EDISON

RedHill Biopharma

Rapid progress with COVID-19 programme

Focus on COVID-19 programme

Pharma & biotech

RedHill's global Phase II/III programme with opaganib against COVID-19 is progressing rapidly. An ongoing Phase IIa study in the US should complete patient recruitment in August, while in July the international Phase II/III study should start enrolment in several other countries. If these studies are successful, RedHill could file for emergency use as soon as Q420. Extensive preclinical studies describe opaganib's rather unique mechanism of action. It not only has an anti-viral effect, but can also reduce inflammation in the lungs. This makes it an attractive option in severe COVID-19 cases, where an overactive immune response can worsen the outcomes. We maintain our last published valuation ($593m or $16.5/ADS), but can see potential to expand our R&D model depending on the progress of COVID-19 trials.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/18	8.4	(38.8)	(0.17)	0.0	N/A	N/A
12/19	6.3	(42.1)	(0.14)	0.0	N/A	N/A
12/20e	93.0	(9.7)	(0.03)	0.0	N/A	N/A
12/21e	137.0	3.2	0.01	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles and exceptional items.

First results from compassion use programme

Treatment of five severe COVID-19 patients with opaganib led to better clinical outcomes compared to matched case controls at the same hospital. All patients in the opaganib group were discharged from hospital without requiring mechanical ventilation whereas 33% of the matched case control group required mechanical ventilation. Median time to weaning from high-flow nasal cannula was reduced to 10 days in the opaganib-treated group, compared to 15 days in the matched case control group. An improvement in inflammatory markers was also observed.

Potentially large market size, but still developing

Globally more than 10.5 million people have been afflicted by COVID-19 just this year, which has resulted in around 510,000 deaths so far. While 81% of patients have mild disease with no need for hospitalisation, 14% have a severe form and 5% become critically ill with organ failure (Berlin et al, 2020). However, the market for COVID-19 treatment is still developing, therefore market size calculations are very preliminary. Ultimately, the potential for a therapeutic drug will depend on the future patient numbers and the competitive landscape, including any available therapies, but also preventative measure like vaccines.

Valuation: $593m or $16.5 per ADS

We do not yet include RedHill's COVID-19 programme in our valuation, but there is potential to expand our R&D model depending on its further progress. We keep opaganib for cholangiocarcinoma in our R&D model. Ahead of the upcoming quarterly report, due shortly, we maintain our last published valuation of $593m or $16.5 per ADS. In addition to an update on the COVID-19 programme, other focus areas in the Q220 report include updates on the three marketed GI drugs in the US and the rest of the R&D pipeline.

24 July 2020

Price	**US$6.56**
Market cap	**US$235m**
Net cash ($m) at 1 April 2020	62.5
Shares in issue	358.9m
Free float	90%
Code	RDHL
Primary exchange	Nasdaq

Share price performance

%	1m	3m	12m
Abs	0.9	(13.8)	(10.0)
Rel (local)	(2.3)	(25.5)	(16.4)
52-week high/low	US$8.60	US$3.51	

Business description

Speciality pharma company RedHill Biopharma focuses on gastrointestinal diseases and promotes several GI products in the US. The commercial portfolio includes Movantik (opioid-induced constipation), Talicia (H. pylori eradication) and Aemcolo (travellers' diarrhoea). The most advanced R&D assets are RHB-204 for NTM, RHB-104 for Crohn's disease and Bekinda for gastroenteritis and IBS-D.

Next events

Initiation of pivotal Phase III study with RHB-204 for NTM infections	Q320
Initiation of the Phase IIa study with COVID-19 patients in the US; update on the European COVID-19 study	Q320
Updates on the promotion of the commercial portfolio drugs	2020

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Edison profile page

Opaganib's unique mechanism of action for COVID-19

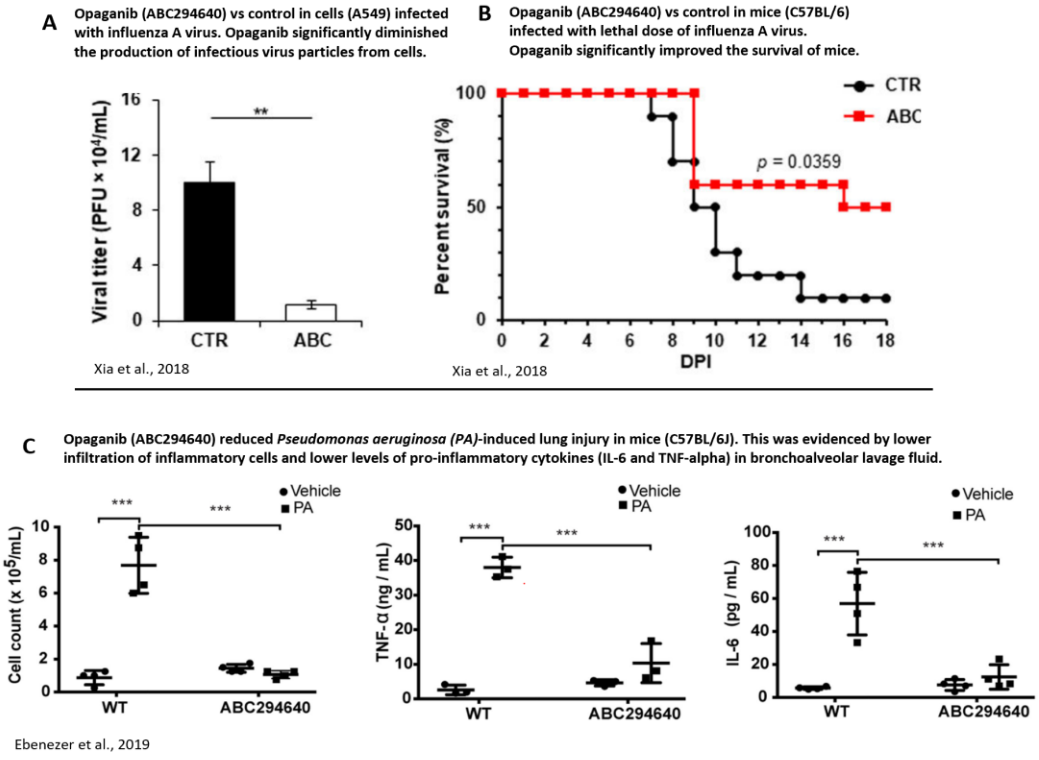
RedHill has identified its anti-cancer/anti-inflammatory candidate opaganib (Yeliva, formerly ABC294640) as a potential treatment for COVID-19. The company was able to make rapid progress with this programme because opaganib is already being investigated in Phase II clinical trials. It has also completed a Phase I study, as well as safety and pharmacokinetics studies in healthy volunteers and had been given to over 130 subjects.

Mechanism of action

Opaganib is a sphingosine kinase-2 (SK2) inhibitor. Sphingomyelin is not only a building block for cellular membranes but also acts as a precursor for lipid messengers for the potent bioactive lipid ceramide and the pro-inflammatory lipid sphingosine 1-phosphate (S1P) that have profound cellular effects. During one of the downstream processes, sphingosine kinases (there are two isoforms SK1 and SK2) promote rapid production of S1P from sphingosine. S1P in turn promotes cancer growth, proliferation and inflammation processes. Opaganib is a specific SK2 inhibitor that decreases S1P synthesis. This approach has been demonstrated to have an effect on a broad range of fundamental biological processes and has potential in oncology, inflammatory diseases and as an anti-viral agent.

Prior pre-clinical studies with opaganib support the potential role of SK2 in the replication-transcription complex of positive-strand single-stranded RNA viruses, which includes coronavirus, and its inhibition may potentially stop viral replication. In vivo studies have demonstrated that opaganib decreased fatality rates from influenza-virus infection (Exhibit 1A and 1B). In vivo studies with bacterial-induced lung injury models (*Pseudomonas aeruginosa* in mice) also showed that the damage is ameliorated (Exhibit 1C).

Exhibit 1: Selected preclinical data demonstrating opaganib



Source: Xia et al, 2018; Ebenezer et al, 2019

It is the combination of the anti-inflammatory and anti-viral effects that makes this drug a unique potential treatment for SARS-CoV-2 infections. Theoretically, it should not only treat the cause of the disease, the virus, but also alleviate the inflammation, which triggers severe acute respiratory syndrome (SARS). SARS is a known severe, life threatening condition, but it also increases the risk of pulmonary fibrosis. There is growing concern that pulmonary fibrosis could be a long-term negative consequence for many individuals affected by COVID-19, even for those who avoided the most severe form of the disease with the need for admission to intensive care units. It is fair to say that we are still in an acute phase of the COVID-19 pandemic. At this point, it is impossible to predict what the longer-term public health consequences will be, but if COVID-19 infection is proven to increase the risk of pulmonary fibrosis in the wider affected population, we believe this will be a major public health issue in addition to the acute phase, as the patients who are recovering currently may start experiencing disabling complications years later. In this scenario, drugs with a mechanism of action like opaganib's could be of major interest.

First clinical insights

Opaganib has been given to a total of 131 subjects to date (cancer patients and healthy volunteers in the previous Phase I and Phase II studies and participants in expanded access programmes). Currently opaganib is being investigated in a Phase I/IIa study for cholangiocarcinoma and in another Phase II study in prostate cancer.

In early April, RedHill announced compassionate use programmes in Israel, but it is also working with other countries. Later that month, the company reported findings from the first evaluable patients, who were hospitalised in Israel at one of the tertiary academic hospitals (the preprint article was made available in June).

Before the treatment with opaganib, all patients had severe disease requiring oxygen support via high-flow nasal cannula. The investigators reported findings from five evaluable patients treated with opaganib versus matched case controls:

- All patients in the opaganib group were discharged from hospital without having required mechanical ventilation; 33% of patients in the control group required mechanical ventilation (a trend with a p value of 0.13).
- The median time to weaning from nasal cannula was to be lower on average at 10 days in the opaganib group, compared to 15 days in the control group (p=0.2).
- Improvement in lymphocyte counts was significantly faster in opaganib-treated patients as compared to patients in the control group (p=0.001). Low lymphocyte counts are associated with a more severe COVID-19 disease and with a more rapid deterioration.
- Improvement in C-reactive protein (an inflammatory biomarker) levels was to be faster in the opaganib group compared to the control group (p=0.08).

One patient, who received hydroxychloroquine and azithromycin (macrolide class antibiotic) on top of opaganib, developed diarrhoea after two doses of opaganib and the treating physicians decided to discontinue all his medications. This patient was not included in the results analysis. We believe, it is difficult to say whether this was a side effect of opaganib, as both hydroxychloroquine and azithromycin (macrolide class antibiotic) can cause diarrhoea. No other side effects that were deemed opaganib-related were reported.

Comparability of results between treatment and control groups

As a control group, the investigators selected similar group of patients (n=18, same sex, same severity and similar age group), who met the inclusion and exclusion criteria at the same hospital. The descriptive baseline characteristics of both groups of patients were largely similar, but the key

difference, in our view, was the fact that a third of control patients received methylprednisolone and no opaganib group patients received it.

In mid-June, the preliminary results from a separate study conducted in the UK to test a range of potential treatments for COVID-19 patients were published (the RECOVERY study – **R**andomised **E**valuation of **COV**id-19 th**ER**ap**Y**). This study was unrelated to RedHill and opaganib. The key new finding was that for patients on ventilators, low-dose dexamethasone treatment was shown to reduce mortality by about one-third, and for patients requiring oxygen therapy mortality was cut by about one-fifth. In total 2,104 patients were randomised to receive dexamethasone. Because of this large sample size, the fact that synthetic corticosteroids are a very well-established class of drugs, easily available and cheap, the use of dexamethasone for severe COVID-19 patients immediately became widespread in the UK.

Both methylprednisolone and dexamethasone are synthetic corticosteroids, and while there are some pharmacokinetic and pharmacodynamic differences, these drugs can be interchangeable in certain cases if the correct dosing is chosen (eg, in chronic obstructive pulmonary disease exacerbation). The authors of the of RedHill's opaganib article were not aware of the benefit of corticosteroids, as the article was submitted for publication before the UK study results were published. We believe it is possible that the use of methylprednisolone in the control arm increased the hurdle for opaganib. If corticosteroids had not been administered to patients in the control arm, the benefit of opaganib might have been even more pronounced.

Next steps: Clinical studies in the US and Europe

In our view, the first compassion use results are interesting, but the patient sample is small and a controlled trial is still needed for regulatory approval. RedHill filed for an IND with the FDA, which was approved in May. This will be a randomized, double-blind, placebo-controlled Phase IIa study with the goal of enrolling up to 40 COVID-19 patients with severe-to-critical infection requiring hospitalisation and high-flow supplemental oxygenation. Patients randomized at a 1:1 ratio will receive either opaganib or placebo in combination with standard-of-care. The **primary endpoint** is to evaluate the reduction in total oxygen requirement over the course of treatment (up to 14 days). **Secondary endpoints** include time to 50% reduction in oxygen requirements, the proportion of patients without fever at day 14 and the proportion with negative nasal swabs at day 14. By mid-July more than 25% of patients were enrolled in the study and RedHill expects to complete enrolment in August.

In July, RedHill plans to initiate a Phase II/III multi-centre, randomized, double-blind, parallel-arm, placebo-controlled study with opaganib and aims to enrol 270 severe COVID-19 patients in up to 40 clinical sites across the UK, Italy, Russia, Mexico and Brazil. The patients will be randomized at a 1:1 ratio. The **primary endpoint** will be the proportion of patients requiring intubation and mechanical ventilation by day 14.

If these studies are successful, RedHill plans to submit opaganib for emergency use approval as early as Q420.

Upamostat (RHB-107): Second potential asset against COVID-19

RedHill also has another potential asset against COVID-19, RHB-107 (upamostat). RHB-107 is an inhibitor of the S1 family of trypsin-like serine proteases with potential for use in the treatment of cancer, inflammatory lung diseases and irritable bowel syndrome. Inhibition of serine proteases, including trypsins, may inhibit viral attachment and replication, and alleviate lung damage in viral pneumonia. Based on its possible mechanism of action, RHB-107 was selected for in vitro testing by the US National Institute of Allergy and Infectious Diseases (NIAID).

Exhibit 2: Financial summary

$'000s	2018	2019	2020e	2021e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	8,360	6,291	93,006	136,969
Cost of Sales	(2,837)	(2,259)	(33,652)	(49,013)
Gross Profit	5,523	4,032	59,354	87,956
Research and development	(24,862)	(17,419)	(11,200)	(11,200)
EBITDA	(39,241)	(41,988)	(9,513)	3,377
Operating Profit (before amort. and except.)	(39,331)	(42,985)	(9,651)	3,208
Intangible Amortisation	0	(216)	0	0
Exceptionals	0	0	0	0
Other	0	0	0	0
Operating Profit	(39,331)	(43,201)	(9,651)	3,208
Net Interest	511	897	0	0
Profit Before Tax (norm)	(38,820)	(42,088)	(9,651)	3,208
Profit Before Tax (reported)	(38,820)	(42,304)	(9,651)	3,208
Tax	0	0	0	(802)
Profit After Tax (norm)	(38,820)	(42,088)	(9,651)	2,406
Profit After Tax (reported)	(38,820)	(42,304)	(9,651)	2,406
Average Number of Shares Outstanding (m)	231.2	296.9	355.9	359.2
EPS - normalised ($)	(0.17)	(0.14)	(0.03)	0.01
EPS - normalised fully diluted ($)	(0.17)	(0.14)	(0.03)	0.01
EPS - (reported) ($)	(0.17)	(0.14)	(0.03)	0.01
Dividend per share ($)	0.0	0.0	0.0	0.0
Gross Margin (%)	66.1	64.1	63.8	64.2
EBITDA Margin (%)	N/A	N/A	N/A	2.5
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	2.3
BALANCE SHEET				
Fixed Assets	5,623	20,885	73,450	88,484
Intangible Assets	5,320	16,927	69,462	84,497
Tangible Assets	163	228	258	257
Investments	140	3,730	3,730	3,730
Current Assets	56,788	53,214	78,725	69,124
Stocks	769	1,882	1,882	1,882
Debtors	2,834	3,460	3,460	3,460
Cash	29,005	29,023	54,534	44,933
Other*	24,180	18,849	18,849	18,849
Current Liabilities	(10,381)	(10,616)	(10,616)	(10,616)
Creditors	(10,381)	(10,616)	(10,616)	(10,616)
Short term borrowings	0	0	0	0
Long Term Liabilities	(844)	(3,481)	(82,981)	(82,981)
Long term borrowings	0	0	(80,000)	(80,000)
Other long-term liabilities	(844)	(3,481)	(2,981)	(2,981)
Net Assets	51,186	60,002	58,577	64,011
CASH FLOW				
Operating Cash Flow	(34,462)	(40,749)	(6,486)	6,404
Net Interest	0	0	0	0
Tax	0	0	0	(802)
Capex	(23)	(168)	(168)	(168)
Acquisitions/disposals	0	0	0	0
Financing	42,263	36,305	4,700	0
Other**	4,772	4,630	(52,535)	(15,035)
Dividends	0	0	0	0
Net Cash Flow	12,550	18	(54,489)	(9,601)
Opening net debt/(cash)	(16,455)	(29,005)	(29,023)	25,466
HP finance leases initiated	0	0	0	0
Other	0	0	0	0
Closing net debt/(cash)***	(29,005)	(29,023)	25,466	35,067

Source: RedHill Biopharma accounts, Edison Investment Research. Note: *Bank deposits and financial assets at fair value. **Mainly Movantik acquisition payments to AstraZeneca. ***Net cash does not include bank deposits and financial assets.

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