down the scarring of the lungs, – i.e. simply slow the progression of the disease. The standard-of-care includes the use of medications such as:

- **Esbriet** (pirfenidone, Roche), approved in the US (2014) and Europe (2011), and expected to have sales in 2018 of $950m, giving cumulative sales since launch of ca.$3.3bn. This drug helps to slow the development of scarring in the lungs by reducing the activity of the immune system and the lung fibrosis through down-regulation of the production of growth factors and procollagens I and II.
- **Ofev/Vargatef** (nintedanib, Boehringer Ingelheim) approved in the US (2014) and Europe (2015); it has generated cumulative sales in excess of $3.2bn to end-2018. It works by targeting the vascular endothelial growth factor receptor (VEGFR), the fibroblast growth factor receptor (VGFR) and the platelet derived growth factor receptor (PDGFR).

Competition

Samumed, a San Diego-based biotech company, is progressing SM04646, a small molecule Wnt signalling pathway inhibitor nebulised in the lung, and currently in a Phase I study. It is worth noting that at this stage, Samumed has not disclosed the target of SM04646 and where in the Wnt pathway it is acting. In a Phase I study in healthy volunteers, SM04646 was shown to be safe and well tolerated. On 17 September 2018, Samumed announced that it had entered into an exclusive licence agreement with United Therapeutic Corp. (NASDAQ: UTHR) for the North American rights to SM04646, in return for a $10m upfront payment, up to $340m

potentially in development milestones and up to low double-digit royalties. Samumed retains development and commercialisation rights for all markets outside North America. SM04646 has been granted Orphan Drug Designation from the FDA for the treatment of IPF. Interestingly, the ClinicalTrials.gov website indicated that the Phase IIa trial (NCT03591926) with SM04646 was withdrawn on 9 October 2018 for business reasons, and prior to screening or enrolling any subjects. No further information is available on Samumed's website.

RXC004 and RXC006 in other fibrotic models

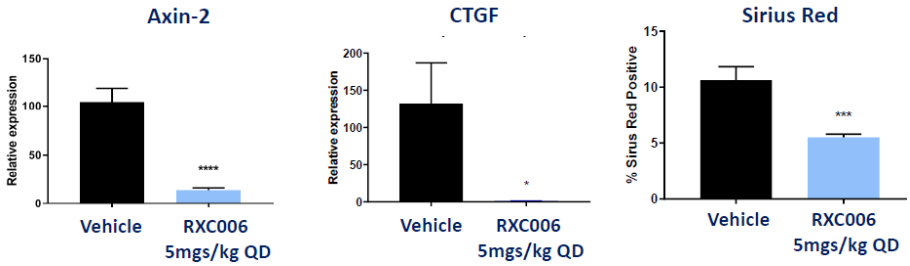
REDX has also demonstrated RXC006 potentials in other fibrotic conditions

RXC006 in kidney fibrosis

The unilateral ureteral obstruction (UUO) procedure represents an *in vivo* model whereby a ureter from one kidney is tied up to induce tissue injury (day 1-2), followed by inflammation (day 3-5), and then fibrosis (day 5-7). At day seven, when the fibrosis event takes place, animals start receiving a daily oral dose of RXC006. This experiment highlighted that RXC006 supressed fibrosis genes *in vivo*:

- RXC006 induced a reduction on markers of Wnt pathway activation (Axin-2).
- RXC006 induced a reduction in fibrosis (CTGF and type 1 collagen – Sirius Red).
- RXC006 was well tolerated (no weight loss, distress or diarrhoea).

Wnt inhibition with RXC006 in a kidney fibrosis model



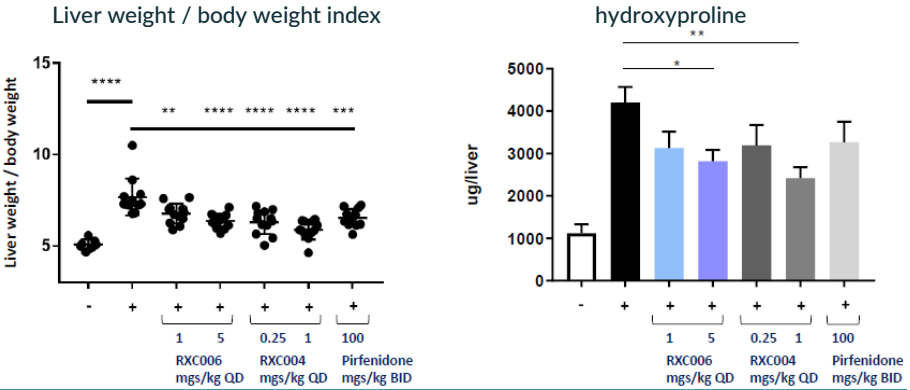
Source: REDX, 2nd anti-fibrotic drug development summit in Cambridge, MA, Thursday 29 November

In addition, the effect of RXC006 in controlling fibrosis events was seen to occur both in a prophylactic (before fibrosis occurs) and therapeutic (when fibrosis is established) manner in this animal model.

RXC006 in liver fibrosis

Therapeutic efficacy of the porcupine inhibitors has also been demonstrated in a liver fibrosis model induced by carbon tetrachloride (CCl_4).

Wnt inhibition with RXC006 and RXC004 in a liver fibrosis model



Source: REDX, 2nd anti-fibrotic drug development summit in Cambridge, MA, Thursday 29 November

Inhibition of porcupine with RXC006 and RXC004 reduced significantly the increase in liver weight caused by repeated administration of CCl_4. This suggests that Wnt suppression is able to ameliorate deleterious tissue remodelling caused by hyperplasia and fibrosis. Fibrosis suppression was confirmed by the reduction in the liver of hydroxyproline, a biomarker of liver fibrosis.

Conclusion

With its orally bioavailable inhibitor RXC006, REDX has the potential to be first-in-class in treating lung fibrosis through inhibition of the Wnt signalling pathway. Designation of RXC006 as a potential clinical candidate represents an important milestone, as it is the first candidate in REDX's anti-fibrotic programme. In its oral and poster presentations at the conference, REDX disclosed for the first time its development candidate and demonstrated that its porcupine inhibitors RXC004 and RXC006 are effective in modulating the Wnt pathway in several fibrosis models affecting the lung, liver and kidney.

REDX has leveraged its medicinal chemistry expertise to develop a selective series of porcupine inhibitor compounds that are distinct chemically, and with a different PK profile from RXC004, its clinical-stage cancer candidate. REDX anticipates that RXC006 will be ready for Phase I clinical trials during 2020.

In addition to the porcupine inhibitor programme, REDX is progressing two other projects in anti-fibrotic diseases, both of which are approaching candidate selection milestones in 2019:

- The ROCK2 selective inhibitor targeting liver fibrosis (NASH). REDX has previously announced positive *in vivo* data for kidney fibrosis.
- The locally-acting ROCK inhibitor (GI-targeted ROCK). This targets the gastro-intestinal region for Crohn's-related fibrosis.

REDX's anti-fibrosis near-term milestones and value drivers to 2020

Years		2018	2019	2020
Anti-Fibrotics	PORCN/ RXC006	✓ *Patents filed,* ✓ *Development candidate selected*	**1H** IND preparation **2H** GLP toxicity	**1H** First time in man ready (IPF)
	ROCK2 selective	✓ *Patents filed, series assessment ongoing* ✓ *Data presented*	**1H** In vivo data completed **1H** Development candidate selected for NASH	**2H** First time in man ready
	GI targeted ROCK	✓ *Patents filed, series assessment ongoing*	**1H** Development candidate selected for Crohn's Disease	**2H** First time in man ready

Source: REDX

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