EDISON

RedHill BioPharma

Clinical data

RHB-104 data look good

Pharma & biotech

RedHill reported top-line results from its Phase III trial with RHB-104 in Crohn's Disease (CD). The primary endpoint was met with 37% of patients in the active arm achieving remission at week 26 compared to 23% in placebo (p=0.013). Several other key secondary endpoints also demonstrated efficacy but, judging from the share price volatility on the day of the announcement and various comments in the public space, a lot of attention was paid to the secondary endpoint dealing with isolated late induction of remission at week 52, which introduced confusion, in our view. The initial share price reaction was positive with a >60% gain, but retracted, closing down 7.2%. We note that RedHill's share price is up by more than 40% versus the current price since May 2018 and given that the RHB-104 data readout was the single biggest catalyst in mid-2018, we believe the share price appreciation over the last few months reflects the value added by RHB-104. Our new valuation is $423m or $19.8/ADS.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/16	0.1	(29.4)	(0.23)	0.0	N/A	N/A
12/17	4.0	(45.5)	(0.26)	0.0	N/A	N/A
12/18e	16.6	(39.3)	(0.18)	0.0	N/A	N/A
12/19e	30.2	(35.8)	(0.17)	0.0	N/A	N/A

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

Primary endpoint met with high significance

The trial enrolled 331 CD patients (166 in the active arm) who presented with moderate to severe disease (CDAI score ≥220 and ≤450) and received RHB-104 for 26 weeks. Interestingly, all patients received standard of care and had active disease despite it. Subgroup analysis is yet to be done, but as these patients had at least moderate CD, it is likely that a number of them received anti-TNF-α agents (infliximab [Remicade] or adalimumab [Humira] were allowed), which are known to be effective and set a high bar for RHB-104. The primary endpoint remission at week 26 was reached with a high statistical significance (37% vs 23%; p=0.013).

Most other data positive; long-term efficacy question

Key secondary endpoints include: response at week 26 (decrease in CDAI score ≥100 points; 44% vs 31%, p=0.028); early remission at week 16 (42% vs 29%; p=0.019); and remission at week 52 (27% vs 20%; p=0.155). RedHill explained the lack of significance in the latter endpoint as a potential outcome of the fact that the trial was not powered to test such a long-term effect. Furthermore, this specific standalone week 52 endpoint is unlikely to be relevant in further development. However, we believe this still caused confusion about long-term efficacy.

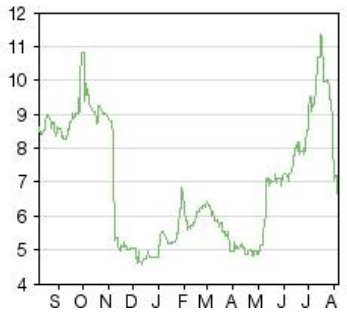
Valuation: Upped on improved success probability

We increase our valuation of RedHill to $423m or $19.8/ADS, from $405m or $19.0/ADS, after we upped the success probability for RHB-104 in CD in our model from 40% to 50% on the back of the top-line results. We will consider revisiting the probability following the release of additional results from the trial and feedback from the FDA.

8 August 2018

Price*	**US$6.66**
Market cap	**US$142m**
*Priced at 6 August 2018	NIS3.68/US$
Net cash ($m) at end-Q118 (including short-term investments)	36.4
Shares in issue	21.3m
Free float	90%
Code	RDHL
Primary exchange	TASE
Secondary exchange	NASDAQ

Share price performance



%	1m	3m	12m
Abs	(28.4)	33.7	(26.2)
Rel (local)	(30.7)	25.0	(35.9)
52-week high/low	US$11.3		US$4.6

Business description

RedHill is a speciality company with an R&D pipeline focusing on gastrointestinal and inflammatory diseases, while earlier-stage assets also target various cancers. The most advanced products are TALICIA for H. pylori infection, RHB-104 for CD, RHB-204 for NTM infections, and BEKINDA for gastroenteritis and IBS-D. RedHill also promotes three GI products in the US.

Next events

Top-line results from confirmatory Phase III trial with TALICIA for *H. pylori*	Q418
Initiation of pivotal Phase III trial with RHB-204 for NTM infections	H218

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Exhibit 1: Top-line results of the Phase III trial with RHB-104 in CD

Endpoint (primary in bold)	Active arm (RHB-104 and SoC)	Placebo arm (SoC)	p value
Remission at week 26 (CDAI<150)	**37%**	**23%**	**0.013**
Early remission at week 16	42%	29%	0.019
Remission at week 52	27%	20%	0.155
Durable remission week 26–52 (remission seen at every visit, weeks 26, 35, 44 and 52)	18%	13%	0.319
Durable remission over weeks 26–52 (remission on at least 3 of 4 visits after week 26)	28%	17%	0.034
Remission seen at week 16 and at week 52	25%	12%	0.007
Durable remission week 16-52 (remission seen at every visit, weeks 16, 26, 35, 44 and 52)	18%	9%	0.038
Response at week 26 (≥ 100 reduction in CDAI)	44%	31%	0.028

Source: RedHill's data; SoC – standard of care

Inducing the remission and maintaining the remission

With regards to early remission induction, RedHill's data appear to be very solid. Both the primary (remission at week 26) and secondary endpoints (early remission at week 16) reached high statistical significance (p=0.013 and p=0.019, respectively) and were consistent with treatment effect of 14pp and 13pp, respectively (active arm percentage point improvement over placebo). One of the key secondary endpoints not reached was remission at week 52. First of all, the trial was not powered to measure long-term efficacy on this endpoint. For example, dropouts due to adverse events were 18% in the placebo arm and 21% in the active arm (p values were not provided, but it appears there is no a major difference between arms, in our view, these are complex patients and the dropout rates can be high). Secondly, we believe the confusion came from the perception that the standalone endpoint remission at week 52 in all patients that were recruited will actually be needed for the FDA.

The regulatory authorities might not necessarily ask (it may even be unlikely, given how previous trials were designed) to prove long-term remission maintenance using this endpoint specifically. By definition, this measures how many patients are in remission at the end of the trial, but provides no information as to whether and how early the remission was induced, the durability of the remission, and whether the treatment effect dissipated over time or not. A standalone week 52 remission endpoint implies that the drug is expected to be equally effective in all patient populations over the long run. However, when it comes to clinical relevance, one needs to identify the responder population and evaluate for how long the remission can be maintained in these patients. During the analyst conference call, RedHill confirmed that the FDA will likely ask for evidence that the drug's effect is still noticeable at week 52, as was the case in past CD trials; however, as RedHill clarified later this is unlikely to be the straightforward remission at the week 52 endpoint in all patients that entered the trial, but a combination of early remission induction and a long-term maintenance of it in the responder population.

- **An example of trial design**: "The CHARM trial of adalimumab in Crohn's disease" (J F Colombel, Gastroenterology&Hepatology, July 2006). The trial examined an anti-TNF-α agent adalimumab, Humira (AbbVie, sales of $4.3m in CD alone in 2017), one of the biologicals allowed in RedHill's trial:
  - Population: moderate or severely active Crohn's disease.
  - The efficacy measure was a remission with a decline in CDAI score to less than 150, same as in RedHill's trial.
  - Initially enrolled 854 patients – one of the largest studies of anti-TNF therapy.
  - First phase was open-label treatment with adalimumab, common to all early anti-TNFs because of ethical issues to avoid true placebo arms. All patients were allowed background therapy during the trial.
  - All 854 patients received open-label induction treatment with adalimumab.

- At week 4, 778 patients (both responders and non-responders) remained, who were randomised to two different doses of adalimumab or placebo.
- Of this group of 778 patients, only 499 were responders at week 4 and **only** these patients were considered for primary efficacy analysis, as opposed to the total of 854 patients who were enrolled initially. **Primary endpoints were remission at week 26 and week 56 in the patient population that responded early on**.
- **Key take-away**: efficacy endpoint for long-term maintenance of remission was tested in the responder population, while RedHill's standalone remission at the week 52 endpoint was tested in all patients who were recruited, even those who may have never responded.

Top-line RHB-104 and TNF-α inhibitors data compare well

RedHill issued a separate press release a couple of days later addressing this issue:

- the company reiterated the successful outcome from the MAP US study with primary and key secondary endpoints met;
- RedHill clarified that the standalone week 52 endpoint should be considered as exploratory and should not be expected to play a role in future development;
- the clinically and regulatory relevant long-term efficacy endpoint should be "maintenance of remission". Typically, this means a combination of an early induction of remission, which is then observed at the end of the treatment period in the patient population where early remission was achieved. Within this context a relevant combination used in the US MAP trial would be week 16 and week 52. RHB-104 was twice as effective versus placebo (25% vs 12%, p=0.007) in maintaining remission from the induction of remission at week 16 to week 52.

The trials with biologicals currently used in CD (infliximab, adalimumab, vedolizumab and ustekinumab) were all designed to evaluate remission maintenance endpoints in the population of patients that achieved initial response. The biologicals achieve around 40–50% remission maintenance after one year of treatment in this subset of patients. This percentage falls to 20% if all patients who started treatment are considered. When comparing apples to apples (as close as possible, as these trials were not head-to-head trials), RHB-104 looks good with regard to long-term remission maintenance (Exhibit 2). Week 16 was the earliest time point when remission with RHB-104 was checked. We believe there will be no pressure for RedHill to move even earlier, as RHB-104 is a combination of antibiotics meant to eradicate MAP, whereas anti-TNF-α agents directly suppress autoimmune response; therefore, mechanism of action and expected onset of effect are not comparable. The clinically relevant endpoints for the next trial could be induction of remission at week 16, which is then maintained through to week 52.

Exhibit 2: RHB-104 comparison with anti-TNF-α agents

Drug	Induction of response or remission	Maintenance of remission in responders	Maintenance of remission in all patients enrolled
RedHill's RHB-104	42% (week 16)	59% (week 52)	25% (week 52)
Infliximab (Remicade)	57% (week 2)	39% (week 30)	22% (week 30)
Adalimumab (Humira)	58% (week 4)	36% (week 56)	21% (week 56)
Ustekinumab (Stelara)	48% (week 8)	53% (week 52)	25% (week 52)
Vedolizumab (Entyvio)	31% (week 6)	39% (week 52)	12% (week 52)

Source: Compiled by RedHill

The RHB-104 data include several measures of how the maintenance of remission was measured (**Exhibit 2**):

- Patients with induction of remission early at week 16 maintained this remission to week 52, **p=0.007**;
- This was also the case when measuring what RedHill defined as durability, ie when patients were in remission at every visit week 16, 26, 35, 44 and 52, **p=0.038**.

- Durable remission throughout weeks 26-52 was statistically not significant (p=0.319), but slightly lowering the hurdle and requiring only three out of four visits to show remission, this led to p value of **0.034**.

We take this data as supportive for remission induction in a standard of care CD patient population with strong hints of long-term remission maintenance, from a trial that was primarily designed to measure acute phase of treatment with RHB-104. Given the use of background treatment, RedHill now has a rich data set and the additional analysis should provide insights into influence of MAP status, combinations with other therapies used, potential positioning in the clinic and mucosal healing. RedHill may also gain more insights from the ongoing open label trial that enrolled those patients in RHB-104 who did not achieve remission at week 26. The meeting with the FDA could happen by end of this year, which will give more clarity about future trial design.

Putting RHB-104 in context of changing R&D CD landscape

The advent of biologicals meant that (1) because of their relatively good efficacy (compared to previous options) it made the inclusion of CD patients in placebo arm increasingly unethical (P Hindryckx *et al*), which means that (2) in order to test a novel mechanism of action in a setting where patients receive anti-TNF-α agents is increasingly high hurdle. On top of that, CD is a chronic disease with multiple therapeutic and surgical options how to manage it and dropout rates can be high. RedHill's current trial was the first company's attempt to gather as much information to understand how to position MAP eradication therapy, a novel strategy, within the CD treatment paradigm. Powering the study to reach long-term remission would have required substantial additional investments.

Unmet need in CD management is still very significant. Despite advances in treatment there is no cure and patients usually are not maintained on long-term remission with one therapy. During the call, Prof Scott Harris MD, who is on advisory board of RedHill, described some ideas about how to position RHB-104 in the clinic. Currently there is a lack of early effective interventions because all medical options for CD are rather toxic. The safety profile of RHB-104, while analysis not fully complete, showed no substantial differences between arms. This means the RHB-104 could be used in mild to moderate CD as a convenient, oral frontline therapy or it could be combined with existing treatment options in across the CD severity spectrum without significantly increasing the toxicity.

Valuation

Our RedHill valuation is increased to $423m or $19.8/ADS, from $405m or $19.0/ADS, after we upped the success probability in our model from 40% to 50% on the back of the Phase III top-line results. We will consider revisiting the probability of success following the release of more detailed/additional results from the trial and feedback from the FDA. Our detailed assumptions for each of the indication are discussed in our last outlook report. Top-line readout from confirmatory Phase III trial with TALICIA for *H. pylori* is another key catalyst in the near term (expected Q418).

Exhibit 3: Sum-of-the parts RedHill valuation

Product	Launch	Peak sales ($m)	NPV ($m)	NPV/share ($)	Probability	rNPV ($m)	rNPV/share ($)
TALICIA, - *H. pylori* infection	2021*	86	106.6	5.0	70%	72.2	3.4
RHB-104, - Crohn's disease	2023	145	69.5	3.3	50%	29.3	1.4
- NTM infections	2022	50	57.1	2.7	30%	14.4	0.7
BEKINDA, - Gastroenteritis	2022	21	29.0	1.4	85%	24.1	1.1
- IBS-D	2023	201	140.9	6.6	60%	103.0	4.8
YELIVA, - Cholangiocarcinoma	2024	115	163.3	7.7	10%	10.8	0.5
- r/r MM	2025	565	249.8	11.7	10%	62.2	2.9
- Advanced HCC	2025	649	149.6	7.0	10%	45.7	2.1
GI specialty products: **Donnatal, EnteraGam & Esomeprazole**	Market	48	25.0	1.2	100%	25.0	1.2
Net cash (end-Q118)			36.4		100%	36.4	1.7
Valuation			**1,027.0**	**46.4**		**423.1**	**19.8**

Source: Edison Investment Research. Note: WACC = 12.5% for product valuations. IBS-D: irritable bowel syndrome; r/r MM: refractory/relapse multiple myeloma; Advanced HCC: hepatocellular carcinoma; NTM: nontuberculous mycobacteria. *TALICIA could potentially reach the market before 2021, given its fast-track status and depending on the timelines for the upcoming confirmatory Phase III trial.

Exhibit 4: Financial summary

$000s	2016	2017	2018e	2019e
December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	101	4,007	16,584	30,157
Cost of Sales	0	(2,126)	(8,292)	(15,079)
Gross Profit	101	1,881	8,292	15,079
Research and development	(25,241)	(32,969)	(26,584)	(29,084)
EBITDA	(30,499)	(51,891)	(39,210)	(35,670)
Operating Profit (before amort. and except.)	(30,543)	(51,972)	(39,317)	(35,801)
Intangible Amortisation	0	0	0	0
Exceptionals	0	0	0	0
Other	0	0	0	0
Operating Profit	(30,543)	(51,972)	(39,317)	(35,801)
Net Interest	1,173	6,428	0	0
Profit Before Tax (norm)	(29,370)	(45,544)	(39,317)	(35,801)
Profit Before Tax (reported)	(29,370)	(45,544)	(39,317)	(35,801)
Tax	0	0	0	0
Profit After Tax (norm)	(29,370)	(45,544)	(39,317)	(35,801)
Profit After Tax (reported)	(29,370)	(45,544)	(39,317)	(35,801)
Average Number of Shares Outstanding (m)	128.5	175.3	213.6	213.8
EPS - normalised (c)	(22.85)	(25.99)	(18.41)	(16.74)
EPS - normalised	(0.24)	(0.26)	(0.18)	(0.17)
EPS - (reported) ($)	(0.23)	(0.26)	(0.18)	(0.17)
Dividend per share (c)	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	46.9	50.0	50.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	6,397	5,667	6,211	6,995
Intangible Assets	6,095	5,285	5,820	6,605
Tangible Assets	165	230	239	238
Investments	137	152	152	152
Current Assets	67,815	51,676	6,497	5,471
Stocks	0	653	653	653
Debtors	1,661	4,818	4,818	4,818
Cash	53,786	16,455	1,026	0
Other*	12,368	29,750	0	0
Current Liabilities	(5,356)	(11,830)	(4,276)	(3,849)
Creditors	(5,356)	(11,830)	(4,276)	(3,849)
Short-term borrowings	0	0	0	0
Long-Term Liabilities	(6,155)	(448)	(448)	(34,200)
Long-term borrowings	0	0	0	(33,752)
Other long-term liabilities	(6,155)	(448)	(448)	(448)
Net Assets	62,701	45,065	7,983	(25,583)
CASH FLOW				
Operating Cash Flow	(28,258)	(44,769)	(44,528)	(33,862)
Net Interest	0	0	0	0
Tax	0	0	0	0
Capex	(85)	(146)	(116)	(131)
Acquisitions/disposals	0	0	0	0
Financing	36,017	25,653	0	0
Other**	24,596	(18,069)	29,215	(785)
Dividends	0	0	0	0
Net Cash Flow	32,270	(37,331)	(15,429)	(34,778)
Opening net debt/(cash)	(21,516)	(53,786)	(16,455)	(1,026)
HP finance leases initiated	0	0	0	0
Other	0	0	0	0
Closing net debt/(cash)	(53,786)	(16,455)	(1,026)	33,752

Source: Edison Investment Research, RedHill accounts. Note: *Bank deposits and financial assets at fair value. **Includes bank deposits converted to cash and cash equivalents.

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