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Initiation of Coverage

July 12 2017

RedHill Biopharma Ltd.: Strategic Expansion from R&D to Sales of Drugs in the US

Primary exchange: TASE

Secondary exchange (ADS/share 1:10): NASDAQ

Symbol: TASE, NASDAQ:RDHL

Sector: Biotechnology

Sub-sector: Drug Development

Stock price target: NIS 4.44

As of July 11th, 2017

Closing price: NIS 2.93

Market cap: NIS 514.7 million

# of shares: 171.6 million

Stock performance (YTD): -36%

Daily-trading-vol. (12 months): NIS 1.083 million

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Company overview

RedHill Biopharma Ltd. ("the Company" and/or "RedHill") is an Israeli publically-traded specialty biopharmaceutical company focused on the development and commercialization of late clinical-stage drugs candidates. The Company's main focus is advanced clinical development and commercialization in the US of orally-administered, proprietary, small molecule drugs for the treatment of gastrointestinal and inflammatory diseases and cancer.

RedHill is currently promoting two gastrointestinal products and is advancing multiple clinical programs: three Phase III for gastrointestinal and inflammation indications and four Phase II for multiple indications including multiple myeloma, hepatocellular carcinoma, pancreatic cancer, and irritable bowel syndrome with diarrhea.

Highlights

- RedHill is expanding its business model from a "classic" biotechnology small size firm to a specialty pharma company, with a sales force in the US, specialized in Gastrointestinal (GI) diseases. This sales platform will also be utilized for future candidate drugs.
- RHB-104, for the treatment of Crohn's disease, is RedHill's largest ongoing Phase III program, providing the highest contribution to the Company's valuation.
- On June 2017, a confirmatory Phase III study for treatment of H. pylori infection commenced with RHB-105 (TALICIA™).
- As Phase III study with BEKINDA™, for the treatment of Gastroenteritis and Gastritis, has been completed with successful top line results published in June 2017. A New Drug Application (NDA) for RIZAPORT® drug for treatment of migraine is planned to be re-submitted to the FDA in Q3 2017 (marketing authorization has already been granted under the Decentralized Procedure, in Germany and Luxembourg, during October 2015 and April 2017 respectively).
- RedHill has signed an agreement with Concordia for the co-promotion of Donnatal® in the US. Donnatal® is a prescription oral adjunctive drug for the treatment of Irritable Bowel Syndrome and Acute Enterocolitis, which will also provide additional potential revenue for the Company.
- RedHill has a license-in agreement with Entera Health Inc. ("Entera Health"), granting RedHill the exclusive rights to sell EnteraGam® in the US. EnteraGam® is a medical food intended for the dietary management of Chronic Diarrhea and loose stools (that must be administered under medical supervision), which will also increase revenue for the Company.
- **Financially, the company has sufficient funds to finance this strategy in during the next coming years.**
- **We estimate the company's equity value at $214.1 million/NIS 762.2; price target of NIS 4.44 per share (range of NIS 4.36-4.52).**

Stock overview YTD (Source: TASE website)

Executive Summary

Investment Thesis

RedHill Biopharma Ltd. (“the Company" and/or "RedHill”) is a publicly-traded specialty biopharmaceutical company focused on the development and commercialization of late clinical-stage proprietary, orally-administered, small molecule drugs for the treatment of gastrointestinal and inflammatory diseases, and cancer.

Currently, RedHill is advancing multiple clinical programs, including three Phase III programs for gastrointestinal and inflammation indications and four Phase II programs for multiple indications including multiple myeloma, hepatocellular carcinoma, diffuse large B-cell lymphoma and Kaposi sarcoma, and irritable bowel syndrome with diarrhea. RedHill has several additional Phase I/II studies planned for the following indications: pancreatic cancer (Mesupron), chlangiocarcinoma, radioprotection (prevention of mucositis in head and neck cancer patients undergoing radiotherapy), and ulcerative colitis (YELIVA).

The Company is addressing a combined market size of more than $10 billion.

Recently, after years of successfully implementing a "standard" drug development strategy, with a business model based on licensing out its IP, the Company has decided to expand its strategy and set up a sales organization in the US that will drive revenues from selling drugs. The Company will continue its current business model in Rest of World markets.

We assume that the reason for this decision is based on the Company's assessment that there is a significantly higher financial value in selling its drugs versus licensing them.

The successful implementation of this new strategy will result in RedHill having a sales platform for its future late-stage drugs candidates. This approach will elevate the Company within the value chain and position it as a player in the Gastrointestinal & Inflammation (GI&I) market rather than as a development company. However, the new strategy has additional implications, including:

1. Headcount will be nearly doubled with the recruitment of a US-based sales and marketing staff
2. Management attention will need to focus on marketing, sales, distribution, logistics, reimbursement and collection
3. Investors will start to benchmark the Company against other drug companies, and not only drug development companies
4. Building a sales organization requires significant investment and costs during the initial years.

The Company is led by a management team, Board of Directors and Advisory Board based in Israel, the U.S., Canada and Europe, with extensive managerial, financial and transactional experience, as well as a successful track record in bringing patented drugs to the market, at both large and small pharma companies.

We evaluate this strategic turning point with high potential, positioning Red Hill as a long-term investment, however, with a relative risk during the next coming years due to minimal sales experience in the “big pharma” playground and an unknown level of acceptance by physicians.

Pipeline Summary

RedHill is currently advancing multiple clinical programs:

BEKINDA® (RHB-102) - a once daily controlled release formulation of Ondansetron for the treatment of acute gastroenteritis and gastritis (successful top-line results from the Phase III study were announced in June 2017) and for irritable bowel syndrome with diarrhea (ongoing Phase II study, with top-line results expected in September 2017).

RHB-104 - a proprietary antibiotics drug combination for treatment of Crohn's disease (ongoing first Phase III study), multiple sclerosis (completed proof-of-concept Phase IIa study) and granted Qualified Infectious Disease Product (QIDP) designation by the U.S. FDA for the Treatment of Nontuberculous Mycobacteria (NTM) Infection.

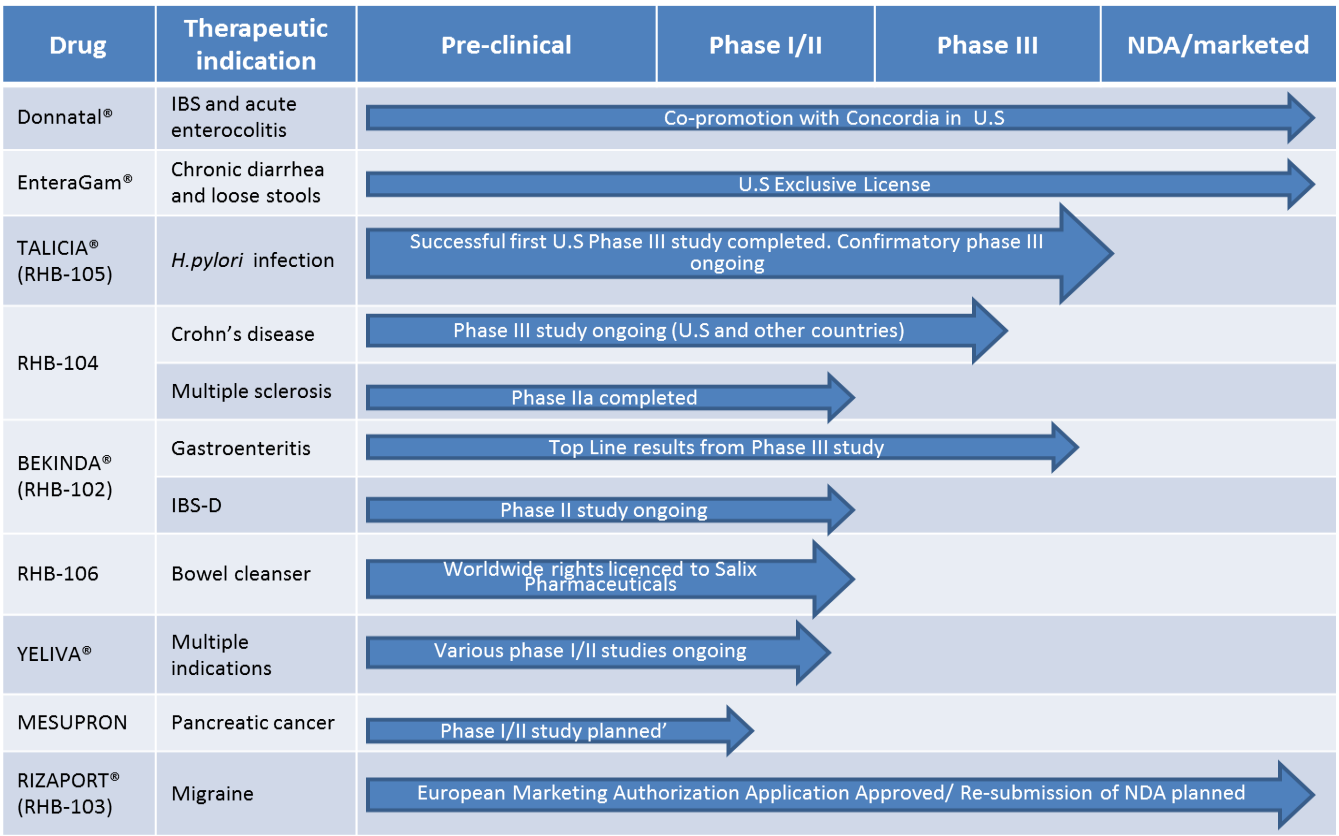
TALICIA™ (RHB-105) - antibiotics and proton pump inhibitor drug combination for the eradication of *Helicobacter pylori* infections (successfully completed first Phase III study, confirmatory Phase III initiated in June 2017).

RHB-106 - a proprietary oral bowel preparation capsule for GI tract procedures with worldwide rights licensed to Salix Pharmaceuticals (now Valeant).

YELIVA® (ABC294640) – orally-administered, first-in-class SK2 selective inhibitor targeting multiple oncology, inflammatory and gastrointestinal indications (multiple Phase I/ II programs initiated and planned).

MESUPRON – an orally-administered protease inhibitor, targeting gastrointestinal and other solid tumors such as pancreatic cancer (Phase I/II study planned to be initiated in H2/2017).

The diagram below represents the estimated timeline/indication in the pipeline, subject to changes in development plans and regulatory requirements/clarifications, including complementary /additional studies.



BEKINDA®, YELIVA®, TALICIA®, and RIZAPORT® are proposed trade names which are subject to FDA review and approval.
Source: Company's data

Upside scenarios	Downside scenarios
Multiple late clinical-stage indications supporting further development and a risk-mitigation position	RedHill establishment of US GI&I specialty pharma may demand high investment and on-going expenses (including a sales force and offices) while significant revenues are yet to come
The strategic turning point in forming a sales force may position RedHill as a "pharma" company with revenue streams, creating value for investors from sales, rather than only from long licensing-out deal processes	The turning point is a risk due to financial resources allocation and management attention requirements. However, we assume that even if the Company does not succeed in establishing this model, it still has sufficient funds and drug candidates to continue its "classic" path
Strong management team with successful track record (RHB-106 to Salix) backed with sufficient funds to support the Company's activities	RHB-104 is RedHill's lead program, currently in ongoing phase III. If this phase is unsuccessful, it may hamper the Company's pipeline

Upcoming Potential Catalysts

Program	Event	Significance	Timeline
BEKINDA® - RHB-102 (gastroenteritis and IBS-D)	Top-line Phase II results (IBS-D)	Medium	**Sep. 2017**
	Clinical Study Report (CSR) from the successful Phase III study (gastroenteritis)	Medium	**Q3 2017**
RHB-103 - RIZAPORT® (Migraine)	U.S. NDA re-submission	Low	**Q3 2017**
RHB-104 (Crohn's Disease)	Meeting with Data and Safety Monitoring Board Group for the MAP U.S. Phase III study for Crohn's disease including safety and interim efficacy analysis, with evaluation of option of early stop for success for overwhelming efficacy	High	**Mid-2017**
TALICIA™ (RHB-105) (*H. pylori*)	Initiation of a confirmatory Phase III study for treatment of H. pylori infection	Medium	**Mid-2017**
YELIVA®	Initiation of Phase Ib study to evaluate YELIVA® as a radioprotectant for prevention of mucositis in head and neck cancer patients undergoing therapeutic radiotherapy	Medium	**Q3 2017**
	Initiation of Phase IIa study with YELIVA® for cholangiocarcinoma	Medium	**Q3 2017**
	Initiation of a Phase II study with YELIVA® for ulcerative colitis	Medium	**Q4 2017**
MESUPRON	Initiation of Phase I/II study in Germany with MESUPRON for pancreatic cancer	Low	**Q4 2017**

Source: Frost & Sullivan analysis

Valuation Methodology

R&D company valuations are challenging due to non-cash valuation with long time to market in the majority of cases. The methods typically used for company valuations, such as Asset Valuation or Multiplies Method, are incompatible for valuation of R&D companies. In such companies, the current business status cannot be analysed through the capital in the balance sheet, and in most cases cannot be compared to similar companies due to uniqueness, from both technological and financial aspects.

As part of the accepted method used in financial valuations – Discounted Cash Flow (DCF), there are several modifications to an R&D company's valuation. In general, a DCF valuation comprises three primary methods:

- **Real Options** - designated for pre-clinical and early-stage clinical programs/companies where the assessment is binary during the initial phases, and based upon scientific-regulatory assessment only (binomial model with certain adjustments).
- **Pipeline assessment** - used for programs/companies prior to the market stage. The company's value is based on the total discounted cash flow plus unallocated costs, and an assessment of the future technological basis. The latter is established based on the company's capability to "produce" new clinical and pre-clinical projects and their feed rate potential.
- **DCF valuation** - similar to companies not operating in the Life Sciences field, this method applies to companies with products that have a positive cash flow from operations.

RedHill is a biopharmaceutical company focused on the development and commercialization of late clinical-stage drug candidates. The Company advances clinical development and commercialization in the US of orally-administered, proprietary, small molecule drugs for the treatment of gastrointestinal and inflammatory diseases and cancer. Thus, the Company's valuation is conducted by examining the company as a holding company vis-à-vis existing projects, with Risk-adjusted Net Present Value (rNPV) capitalization to the net present value, including weighting of several scenarios. These primarily include analysis of the Company's income, evaluated in accordance with scientific / technological assessment, based on various sources and estimates relating to the market scope, degree of projected market success, and the regulatory risk.

The weighted average of a company's revenue in the pharmaceutical and medical equipment market is based on the following data[1]:

- Total Market - examining the extent of market potential for the product / product line
- Market Share - company's ability to penetrate the market during the forecast period
- Peak Sales - peak sales of the company/product during the forecast period
- Annual Cost of Treatment – estimated annual cost per patient, based upon updated market studies
- Success Rate - chances for success of clinical trials and transition to the next phase in the examined sub-field.

Valuation of RedHill's "technological basis" is in fact a valuation of the company's "residual value". This valuation was conducted using the Feed Rate methodology that is common in the field of Life Sciences, rather than using the conventional terminal value, normally used by non- Life-Science companies**.**

[1] Bogdan & Villiger, "Valuation in Life Science - Practical Guide", 2008, Second Edition. pp 84-88.

Valuation Summary

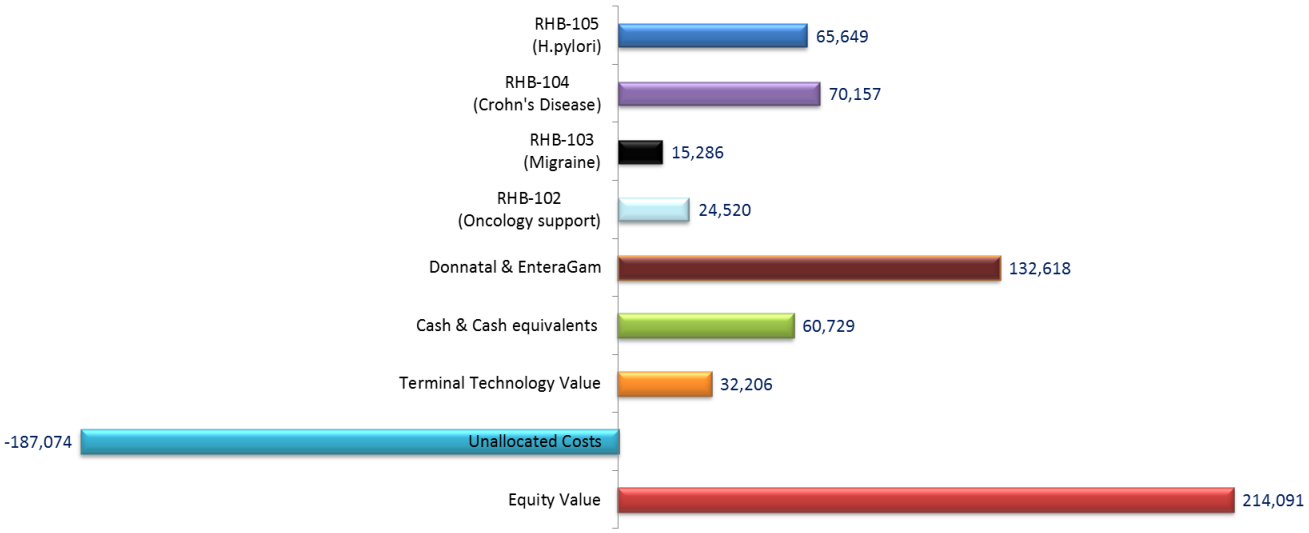
RedHill is currently traded on the TASE and on NASDAQ with American Depositary Shares (ADS), each representing ten of its ordinary shares. We will estimate the Company's price target on the TASE .

RedHill's primary focus is advanced clinical development and commercialization in the US of orally-administered, proprietary, small molecule drugs for the treatment of gastrointestinal and inflammatory diseases and cancer.

The Company is currently promoting two gastrointestinal products in the US and is advancing multiple clinical programs: three Phase III programs for gastrointestinal and inflammation indications, and four Phase II programs for multiple indications including multiple myeloma, hepatocellular carcinoma, pancreatic cancer, and irritable bowel syndrome with diarrhea.

We value the Companys pipeline and its technoligical platform (equity value) as follows at $214.1 million:

RedHill Pipeline and technology platform value in 000K:



Source: Frost & Sullivan analysis

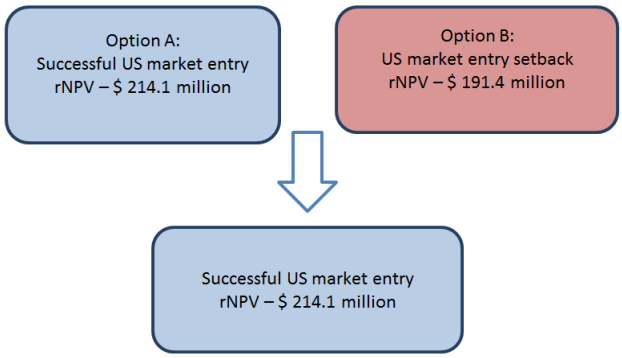
The Company is expanding its business model from a "classic" biotechnology small size firm to a specialty pharma company, with a sales force in the US, specialized in Gastrointestinal and Inflammation (GI&I) diseases. This sales platform will also serve future candidate drugs. On the one hand, this strategic turning point may be a leap forward, as this move elevates the Company within the value chain and positions it as a market player in the GI&I market rather than a development company. On the other hand, it has embedded risks and can result in significant costs without achieving its strategic goals.

Hence, we have conducted an economic analysis of these two scenarios:

- Scenario A: a successful entry to the US market as a "big-pharma" company for GI&I - our primary assumption
- Scenario B: a setback in this turning point.

We have implemented several changes to our analysis regarding Scenario B, including that the business model in the US will be based on an out-licensing deal while the company will lose two years of sales and marketing expenses.

At this point of time, we view RedHill's position as consistent with Scenario A



Given the aforementioned parameters, we estimate RedHills' equity value at $214.1 million / NIS 762.2 billion.

Sensitivity Analysis

In the table below we present RedHill's price target in relation to capitalization rate. We set a range of 0.5% change from our CAPM model (as presented in Appendix C) as the stock range.

Sensitivity analysis - Capitalization rate vs. price target

Cap. rate	Price Target (NIS)
19.6%	4.61
20.1%	**4.52**
20.6%	**4.44**
21.1%	**4.36**
21.6%	4.29

Thus, we estimate the price target in the range of NIS 4.36 - NIS 4.52, with a mean of NIS 4.44 (1 ADS is equal to $0.125)[2]

[2] Calculation is NIS 4.44 divided by 10 ordinary shares, i.e. NIS 0.444 (44.4 Agorot) divided by 3.56 NIS/$ = $ 0.125

Company Activity and Strategy

RedHill Biopharma Ltd. (“the Company" and/or "Red Hill”) is a publicly traded specialty biopharmaceutical company focused on the development and commercialization of late clinical-stage proprietary, orally-administered, small molecule drugs for the treatment of gastrointestinal and inflammatory diseases and cancer. The Company is also undertaking a strategic transition towards revenue-generation via a recently announced US co-promotion agreement for Donnatal® and a license agreement for US rights to EnteraGam®.

The Company’s business model is “finance” orientated, based on a lean, fully outsourced business model that relies on effective project management and is built on expertise, supported by the Company's Board of Directors and Advisory Board, based in Israel, the US, Canada, and Europe.

RedHill assembled an experienced gastrointestinal commercial team in the US and initiated promotion of Donnatal® and EnteraGam®, further enhancing its capabilities.

The majority of RedHill's product pipeline comprises therapeutic candidates acquired from pharmaceutical companies that encountered cash flow or operational difficulties, resulting in low purchasing prices and leading to maximal potential capitalization of those assets. RedHill's pipeline can be segmented into two primary groups: (1) new, patent-protected formulations of existing drugs and (2) new, patent-protected fixed-dose combination drugs - a formulation of two or more existing drugs, combined in a single dosage form. Drug candidates in both groups are designed to improve the currently approved drugs they are based on. Such improvements may include more convenient administration forms, reduced daily administrations, improved safety and efficacy profiles, introduction to new therapeutic indications and reduced costs of treatment. A third group is aNew Chemical Entity (NCE), a drug that contains no active moiety and has been approved by the FDA in any other application such as YELIVA® and MESUPRON®.

The Company's focus on such therapeutic products lowers the risks associated with clinical development since those products are based on previously approved drugs, with proven safety and efficacy data. Additionally, the development of such products usually involves reduced costs and faster time to market compared to the development of new chemical entities (see in "505(b)(2) regulatory pathway"), which further enhance their potential profitability. RedHill’s flagship products, such as RHB 104, RHB 105, and Yeliva, have the greatest market potential. For instance, RHB-104 for Crohn’s disease has a potentially significant impact on the affected population (see more information on the 505(b) (2) regulatory pathway in Appendix B).

Contents

Clinical Programs

RHB-104: antibiotics combination for the treatment of Crohn's disease

Background

Crohn's Disease

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract. CD, along with ulcerative colitis (UC) and indeterminate colitis, belongs to a group of conditions known as inflammatory bowel diseases (IBD) with an unknown etiology. All IBD-related pathologies are associated with intestinal inflammation, resulting from uncontrolled inflammatory processes in the gastrointestinal (GI) tract lining, which involves the attack of the tissues by the body's own immune system (i.e. auto-immune disease). CD generally affects the lower part of the small intestine, but can actually affect any area of the GI tract from the mouth down to the anus (Figure 1). The inflammation in CD often spreads deep into the layers of the affected bowel tissue. Symptoms associated with CD do vary from patient to patient, but some are more common than others and include abdominal pain, severe diarrhea, rectal bleeding, and loss of appetite leading to malnutrition.

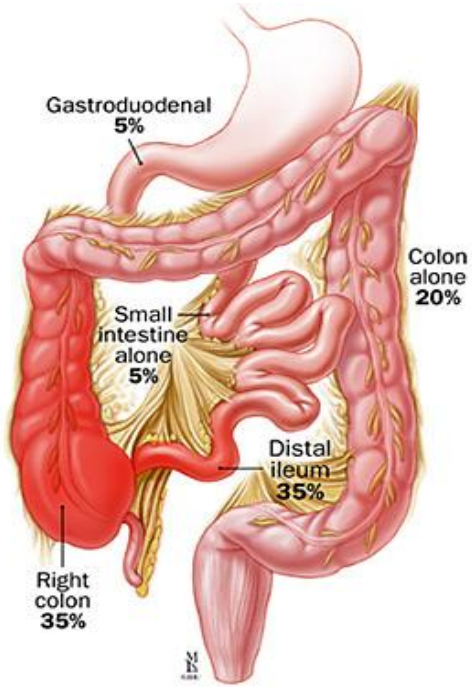


Figure 1: Anatomic distribution of Crohn's disease in the GI tract
(Source: Johns Hopkins Gastroenterology and Hepatology website)

CD complications include abscesses and fistulae, bowel obstructions, perianal disease and colon cancer. Abscesses and fistulae are formed due to the extension of fissure or ulcers through the intestinal wall, with the terminal ileum (the distal part of the small intestine) the most likely point of origin for abscesses, occurring in 15–20% of CD patients. Fistulae occur in 20–40% of patients. Obstructions, mainly in the small intestine, usually result from intestinal mucosa thickening due to acute inflammation, adhesions, and scarring. Bowel obstructions are a major trigger for surgical intervention among CD patients. Perianal disease is a frequent complication characterized by fissures, fistulae or abscesses in the anal region. CD patients have an elevated risk for developing colon cancer, which is regarded to be related to disease severity, duration, and age of onset.

The onset of CD frequently occurs in adolescence or early adulthood, and the disease's course spans throughout the lifetime of the patient, requiring long-term care. CD progression is characterized by periods of active inflammation and symptoms, termed relapse, and periods of symptom improvement and termed remission. The time period between relapse and remission is individual and can rarely be predicted[3].

Although significant progress has been achieved in interpreting the aspects of the molecular pathogenesis of CD, the disease's etiological origins remain unknown and widely debated, as no single factor has consistently met the criteria necessary to be recognized as the sole or major cause of this condition. At present, CD is considered a result of multifactorial causes, including genetic, immune-related, environmental, and infectious triggers.

[3] https://www.crohnsandcolitis.org.uk/. Accessed 28th of June 2017

The MAP connection

Mycobacterium avium subspecies paratuberculosis (MAP) is a gram-positive, small rod-shaped bacterium, characterized by a unique cell wall structure rich in complex lipids (Figure 2). This thick and chemically distinctive cell wall is largely responsible for the bacteria's robust nature, both within the host cell and in the environment, by providing an increased resistance to low pH, high temperature, and a variety of chemicals, and resulting in high endurance and pathogenic potential in harsh and varied environments. MAP bacteria are able to evade host defenses and their resistance mechanisms allow them to survive within phagosomal compartments for more than two weeks.

Historically, Crohn's disease has been suspected to be associated with bacterial infection, with MAP being the prominent candidate. This suspicion became a viable theory only during the 1980's, following successful growth of MAP bacteria from patients with Crohn's disease.. Since then, data has been generated to establish an association between MAP infection and Crohn's disease[4]. More specifically, it is claimed by some that CD is caused by an interaction between MAP bacteria and the immune system in individuals with a predisposition to the pathological inflammatory reaction[5]. However, controversy exists over the nature of this association, and scientists are still debating whether MAP infection is the sole cause of Crohn's disease or only a contributing factor for the disease's development in some patients. This theory has also been reviewed and investigated by Food Safety Authorities in the United Kingdom, Ireland and the European Union, and all have concluded that the evidence for MAP being a causative agent for Crohn's disease is inconclusive. The main arguments of each side are presented in the following table.

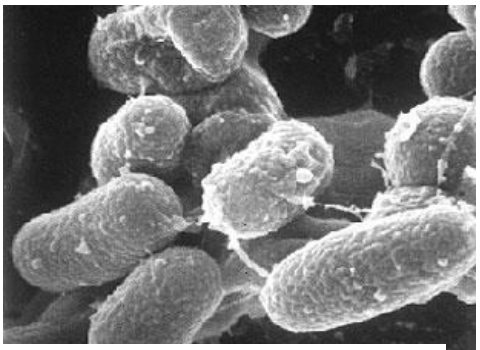


Figure 2: Scanning electron micrograph of MAP bacteria.
(Source: microbewiki.kenyon.edu)

[4] Martin Feller et al. Mycobacterium avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis. The Lancet Infectious Diseases 2007:607-613
[5] Robert J Greenstein. Is Crohn's disease caused by a mycobacterium? Comparisons with leprosy, tuberculosis, and Johne's disease. The Lancet Infectious Diseases 2003:507-514

Pro and con arguments for MAP as a sole causative factor in CD

	MAP is the sole cause of CD	MAP is a contributing factor in some CD patients
Pathological similarity	MAP is the etiologic agent of Johne's disease – a mammalian disease that resembles some clinical and pathological aspects of Crohn's disease. MAP isolated from a Crohn's disease patient induced Johne's disease in goats and mice.	Other microbial species have been detected in Crohn's disease patients such as M. avium complex, Helicobacter species, Listeria monocytogenes an, E coli, Bacteriodes vulgaris and measles virus.
Means of transmission	MAP is transmitted to humans through various means, including infected water, milk, and meat.	
Prevalence in CD patients	MAP infection appears to be present in about 30-50% of CD patients, and is more prevalent in CD patients than in Ulcerative Colitis patients[6][7]. There are also other publications demonstrating prevalence of MAP in CD patients as high as 92%[8]	The presence of MAP in a patient's tissues does not prove causality. MAP has been detected in some healthy controls and in patients with other inflammatory bowel disorders
MAP detection	Current MAP detection methods are sub-optimal	Not all patients with Crohn's Disease have MAP infections.
Anti-mycobacterial treatment	Existing anti-mycobacterial drugs are not efficient enough to eliminate this resistant bacterium	So far there have not been sufficient studies showing that anti-mycobacterial drugs do cure CD.
Contra-indication with steroid therapy	NA	The widespread steroid-based treatment of Crohn's patients would be contra-indicated in a mycobacterial disease, making the disease worse rather than better.
Epidemiology	MAP has been convincingly epidemiologically correlated with CD patients in Wales and Sardinia.	Isolated clusters of cases do not necessarily indicate a comprehensive effect.

Currently, there is insufficient scientific evidence to prove a causal link between Johne's disease (or MAP) in animals and Crohn's disease in humans. Most investigators acknowledge that Crohn's disease is unlikely a single disease entity and probably represents a syndrome with multiple etiologies. However, MAP infection could be the sole cause, or at least a major contributing factor, for a significant sub-population of Crohn's disease patients.

Market, standard of care and unmet needs

Approximately 1 million residents in North America and 2.5 million in Europe are estimated to have IBD[9]. The incidence of Crohn's disease itself ranges from 5.0 - 10.7 per 100,000 person-years globally. However, it is estimated that the real number of patients is considerably higher due to under-diagnosis.

There is geographical as well as ethnic variation observed. The condition is more common in urban areas and in northern developed countries, although it has been observed to be on the increase in developing nations.

[6] Sandborn WJ. The Present and Future of Inflammatory Bowel Disease Treatment. Gastroenterology & Hepatology. 2016;12(7):438-441
[7] Selby et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. Gastroenterology. 2007;132(7):2313-9
[8] Bull, Tim J. et al. "Detection and Verification of Mycobacterium Avium Subsp. paratuberculosis in Fresh Ileocolonic Mucosal Biopsy Specimens from Individuals with and without Crohn's Disease." Journal of Clinical Microbiology 41.7 (2003): 2915–2923. PMC. Web. 29 June 2017.
[9] Gilaad G. Kaplan The global burden of IBD: from 2015 to 2025. Nature Reviews Gastroenterology & Hepatology 12, 720–727 (2015)

Historically, the geographic distribution of Crohn's disease proposed a north-south gradient of incidence, as the disease was originally recognized in Northern Europe and North America. However, recent data have shown increased prevalence also in South Africa and Australia (Figure 3). Generally, urban areas have higher disease incidence rates compared to rural populations. Several ethnic minorities, such as Jews originating from Europe (Ashkenazi Jews) and individuals of Scandinavian descent are at increased risk.

Figure 3: Geographic segmentation of Crohn's disease incidence rates.
The rates range between >7 cases per 100,000 people (red) to <1 per 100,000 (blue)[10]
Source: Johns Hopkins Gastroenterology and Hepatology website)

The 2014 global Crohn's disease therapeutics market was estimated at $3.17 billion. Over the next years, this market is predicted to expand moderately at a CAGR of 3% and reach $4.2 billion by 2020[7]. The US will continue to hold the highest market share followed by Canada and Japan. The slow expected market growth is attributed mainly to patent expiries of commonly prescribed therapies, such as Remicade and Entocort EC and the subsequent launch of generics / biosimilars.

Since the causation of Crohn's Disease has not been fully understood, conventional treatment is directed almost exclusively at suppressing the inflammatory processes, although the dysregulation of the immune system is likely secondary to the disease's actual trigger. This anti-inflammatory therapeutic strategy is usually efficient in the short term, but the disease almost invariably relapses. The standard approach to CD management is divided into treatment of an active disease (induction of clinical response and remission), and maintenance therapy, aimed at maintaining clinical remission and prevent relapses. Treatment for active disease is given to the point of symptomatic remission, with maximal improvement expected to occur within 12 to 16 weeks. Surgery is used for removal of cancerous/pre-cancerous lesions, bowel obstructions, or when the disease is medically intractable. Since CD is highly variable among patients, as well as during the course of the disease in specific patients, therapeutic regimens are adjusted according to the disease's location, severity, and associated complications. Therapeutic approaches are further individualized according to the symptomatic response and tolerance to medical intervention.

[10] Economou and Pappas. New Global Map of Crohn's Disease: Genetic, Environmental and Socioeconomic Correlations. Inflamm Bowel Dis 2007, 14 (5): 709–720

Current CD management is based on several drug classes:

Anti-Inflammatory Drugs

5-aminosalicylic acid (5-ASA) derivatives (mesalamine, mesalazine, and sulfasalazine) are bowel-specific anti-inflammatory agents. These drugs are metabolized in the GI tract, which enables them to exert their pharmacological effects at the site of inflammation (the intestinal mucosa), rather than systemically. 5-ASA derivatives have few adverse effects. Drugs of this class are typically used for inducing remission in mild to moderate disease and are not very effective for patients with active disease limited to the small intestine, or as maintenance therapy.

Steroid Drugs

Corticosteroids (such as prednisolone and budesonide) are very efficient for short-term symptom improvement and induction of remission. A newer type of corticosteroid, budesonide (Entocort EC), works faster than traditional steroids and is associated with fewer side effects. Corticosteroids are often combined with a 5-ASA drug for inducing remission.

While corticosteroids are an integral part of therapy for moderate to severe CD, chronic treatment is associated with numerous side effects, ranging from insomnia and hyperactivity to diabetes, osteoporosis, high blood pressure, glaucoma and an increased susceptibility to infections. Additionally, more than 50% of patients treated acutely with corticosteroids become steroid dependent or steroid resistant.

Immuno-suppressant drugs

Immuno-suppressant therapy (azathioprine, 6-mercaptopurine, and methotrexate) alters the immune response by inhibition and suppression of cellular components of the immune system. This therapy has been shown to be effective for both inducing and maintaining remission; however, two to three months of Immuno-suppressant therapy are usually required before results are achieved. These drugs are usually indicated for inducing remission in patients that have not responded to corticosteroids/5-ASA therapy, as first-line remission maintenance therapy, and as a mechanism for steroid sparing. Potential side effects of the drugs in this class include fever, rash, nausea, leukopenia, hepatitis, increased susceptibility to infections and pancreatitis. Those drugs are not approved by the FDA for the treatment of Crohn's disease.

Antibiotics

Antibiotic treatment, mainly Metronidazole and Ciprofloxacin, is currently used in Crohn's disease following intestinal surgery, for the treatment of perianal disease complications, and for the treatment of infection or abscess. So far, controlled clinical trials with anti-bacterial agents have not been consistent in terms of their effectiveness for treating active disease, and their efficacy in maintaining remission has yet to be properly evaluated in clinical trials.

Biologic Therapies

Anti-TNFα antibodies, such as Infliximab (Remicade), Adalimumab (Humira) and Certolizumab pegol (Cimzia), as well as integrin receptor antagonists such as vedolizumab (Entyvio) and Natalizumab (Tysabri), and Targeting Interleukin-12 and Interleukin-23 cytokines ustekinumab (Stelara), are relatively new and potent biologic agents used for treatment of several inflammatory diseases, including CD. These treatments are approved for patients with moderate to severe active disease, refractory to immuno-suppressants, as a third line therapy. These drugs have also shown efficacy in sustaining clinical remission with re-infusion at 8-week intervals.
Drawbacks of treatment with anti-TNFα antibodies include invasive administration (intravenous or subcutaneous), high treatment costs ($13,000-20,000 a year), loss of response (in nearly 60% of patients during the first year of treatment), and adverse events, such as reactivation of latent tuberculosis, acute and delayed hypersensitivity,

development of antibodies against the therapy and anergy (lack of reaction to infections by the body's defense mechanisms).

Main brand names of the different drug classes used for the treatment of CD are presented in the following table.

Leading marketed Crohn's disease therapies[11]

Trade name (Generic name)	Company	Patent expiry	Sales (2016)*	Remarks
5-aminosalicylic acid (5-ASA) derivatives				
Asacol/Asacol HD (Mesalazine)	Allergan	2013 / 2021(HD)	$618.5m (2015)	- Coated with a pH-sensitive acrylic polymer, releases 5-ASA in the distal ileum and colon. - Asacol HD is a double dose tablet. - ASACOL® HD lost exclusivity on August 1, 2016.
Pentasa (Mesalamine)	Shire/Ferring	Expired (2012)	$305.8m (2015)	Coated granules that release 5-ASA in the upper GI tract, ileum, and colon.
Lialda (Mesalazine)	Shire	2020	$684.4m (2015)	A sustained release version of Pentasa for once daily administration.
Corticosteroids				
Entocort EC (Budenoside)	AstraZeneca/ Perrigo	Expired (2012)	~$90m	Sustained-release capsules. The first drug to be approved by FDA for use in children with the active disease.
Biologic Therapies				
Remicade (infliximab)	Janssen	2013-14	$6,966m	Infliximab-dyyb (Inflectra), a biosimilar to Remicade
Humira (adalimumab)	AbbVie	2016-18	$16,078m	Adalimumab-atto (Amjevita), a biosimilar to Humira.
Cimzia (Certolizumab pegol)	UCB	2024	$1,170m (2015)	
Tysabri (Natalizumab)	Biogen	2015	$1,964m	
Entyvio (Vedolizumab)	Takeda		$241m (2015)	Approval date May 20th, 2014
Stelara (ustekinumab)	Janssen	2022	$3,232m	Anticipated peak year sales $399.5M in 2022

* Sales figure represents income from all approved therapeutic indications. Frost & Sullivan analysis.

Current treatment guidelines of Crohn's, especially in mild-to-moderate disease manifestations, have not changed dramatically in the past years. The market introduction of anti-TNF antibodies shifted treatment guidelines of the moderate-to-severe disease forms, but treatment prices and side effects prevent those therapies from widely advancing to earlier lines of therapy.

The major unmet needs in current Crohn’s disease management include an extension of remission periods and delaying the need for surgery and for treatment with steroids/immuno-suppressants. Those treatment options have

[11] Sandborn WJ. The Present and Future of Inflammatory Bowel Disease Treatment. Gastroenterology & Hepatology. 2016;12(7):438-441

major safety issues and should be ideally avoided. Another important issue that needs to be addressed is lowering the risk of serious infections in moderate-to-severe disease.

RHB-104

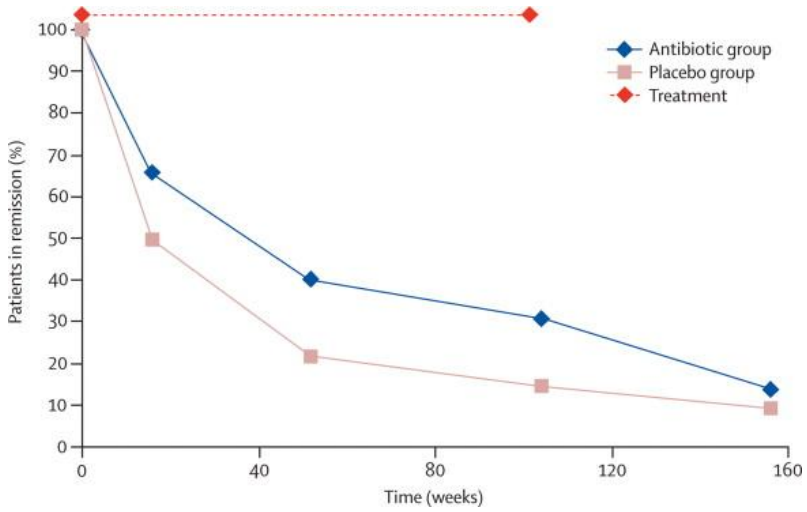
RHB-104 is a patented combination of three generic antibiotic agents - clarithromycin, clofazimine, and rifabutin, in a single capsule for the treatment of Crohn's disease. This treatment's rationale is based on the assumption that CD, at least in some patients, is caused by the presence of MAP bacterium. The drug is currently developed for the treatment of moderate-to-severe active Crohn's disease in adults. However, RedHill obtained an FDA Orphan Drug status for RHB-104 for the treatment of CD in the pediatric population and may pursue a regulatory approval for this population as well.

RHB-104 is based on the studies Professor Thomas Borody, a leading investigator of therapeutic approaches for GI diseases and infections, who formulated the original anti-MAP triple therapy. The triple therapy formula was initially licensed by Pharmacia, which conducted several clinical trials with it prior to its merger with Pfizer, which discontinued the drug's development. Eventually, RHB-104 was acquired by RedHill in 2010 from Giaconda Ltd, a publicly traded Australian company.
In 2011, RedHill acquired the exclusive rights to two separate patented technologies for the identification of the presence of MAP bacteria from the laboratory of Professor Naser of the University of Central Florida in Orlando and from the University of Minnesota. Later on, RedHill entered into an agreement with Q^2 Solutions (formerly Quest Diagnostics Ltd.) to develop a commercial Polymerase Chain Reaction (PCR) diagnostic test for MAP bacteria DNA in the blood, based on the acquired technology. The Company also initiated a collaboration with Baylor College of Medicine intended to further advance the efforts to develop a companion diagnostic for MAP. According to the Company, PCR technology is the most promising approach currently available and it is focusing its efforts in that direction. The development of a companion diagnostic is expected to contribute to the understanding of the role of MAP infection in CD.

Clinical development

Several clinical trials were conducted with an earlier combination of the drug including two Phase II studies (in 2002 and 2005), a Phase III study (published in 2007) and a pediatric study in Australia (published in 2013). The Phase III study was designed to assess the efficacy of the treatment in the reduction of recurrent disease symptoms (disease relapses) during 12, 24 and 36 months, among patients that responded to an initial 16-week treatment. The study's secondary objective was to assess the rate of patients whose clinical condition improved (induction of remission) within the first 16 weeks of treatment.

The study's primary endpoint of reducing long-term relapse rate was not met, due to underpowering of the study; however, the percentage of subjects that achieved remission at week 16 of the treatment was significantly higher compared to patients treated with placebo[8]. A re-analysis of the study's results based on the intent-to-treat (ITT) principle (ITT analysis includes every subject who is randomized according to randomized treatment assignment. It ignores non-compliance, protocol deviations, withdrawal, and anything that happens after randomization) found a statistically significant advantage for the therapy over the placebo, in terms of remission rates, that lasted as long as the therapy was administered.



The therapeutic effect of clarithromycin, rifabutin, and clofazamine combination treatment (RHB-104 – blue line) vs. placebo (red) over time for patients with Crohn's disease.
(Source: Behr and Hanley, The Lancet 2008[12].

Ongoing development

RedHill is currently running a first Phase III study with RHB-104 for the treatment of moderate-to-severe active Crohn's disease. This study will differ from the previous Australian Phase III study in several aspects:

- RHB-104 is a single formulation of all three antibiotics, unlike the triple therapy formula that was used in the Australian study, which comprised three different pills.
- RHB-104 includes increased doses of two out of the three antibiotic agents, as it was suspected that the doses used in the Australian study were sub-optimal.
- The treatment protocol includes titration of the drug to a maximal dose.
- Different clinical endpoints.

The first Phase III study is currently being conducted in North America, Europe, Israel, Australia and New Zealand, under an Investigational New Drug (IND) application ("MAP US Study") through the 505(b) (2) regulatory pathway. The IND application is a process by which a drug developer receives authorization from the US FDA to perform clinical trials in the US to study an unapproved drug treatment. The MAP US Study is a multi-center, randomized, double-blind, placebo-controlled study that was initiated in Q3 2013. In the MAP US Study, 410 CD patients with the active disease will receive RHB-104 or placebo over a 26-week period to determine efficacy and safety, with an additional six months' follow-up period.

The primary endpoint for the study is the state of remission at week 26 in the treatment arm, compared to the placebo arm. Secondary and exploratory endpoints will include state of response at 26 weeks, maintenance of remission through week 52 and efficacy outcome measures in relation to the presence of MAP bacterial infection.

A 1st safety-focused DSMB (Data and Safety Monitoring Board) was held in December 2016. The DSMB recommended continuing the study as planned. A 2nd DSMB meeting is expected to take place in mid-2017 to discuss safety and efficacy, with an evaluation of an option for early-stop for success. A 3rd safety-focused DSMB meeting will be expected once 75% of subjects complete 26 weeks of study participation. It is expected that patient enrollment will be completed by the end of 2017.

In addition, an open-label extension study was initiated in Q1 2017 for all subjects in the MAP US study with Crohn's Disease Activity Index (CDAI)>150 at 26 weeks.

[12] Behr and Hanley. Antimycobacterial therapy for Crohn's disease: a reanalysis. The Lancet Infectious Diseases 2008, 8(6): 344

As mentioned earlier, RedHill received an Orphan Drug status for RHB-104 for the treatment of pediatric CD patients. Single site, a retrospective study was conducted independently of RedHill by Professor Thomas Borody, MD in Australia and the results were presented at the American College of Gastroenterology 2013 Annual Scientific Meeting and published in The American Journal of Gastroenterology. The results of the study showed clinical remission in 8 out of 10 pediatric Crohn's disease patients with mild adverse events and with no subjects requiring dose adjustment. One patient was excluded due to secondary infection and one patient was non-compliant.

In addition to developing a treatment for CD, RedHill has also acquired the exclusive rights to several technologies and is developing a companion MAP diagnostic test with Q^2 Solutions (Quest Diagnostics). This diagnostic test is aimed at identifying the presence of MAP bacteria in CD patients.

RHB-104 is covered by several issued and pending patents with various patent expiry dates.

Pipeline Competition

The CD therapeutics pipeline is robust and varied, with several first-in-class molecules in late-stage clinical development. The launch of those products is expected to balance the anticipated arrival of several generic/biosimilar drugs (mainly for Entocort EC and Remicade) and expand the current market.

The CD therapeutics pipeline can be segmented into small molecules, biologic therapies, and cell-based therapies. The more advanced drug candidates of each class are presented in the following table.

Advanced Crohn's disease therapeutics pipeline (Phase III drugs)

Drug	Company	Development stage	Mechanism of action	Remarks
Small molecules				
Vercirnon	GSK/ ChemoCentryx	Phase III	C-C chemokine receptor type-9 antagonist	Vercirnon is a Phase III-ready drug candidate for the potential treatment of patients with moderate-to-severe Crohn's disease, a chronic inflammatory condition of the gastrointestinal tract
Mongersen	Celgene	Phase III	Gene expression inhibitor, SMAD7 inhibitor	Oral antisense oligonucleotide
Filgotinib	Abbott	Phase III	Janus kinase 1 inhibitor	The first Janus kinase (JAK) inhibitor showing efficacy in moderate-to-severe Crohn's disease patient
Masitinib	AB Science	Phase III	Tyrosine kinase inhibitor	
Biologic Therapies				
Etrolizumab	Roche	Phase III	Alpha4beta7 integrin antagonist	Humanized Monoclonal antibody
Infliximab	Pfizer	Phase III	Tumor necrosis factor alpha antagonist	Monoclonal antibody therapy
Cell-based therapies				
PROCHYMAL	Osiris Therapeutics	Phase III	Adult human mesenchymal stem cells	Intravenous infusion of adult human mesenchymal stem cells for treatment-refractory moderate-to-severe CD.

Source: Data generated from Pharmaprojects

Small molecules

The CD small molecule pipeline consists of improvements in currently used drugs, as well as molecules aimed at new therapeutic targets. The first group contains several new formulations of budesonide (a corticosteroid) offering sustained or targeted release of the drug in the intestines. The latter group takes up the majority of the small molecules pipeline and comprises molecules with various anti-inflammatory activities, including inhibition of pro-inflammatory cytokines, potentiation of anti-inflammatory cytokines, inhibition of pro-inflammatory cell signaling, and inhibition of gut-specific lymphocyte homing.

There are numerous small molecules being developed, including but not limited to Mongersen (GED-0301, Celgene) - an investigational oral antisense oligonucleotide targeting Smad7; Ozanimod (Celgene) - an oral agonist of the sphingosine-1-phosphate subtype 1 (S1P1) receptor; Xeljanz (Tofacitinib citrate, Pfizer) - an oral, small-molecule Janus kinase inhibitor; and ABT-494 (Upadacitinib, Abbvie) - a JAK1 selective inhibitor.

Biologic therapies

The biologic therapies pipeline consists mainly of monoclonal antibodies (mAbs) targeting several inflammation-associated proteins, such as interleukins and integrins. Most of these mAbs are tested for their ability to induce remission, as well as to maintain it, in patients that failed or are intolerant to anti-TNFα therapy. Clinical data shows that at least some of those antibodies are successful at both.

There are numerous biologic therapies being developed including but not limited to Medi2070 (AstraZeneca/Allergan) – a fully human IgG2 monoclonal antibody that selectively binds the p19 subunit of IL-23 an (anti-cytokine antibodies); Etrolizumab (Roche) - a humanized IgG1 MAb targeting the beta 7 integrin subunit; and PF-00547659 (Pfizer/ licensed to Shire worldwide) - a fully human IgG2 monoclonal antibody targeting MAdCAM on endothelial cells.

Neovacs is taking a different approach, designed to solve the major problems associated with anti-TNF Abs - allergic reactions and loss of response. Neovacs' TNF Kinoid is an active TNFα immunization that stimulates the body's immune system to produce its own antibodies against TNFα. This product is in the pre-clinical state for Crohn’s indication.

Cell-based therapies

These treatments are developed as last line therapies, for patients that have failed all other treatment options. Stem cell treatments, developed by Osiris, are based on the ability of such cells to act as immune modulators by secreting anti-inflammatory mediators. TxCell is taking a different approach to cell-based treatment with OvaSave - a T cell-based vaccine, based on the patient's own T-cells that are activated and infused back into the blood circulation.

Summary of the competitive analysis

In addition to therapies that are being developed for CD as a primary indication, other anti-inflammatory treatments, which are currently marketed or developed for the treatment of other autoimmune/inflammatory indications (such as rheumatoid arthritis or psoriasis) may be repositioned to the CD market. Regardless of the therapeutic approach, characteristics of new treatments for Crohn's should include an extension of remission periods/improvement of remission induction, a good safety profile, fast therapeutic effect and convenient administration in regard to administration route and intervals.

The entire CD therapeutics pipeline is addressed at modulating the inflammatory processes associated with the disease. Moreover, the majority of the drug candidates are directed at moderate to severe CD and aims to dethrone the anti-TNF antibodies, which are responsible for the large share of revenues in the CD market due to their high costs. Clinical advantages over the currently used therapies, in terms of better efficacy and safety, will influence market

penetration of upcoming drugs, with oral enzyme inhibitors having great potential due to their easier administration route compared to the injected antibodies.

Unlike its pipeline competitors, RHB-104 is not an anti-inflammatory agent yet some of the RHB-104 components have an anti-inflammatory effect. This differentiation from the bulk could be an advantage, should this drug candidate prove to be efficient in inducing remission without safety issues. However, the different mechanism of action of RHB-104, and the fact that its relation to CD is not widely accepted in the scientific community could interfere with the drug's commercial potential and complicated ramp-up period, if clinical efficacy will not be remarkable. In our view, utilization of a validated MAP detection kit to screen MAP positive patients can greatly influence the clinical success of RHB-104, and its revenue generation accordingly.

As most repositioned drugs, should RHB-104 reach the market, its sales could be hampered by the off-label use of separate generic antibiotic agents. However, in the specific case of RHB-104, such a scenario is less probable since off-label use will require physicians to prescribe three different pills compared to a single capsule. In addition, the proposed treatment protocol of RHB-104, that includes dose titration, will complicate such off-label use.

Another barrier for wide use of the RHB-104 is limited accessibility to one of the antibiotics, clofazimine, which can be distributed by the World Health Organization as well as the US Department of Health and Human Services. It can also be accessed through Novartis Expanded Access Program for eligible nontuberculous mycobacterial patients. It is not commercially available and generally requires name-based individual import permit for use.

Exploring an additional indication for RHB-104 – Multiple Sclerosis

Based on the same scientific rationale described earlier for the use of anti-MAP treatment for CD, i.e. an infectious background for inflammatory diseases, RedHill is exploring a possible use of RHB-104 for the treatment of Multiple Sclerosis (MS). MS is a neurological autoimmune disease in which the body's immune system attacks the protective myelin sheath around the axons of neurons in the brain and spinal cord. The damage to the myelin causes irreversible nerve deterioration that results in physical and cognitive disabilities.

In December 2016, RedHill completed a Phase IIa proof of concept study to assess the efficacy and safety of fixed-dose combination RHB-104 as add-on therapy to interferon beta-1a in patients treated for relapsing remitting multiple sclerosis.

RedHill also performed multiple pre-clinical studies with RHB-104 for varied indications, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), type 1 diabetes (T1D) and psoriasis. In addition, this molecule was granted QIDP designation by FDA for the treatment of nontuberculous mycobacteria (NTM).

RHB-104 Program valuation

We started our pipeline valuation with RHB-104 for the treatment of Crohn's Disease, examining the program's technological, regulatory and financial aspects.

Clinical/regulatory progress: RedHill is currently preparing two pivotal phase III studies with RHB-104 for the treatment of moderate-to-severe active Crohn's disease. The first study (MAP US study) is expected to end in Q2 2017, following which we assume a phase IIIb study until 2020, and an FDA submission in 2021. Furthermore, we estimate that the MAP EU study will follow the US regulatory path. We embrace the Company's assumptions relating to the costs of these studies at $12.5 million. Upon success in these studies, we estimate regulatory submission during 2021 and market launch during 2022.

Market parameters: RHB-104's target market is based on the current Crohn's Disease therapeutics market. However, we assume that the actual addressable market for RHB-104 will be smaller (~1.8 billion) due to the therapy's relevance only to MAP-positive patients (~50% of patients), high estimated treatment price (~$8000 per patient annually) and presumed adoption as a second or third line of treatment. Top-down market analysis indicates that the global Crohn's disease therapeutics market was estimated at approximately $3.5 billion in 2017 and is predicted to expand moderately at a CAGR of 3%.

Distribution agreement: according to RedHill's business model, the marketing and distribution of RHB-104 will be executed outside the US by third parties (i.e. pharmaceutical companies/distributors) and within the US with RedHill's sales force, which is currently being established. Our valuation is based on Red Hill's attaining similar marketing and distribution agreements, both inside and outside of the US. Reviewing similar agreements may shed light on the eagerness of pharmaceutical companies to sign such agreements in a specific field, the sums they are willing to pay for such technologies, and the structures of such deals. We assume RedHill will be entitled to receive royalties of 20% from the product's net revenues. Capitalization rate: See Appendix C.

The valuation of RHB-104 is a risk-adjusted net present value (rNPV) capitalization to the net present value. The valuation includes weighting of several scenarios, based upon the main assessments described above. The valuation parameters are summarized in the following table.

Main valuation parameters for RHB-104

Territory	Current development stage	Success Rate Phase 3	Regulatory approval success rate	Launch	Patent period
US	Phase 3	50%	80%	2021	2029
ROW		50%	80%	2022	

Total market per product ($'000)	**3,463,945**
Market Growth (CAGR)	**3.0%**
Company share from Market (Peak Sales)	**30.0%**
Royalties to RedHill	**20.0%**
Royalties to original developer	**20.0%**

Given the aforementioned parameters, we estimate the total value of this program at approximately $70.2 million
(see "Company Valuation" for additional details).

TALICIA™ (RHB-105): combination therapy for the eradication of *Helicobacter pylori* infection

Background

Helicobacter pylori

Helicobacter pylori (*H. pylori*) is a spiral shaped gram-negative bacterium that lives in the stomach and duodenum (the intestine's section closest to the stomach) (Figure 5). This bacterium has adapted defense mechanisms that allow it to survive in the hostile, acidic environment of the stomach: using chemical reactions, *H. pylori* bacteria produce a "cloud" of acid neutralizing chemicals around them, for protection from the stomach's acid. In addition, *H. pylori* infiltrate the thick layer of mucus that covers the stomach lining, which provides for two benefits - protection from the acidic gastric juice, and from the host's immune mechanisms in the form of killer T cells, macrophages and other infection fighting agents (Figure 6).

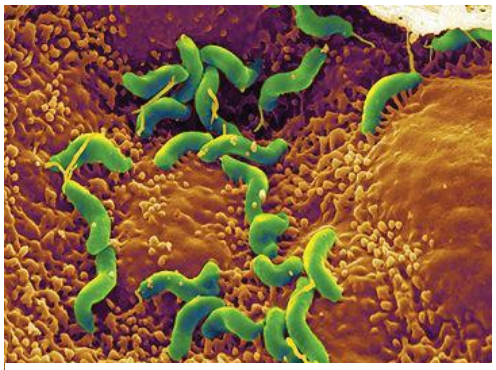


Figure 5: Electron micrograph of *H. pylori* (green) on the mucosal surface.
(Source: Sequella inc.)

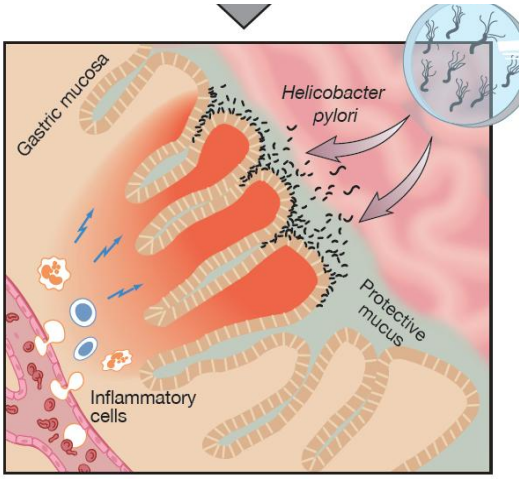


Figure 6: *H. pylori* infect the gastric mucosa below the protective mucus, leaving it protected from both the acidic gastric environment and inflammatory cells. (Source: Sequella inc.)

H. pylori prevalence and incidence differ by geography and race. Prevalence is higher in developing countries and declining in the United States. The incidence of new infections in developing countries is 3-10% of the population annually compared to 0.5% in developed countries. In the former, *H. pylori* infection is associated with a low socio-economic status, the majority of adults are infected, and infection acquisition usually occurs during childhood and adolescence. In developed countries, *H. pylori* affect approximately 20% of people below the age of 40 years, 50% of those above the age of 60 years, and are uncommon in young children. All in all, it is estimated that approximately half of the world's population (approximately 3 billion people) is infected with *H. pylori*.

H. pylori-associated pathologies

The immune system's reduced ability to reach the *H. pylori* infection inside the mucosa lining, results in the accumulation of immune cells in the stomach's/duodenum's tissue and subsequent buildup of destructive pro-inflammatory agents, such as cytokines and reactive oxygen species. Eventually, this sustained immune response leads to inflammation of the stomach lining (gastritis). Many *H. pylori*-infected patients have little or no symptoms, but all eventually develop gastritis. In approximately 15% of *H. pylori* carriers, the infection leads to peptic ulcer disease (PUD) – erosions in the mucosal layer that can be accompanied by abdominal pain, nausea, and vomiting. Nearly all duodenal ulcer cases and 70% of gastric ulcer cases are associated with *H. pylori* infection (Figure 7).

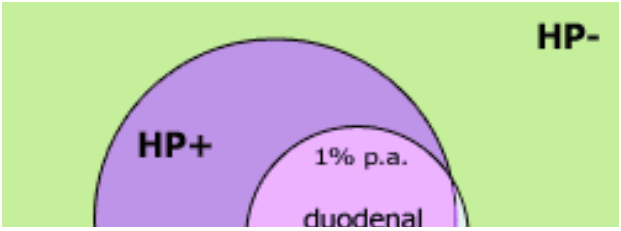


Figure 7: Summary of *H. pylori* associated pathologies in the US. Approximately 30% of the population is infected (big purple circle). The smaller circles represent pathologies associated with *H. pylori* infection and their relative prevalence in *H. pylori* positive cases.
(Source: The Helicobacter Foundation website)

Prolonged and constant *H. pylori* infection can lead to gastric adenocarcinomas (cancer of the stomach) and a rare type of lymphocytic tumor of the stomach called MALT (mucosa-associated lymphoid tissue) lymphoma. In 2013, there were an estimated 79,843 people living with stomach cancer in the United States. 26,370 new cases of gastric cancer were diagnosed in 2016 and approximately 10,730 deaths were

caused by the disease[13]. Gastric cancer is the third most common cause of cancer-related deaths worldwide, killing approximately 754,000 people in 2015[14]. For that reason the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) has classified *H. pylori* as a "Class-I-Carcinogen", which puts it in the same category as cigarette smoking is to cancer of the lung and respiratory tract. In addition, WHO developed a global priority pathogens list (global PPL) of antibiotic-resistant bacteria to help in prioritizing the research and development of new and effective antibiotic treatments and categorized *H. pylori* as Priority 2 (High)[15].

Market, Standard of care and Unmet needs

As mentioned earlier, approximately 30% of the population in developed countries and 70% in developing countries are infected with *H. pylori*. However, treatment for the eradication of the bacteria is almost always performed only upon the occurrence of an associated pathology. Indications for *H. pylori* eradication are presented in the following table:

Indications for *H. pylori* eradication

Strongly recommended indications	Other indications
Duodenal and gastric ulcer	Non-ulcer dyspepsia (indigestion)
Gastric MALT lymphoma	Long-term PPI (proton pump inhibitor) use
Atrophic gastritis	Long-term NSAID (Nonsteroidal anti-inflammatory drugs) use
Partial gastrectomy for gastric cancer	Unexplained iron deficiency anemia
First-degree relatives of gastric cancer patient	

International guidelines for first-line *H. pylori* eradication recommend a triple combination of a proton pump inhibitor ("PPI" – a class of drugs that inhibit the stomach's proton pumps and induce reduction of gastric acid production) and two of three antibiotics (usually amoxicillin, clarithromycin or metronidazole). Guidelines may differ in treatment duration, ranging from 7 days in the European Union to 10–14 days in North America.

These medication combinations typically cure about 70% of infections, with antibiotic resistance being the primary cause of therapeutic failure. During the last two decades, the common use of certain antibiotics in the general population has led to an increase in *H. pylori* resistance to first-line therapy. *H. pylori* resistance to clarithromycin and metronidazole is widespread among patients who have prior exposure to these (or similar) antibiotics. Consequently, the efficacy of standard triple therapy has progressively declined.

When first-line *H. pylori* eradication treatment fails, second-line retreatment usually requires 14 days of a PPI + bismuth subsalicylate (Pepto-Bismol), and two antibiotics, at least one of them different from those used in the first-line antibiotic course. Nevertheless, this treatment fails to eradicate *H.pylori* in approximately 10% of cases.

The different antibiotics and PPIs commonly used for eradication of *H. pylori* are summarized in the following table:

Selected marketed drugs for *H. pylori* eradication

Drug	Dose* Drug class (antibiotics)	Approximate cost of treatment ($)**	Remarks
Standard antibiotics (first-line)			
Amoxicillin	1gr / BID β-lactam	60	

[13] National Cancer Institute (NCI) at the National Institute of Health (NIH), USA.
[14] WHO. Accessed on 14/03/2017. http://www.who.int/mediacentre/factsheets/fs297/en/)
[15] WHO website. Access on 28th of June 2017

Metronidazole	400mg / BID Nitroimidazole	15-30	*H. pylori* resistance to metronidazole is common among patients who have had prior exposure to this agent.
Clarithromycin	500mg / BID Macrolide	15-30	Resistance of *H. pylori* to clarithromycin is common among patients who have had prior exposure to this agent or other similar macrolide antibiotics
Tetracycline	500mg / QID Polyketide	40-50	
	Salvage antibiotics (second/third-line)		
Levofloxacin	300mg / BID Fluoroquinolone	30	
Rifabutin	150mg / BID Rifamycin derivative	100	Rifabutin has rare side effects.
Furazolidone	100–200mg / BID Nitrofuran	60	
	Proton pump inhibitors		
Omeprazole (Prilosec®)	20-40mg / BID	20-40	
Rabeprazole (Aciphex®)	20mg / BID	20-100	
Esomeprazole (Nexium®)	20mg / BID	200	
Lansoprazole (Prevacid®)	30mg / BID	70	
	Combination products		
Omeclamox-Pak	Omeprazole delayed-release (20 mg), clarithromycin (500 mg), amoxicillin (500 mg)	$585	Prepackaged combination of 3 separate drugs / BID
Prevpac	Lansoprazole (30 mg), amoxicillin (500 mg), clarithromycin (500 mg)	$165-1000; (14 day treatment)	Prepackaged combination of 3 separate drugs / BID. First-line of treatment. Manufactured by Takeda.
Pylera	bismuth subcitrate potassium (140 mg), metronidazole (125 mg) tetracycline (125 mg)	$625-960	*3-in-1 capsule* combination treatment although PPI has to be administered separately. Second-line of treatment. Manufactured by Actavis/Allergan.

* QD – once daily; BID – twice daily; QID – four times daily. ** Cost for a 10-day regimen. ***Price taken from Healthcare Bluebook and Redbook

Due to the large daily number of pills required during the course of the therapy, several combination products emerged in the market. These products (for example, Omeclamox-Pak and Prevpac) offer prepackaged pills that simplify administration and increase patient compliance, but do not lower the number of required pills. Nevertheless, these products are sold at roughly double the price of the individual medications. Pylera and Helidac are 3-in-1 capsule combination treatments that contain bismuth and two of the common three first-line antibiotics (but no PPI).

The American College of Gastroenterology (ACG) estimates that 3.5 - 7.5 million Americans suffer from peptic ulcer disease (PUD), and there are approximately 500,000 new cases annually. *H. pylori* are the most significant cause of PUD in the US, with up to 80% of all gastric ulcers and 90% of duodenal ulcers believed to be associated with this bacterium. The US market is approximately $800 million for *H. pylori* related duodenal and gastric ulcers. We estimate the global market to be double that of the US market despite the higher prevalence rate, due to lower treatment seeking rates and preference for lower-cost therapeutic options in developing countries.

The main unmet need in the *H. pylori* eradication treatment paradigm is antibiotic drugs without cross-resistance to nitroimidazole or macrolide antibiotics as components of second and third line combination therapies.

TALICIA™ (RHB-105)

RedHill acquired TALICIA™ (RHB-105) from Sydney-based Giaconda in August 2010. TALICIA™ was invented by ProfessorThomas Borody and it is a proprietary orally administered, single capsule, combination of three approved drugs (omeprazole, a proton pump inhibitor), and two antibiotic agents (amoxicillin and rifabutin). This combination drug is developed by RedHill as a treatment for eradication of *H. pylori* in patients as a first-line treatment. Of the three drugs that comprise TALICIA™, omeprazole and amoxicillin are standard components of first-line *H. pylori* eradication therapy. The third component, rifabutin, is a rifamycin-S derivative, a commonly used antibiotic agent for the treatment of Mycobacterium infections in human immunodeficiency virus (HIV)-infected patients and resistant tuberculosis[16]. Rifabutin's potential utility against *H. pylori* is based on the very low prevalence rate of rifabutin resistance, as well as clinical and pre-clinical efficacy data[1718]. Rifabutin is currently used in some countries as one of the drugs in a third/fourth line drug combination for *H. pylori* eradication.

[16] Maddix et al. Rifabutin: a review with emphasis on its role in the prevention of disseminated Mycobacterium avium complex infection. Ann Pharmaco ther 1994; 28: 1250–4
[17] Gisbert and Calvet. Review Article: Rifabutin in the Treatment of Refractory Helicobacter pylori Infection. Aliment Pharmacol Ther. 2012;35(2):209-221
[18] Graham et al.. A report card to grade Helicobacter pylori therapy. Helicobacter 2007; 12: 275–8

Clinical data

Prior to its acquisition by RedHill, TALICIA™ (RHB-105) went through a Phase II clinical trial in Australia. This study evaluated the safety and efficacy of TALICIA™ (RHB-105) in the eradication of *H. pylori* infection in 130 patients that failed at least one prior treatment, mostly due to antibiotic resistance.

The study's results showed a 90.8% success rate in eradication of *H. pylori* infection. Importantly, the treatment had high success rates among patients with metronidazole- and clarithromycin-resistant *H. pylori* strains (Figure 8). The treatment proved to be safe and tolerable with no serious adverse events and none of the participants stopped therapy due to side-effects.

Eradication rate, *n* (%)

	One previous failed eradication treatment			Multiple previous failed eradication treatments		
	MetS	MetR	Total	MetS	MetR	Total
ClaS	5/5 (100)	7/8 (87.5)	12/13 (92.3)	2/2 (100)	11/14 (78.6)*	13/16 (81.3)
ClaR	10/11 (90.9)	26/28 (92.9)	36/39 (92.3)	12/12 (100)	33/35 (94.3)	45/47 (95.7)
Total	15/16 (93.8)	33/36 (91.7)	48/52 (92.3)	14/14 (100)	44/49 (89.8)	58/63 (92.1)

Figure 8: The effect of TALICIA™ (RHB-105) on *H. pylori* eradication rate in patients with various antibiotic resistance profiles. MetS-metronidazole-sensitive; MetR-metronidazole resistance; ClaR-clarithromycin resistance; ClaS-clarithromycin-sensitive. (Source: Borody et al, Alimentary Pharmacology & Therapeutics 2006)[19]

RedHill performed a Phase III study with TALICIA™ (RHB-105) named ERADICATE-Hp. The study was a randomized placebo-controlled study to assess the safety and efficacy of TALICIA™ (RHB-105) in the treatment of confirmed *H. pylori* infection in dyspepsia patients, regardless of ulcer status. Treatment included 14 days of dosing. Eradication of *H.pylori* was assessed via 13C Urea Breath Test (UBT) testing 28-35 days after completion of treatment.

Final Phase III study results published in March 2016 demonstrated 89.4% efficacy in eradicating *H. pylori* infection. The study successfully met its protocol-defined primary endpoint of superiority over historical standard-of-care (SoC) efficacy levels of 70%. Patients in the placebo arm who were treated with standard of care treatments in an open-label setting after completing treatment with placebo demonstrated low eradication rates of 63%. No treatment-related serious adverse events were noted.

Future development

In April 2016 RedHill announced that it held a meeting with the FDA to plan a second confirmatory US Phase III study to start in Q2 2017. This double blind, randomized trial will compare TALICIA™ (RHB-105) against a high dose amoxicillin/omeprazole. This study is enrolling 444 subjects in up to 65 clinical sites in the US

TALICIA™ (RHB-105) contains certain dishes that are different from those available in generics; therefore the PK/PD profile should be a differentiating aspect. RedHill targets first-line treatment indication, which, if successful, would significantly expand the use of rifabutin-based regimen. This drug is an all-in-one capsule and hence may contribute to improved compliance, and it may appeal to healthcare professionals concerned with overall antibiotic resistance.

TALICIA™ (RHB-105) received FDA Qualified Infectious Disease Product (QIDP) designation under the GAIN Act in 2014 for serious or life-threatening infections. It gives fast-track development status, priority review status, and extended market exclusivity for a total of 8 years in the US.

[19] Borody et al. Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant Helicobacter pylori infection. Aliment Pharmacol Ther 2006; 23: 481–488

Pipeline Competition

The clinical pipeline for *H. pylori* eradication therapies is lean and composed primarily of new antibiotic agents or PPIs, in mid- or early-stage clinical development. Examples of such novel drugs include E-3710 - synthesized proton pump inhibitor developed by Eisai (Phase I); TNP-2092- quinolone antibacterial therapeutic under development by TenNor Therapeutics (Phase I); and anaprazole sodium - a new generation of proton pump inhibitors, under development by Sihuan Pharmaceutical (Phase I).

Other antibiotics are in earlier stages of development such as RECCE-327 – a synthetic antibiotic and anticancer candidate developed by Recce Limited; FROST-900 – a small molecule inhibitor of microtubule polymerization developed by Frost Biologic; and Debio-1453- an antibiotic developed by Debiopharm and Noblex.

There are also a couple of companies developing anti-*H. pylori* vaccines, but they are still in pre-clinical stages.

Probiotics are considered as the next proposed solutions, the majority being in pre-clinical stages. In addition to new molecules, several clinical trials are underway with new combinations of existing antibiotics, but those are being conducted by non-commercial organizations, mainly hospitals.

Summary of the competitive analysis

In the near future, no major changes are expected in the current *H. pylori* eradication guidelines. The insufficient and constantly declining success rates of current treatments, due to antibiotic resistant strains, pose an opportunity for the introduction of new medicine combinations. Such contenders will have to show increased clinical efficacy compared to current treatment methods and are likely to serve as second or third line options, at least in the initial years following market introduction.

In this ecosystem, TALICIA™ (RHB-105) is the only late-stage drug candidate. TALICIA™ (RHB-105) could be embraced as a first, second or third line treatment, with market acceptance dependent on clinical results and pricing. Despite the relatively high efficacy of rifabutin exhibited so far, RedHill might face concerns among physicians regarding the use of this drug as part of a combination treatment for *H. pylori* infections. Such concerns include the possible, though rare, myelotoxicity (bone marrow suppression) side effect that has been linked to the drug, and caution with a broad use of this drug in populations with a high prevalence of tuberculosis in fear of increased resistance of *M. tuberculosis* bacteria to rifabutin. It is worth noting that this possible risk was not mentioned by FDA.

RHB-105 Program valuation

The main valuation parameters for RHB-105 for the eradication of *H. pylori* are:

Clinical/regulatory progress: RHB-105 is being developed as a first-line treatment for patients diagnosed with *H.Pylori* infection. RedHill has completed phase IIIa, planning to show final results by Q2/Q3 2017. Should this study be successful, we anticipate an additional confirmatory phase III study to be conducted during 2018-2019, prior to a New Drug Application (NDA) submission to the FDA during 2019. Market launch is expected during 2020 in the US, and 2021 in non-US markets.

Market parameters: RHB-105's target market was calculated based on several assumptions: (1) we estimate this drug will be used as a second or third line of therapy; (2) price per treatment for RHB-105 was assumed to be $550 per patient, reflecting a 20% premium over prepackaged combination products; (3) low penetration rates are predicted in developing countries due to price premium over generic alternatives. We estimate a maximal share of 10% to the calculated addressable market. In addition to the specified market parameters, the patent family for RHB-105 is set to expire during 2034.

Distribution agreement: according to RedHill's business model, and upon clinical and regulatory success, the marketing and distribution of RHB-105 will be executed by the Company's own sales force in the US, and by third parties (i.e. pharmaceutical companies/distributors) outside the US. Our valuation is based on Red Hill's attaining similar marketing and distribution agreements, both inside and outside of the US.

In the event that RedHill sells the IP for RHB-105, we estimate a total deal value of $28 million, comprised of an upfront payment of $10 million plus sales-based milestone payments. We assume RedHill will be entitled to receive royalties of 20% from the product's net revenues. Capitalization rate: See Appendix C.

The valuation of RHB-105 is a risk-adjusted net present value (rNPV) capitalization to the net present value. The valuation includes weighting of several scenarios, based upon main assessments described above. The valuation parameters are summarized in the following table.

Main valuation parameters for RHB-105

Territory	Current development stage	Success Rate Phase 3	Regulatory approval success rate	Launch	Patent period
US	Phase 3	50%	80%	2020	2034
ROW		50%	80%	2021	

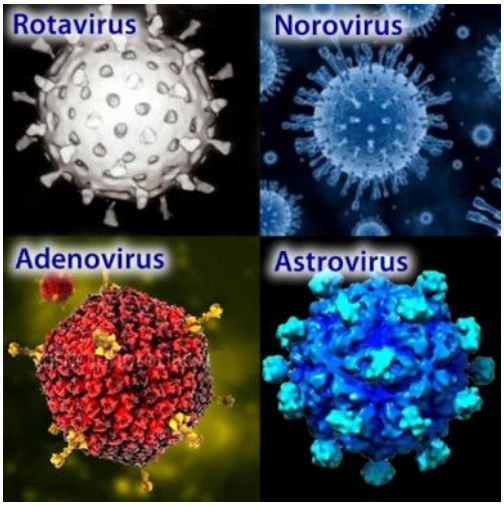
Total market per product ($'000)	**4,600,000**
Market Growth (CAGR)	**0.0%**
Company share from Market (Peak Sales)	**10.0%**
Royalties to RedHill	**20.0%**
Royalties to original developer	**20.0%**

Given the aforementioned parameters, we estimate the total value of this program at approximately $65.6 million (see "Company Valuation" for additional details).

BEKINDA® (RHB-102): a controlled release formulation of Ondansetron for acute gastroenteritis/gastritis

Background

Acute gastroenteritis also known as infectious diarrhea is a common cause of morbidity and mortality worldwide. It refers to the inflammation of the lining of the gastrointestinal tract, mainly stomach and small intestine.



There are two distinguished types of gastroenteritis, namely infectious and non-infectious.

The majority of infectious cases are of viral origin, but there are incidences where the disease is triggered by bacteria or parasite. Most cases in children are caused by rotavirus while cases in adults are caused by norovirus, adenovirus and astrovirus or bacterial food poisoning (Figure 9). The disease is transmitted via contaminated food or water or via close contact with an individual who is infected.

The non-infectious cases of gastroenteritis may follow certain indigestions such as dairy in lactose sensitive patients, medication such as chemotherapeutic agents, and chemical toxins such as heavy metals.

Acute gastroenteritis presents itself with a combination of symptoms that primarily includes diarrhea and vomiting. It can be also associated with abdominal pain, fever and lack of energy. Symptoms usually appear 12-48 hours after contact with a gastroenteritis-causing pathogen and lasts for 1 to 9 days.

The most common complication of gastroenteritis is dehydration. It is generally a mild and self-limiting disease; however acute gastroenteritis is one of the most common causes of hospitalization in non-industrialized countries.

Acute gastroenteritis affects people of all ages. There are currently an estimated 3-5 billion gastroenteritis cases annually worldwide, and 1.5-2.5 million deaths annually in children under five years old[16]. In industrialized countries, diarrheal diseases are a significant cause for morbidity across all age groups.

In the US, there are approximately 179- 350 million cases of gastroenteritis cases annually resulting in 600,000 hospitalizations. Amongst those cases, norovirus was shown to be the main cause of acute gastroenteritis, yet only accounting for 21% of all the cases. More than 21 million people in the United States get infected with this virus while approximately 800 die (Centre of Disease Control and Prevention).

The Centers for Disease Control and Prevention published a report naming norovirus as the leading cause of severe gastroenteritis in children in the US. Acute gastroenteritis causes 1.5 million visits to primary care clinics annually and 220,000 hospital admissions for children under the age of five years, that is, 10% of all hospital admissions of children in the US[17]. This condition imposes significant economic burden and remains the cause of considerable morbidity.

Market, Standard of Care and Unmet Need

Acute gastroenteritis does not normally require medication. Depending on the severity and persistence of the symptoms, oral or intravenous rehydration therapy, or antiemetic medication can be given. Promethazine, metoclopramide, dimenhydrinate, domperidone and ondansetron may be used to reduce vomiting and prevent further dehydration.

There is only limited evidence that promethazine, metoclopramide, and dimenhydrinate can reduce vomiting and those are associated with possible severe side effects.

Ondansetron therapy, on the other hand, can decrease persistent vomiting and may reduce the need for IV therapy; however it should not be used with patients who present moderate-to-severe diarrhea. Ondansetron was developed and marketed by GlaxoSmithKline and Novartis and it is a selective serotonin 5-HT3 receptor antagonist mainly used for post-chemotherapy and post-surgical nausea and vomiting. Ondansetron has a favorable safety profile, does not cause drowsiness and hence, its efficacy in pediatric gastroenteritis patients was evaluated in multiple clinical trials.

RHB-102 (BEKINDA®)

RedHill acquired the rights to RHB-102 in May 2010 under an agreement with SCOLR Pharma, pursuant to which the Company received a worldwide, exclusive license for the development and commercialization of RHB-102. Currently, it has a direct license with Temple University, the original inventor.

BEKINDA® is a bi-modal extended release, once-daily, oral formulation ondansetron. It utilizes a patent-protected technology called Controlled Delivery Technology (CDT®), which uses salts to provide a controlled release of drugs. The CDT® platform enables controlled release drug design (i.e., measured rate of introduction of an active drug) at a relatively low manufacturing cost. RHB-102, which incorporates the 5-HT3 antagonist ondansetron to the CDT technology, is expected to prevent nausea and vomiting over 24 hours - a time window that is significantly longer than the effective time of the majority of oral drugs currently available on the market. The prolonged effectiveness of RHB-102 (approximately 2 hours versus approximately 6 hours for market leader ondansetron) is expected to make this treatment particularly promising.

Clinical Data

Prior to additional indication of RHB-102 for acute gastroenteritis, this drug was tested in a comparative trial assessing the bioequivalence of RHB-102 (24mg) administered once, to Zofran (GSK) 8mg tablet administered three times, over a 24-hour period for prevention of chemotherapy and radiotherapy-induced nausea and vomiting (CINV). The final results of the study, which were received in June 2012, showed bioequivalence of RHB-102 to Zofran and indicated that the efficacy and safety of the two pharmaceutical products would be expected to be similar. A European marketing application was submitted in December 2014, but withdrawn, and RedHill is currently in discussions with EU Member States. In conjunction, a US NDA path is being investigated and will depend strictly on results from ongoing efficacy studies with BEKINDA®.

In September 2014, a new Phase III trial (The GUARD Study) was started. This randomized, placebo-controlled, trial of BEKINDA® (Ondansetron 24 mg bimodal release tablets) was launched to evaluate the safety and efficacy of BEKINDA® in treating vomiting patients due to presumed acute gastroenteritis or gastritis.

The study recruited 320 adults and children over the age of 12, across 29 sites in the US (patient enrollment was completed in February 2017) who attended an emergency center and had at least two vomiting episodes in the four hours preceding consent into the study. The primary endpoint for the study is the absence of vomiting through the protocol-defined period (from 30 minutes post-dose, and subsequently for 24 hours) in the treatment arm, compared to the placebo arm.

The top-line results are expected in Q2 2017. RedHill may be in position to file the NDA in 2017 if highly significant positive results will be presented to the FDA. It may be possible that the GUARD Study would be sufficient as a single Phase III study to support potential future marketing applications in the US

Future development

BEKINDA® is also studied for an additional indication, namely diarrhea-predominant irritable bowel syndrome (IBS-D). The first-in-man pharmacokinetic (PK) study with BEKINDA® 12 mg (RHB-102) proprietary formulation was conducted and demonstrated equivalent dose-adjusted bioavailability and dose-linearity with BEKINDA® 24 mg. It was concluded that half of the normal dose of BEKINDA® was still sufficient to significantly improve stool consistency and frequency. Further, a randomized, double-blind, placebo-controlled, 2-arm parallel group Phase II clinical study was designed to evaluate the safety and efficacy of BEKINDA® 12 mg in patients. It was initiated in April 2016. 120 subjects will be enrolled into this study across 16 clinical sites in the US The primary endpoint for the study is the proportion of patients in each group with response in stool consistency as compared to baseline, per FDA guidance definition. The top-line results are expected in mid-2017.

Pipeline Competition

If BEKINDA® receives approval, it could become the first 5-HT3 antiemetic drug indicated for the treatment of acute gastroenteritis or gastritis in the US

There is no clinical pipeline of gastroenteritis therapeutics aimed at reducing vomiting; however, there is a drug with extended and improved formulations of ondansetron to treat chemotherapy-induced nausea and vomiting. Aptalis Pharma's Eur-1025 is an extended-release oral formulation of ondansetron (patented long-release DiffuCaps® technology). Similarly to RedHill, the company was able to achieve this formulation with the use of a patented extended-release capsule technology. Having completed pilot studies in 2009, the clinical development of Eur-1025 was halted and the compound is currently available to be out-licensed. Even if clinical trials of Eur-1025 resume in the near future, this compound would reach the market a few years after RHB-102.

There are also other drugs in the pipeline for acute gastroenteritis and gastritis including:

- DA-6034 is a flavonoid derivative under development by Dong A; currently in Phase III clinical trial for the treatment of gastritis and dry eye syndrome

- YH-4808 is a 2nd-generation acid pump antagonist (APA; potassium-competitive acid blocker (PCAB)) under development by YuHan; currently in Phase I clinical trial for the treatment of gastritis, duodenal and gastric ulcers, gastrooesophageal reflux

- BGC-001 is an improved new drug under development by Boryung; currently in Phase I clinical trial for the treatment of gastritis

- SGX-201 is an oral formulation of beclometasone dipropionate, under development by Soligenix; currently in Phase II clinical trial for treatment of gastroenteritis

- GC-6101A is an herbal extract, under development by Green Cross, currently in Phase II clinical trial for the treatment of gastritis

The drug pipeline for the treatment of IBS-D is very diversified. There are a couple of drugs in Phase III namely: ATSM (N-acetyl-D-glucosamine) by LeadDiscovery Pharmaceutical and MEN 15596 (non-peptide small-molecule tachykinin neurokinin-2 (NK-2) receptor antagonist) by Menarini. In addition, a few drugs in Phase II clinical trials include linaclotide delayed release-2 by Allergan, and LX-1033 (oral serotonin synthesis inhibitor) by Lexicon Pharmaceuticals.

Program Valuation

The main valuation parameters for Bekinda (formely known as RHB-102) for the treatment of CINV are:

Regulatory progress: Bekinda-24mg is in a phase III clinical trial in the US, with top-line results expected in Q2-Q3 2017. Bekinda 12mg recently began phase II for diarrhea-predominant irritable bowel syndrome (IBS-D), with top-line results also expected in Q2-Q3 2017. We expect submission of an NDA for this product to the FDA during 2019. We anticipate a high probability of FDA marketing approval. Product launch in the US is expected in 2020, and the following year in non-US markets.

Market parameters: The global market size for antiemetic drugs was estimated at $1.5 billion in 2017 (Evaluate Pharma). Specifically, the RHB-102's target market is based on the current Ondansetron market size (approximately $400 million). We estimate a maximal share of 18% from this market by RHB-102.

A range of oral and intravenous anti-emetics are already used by adults and children, however a significant number of concerns have been raised about side effects of older generation anti-emetics. BEKINDA's® advantage lies not only with its limited adverse side effects, but also with extended release formulation. Preventing vomiting in patients affected with gastroenteritis is essential to limit the complications associated with dehydration.

As previously mentioned, BEKINDA® is also considered as a treatment option for patients suffering from IBS-D. The opportunity within IBS market is also significant as market size was valued at $289.3 million in 2015 and is shown to be highly underserved[18]. BEKINDA® will compete with newly approved drugs namely Salix's Xifaxan (rifaximin, an oral antibiotic) and Allergan's Viberzi (eluxadoline, an oral μ-opioid receptor agonist). There are also other drugs including GSK's Alosetron that is approved for the treatment of severe chronic IBS-D in women, however strict prescribing regime needs to be followed due to serious side effects observed.

For CINV indication, there are multiple first-generation 5-HT3 receptor antagonists (azasetron, dolasetron, granisetron, ondansetron, ramosetron, and tropisetron) and one second-generation agent (palonosetron). Azasetron, ramosetron, and tropisetron are not available in the United States. New formulations of the above drugs are also available, such as: orally disintegrating formulation of ondansetron; an extended-release subcutaneous formulation of granisetron (Sustol) which was approved by the FDA in August 2016; APF 530 a long-acting injectable formulation of granisetron (Kytril), developed by A.P. Pharma; Aloxi - a long-acting palonosetron; Netu-Palo a combination therapy which comprises a novel NK-1 blocker, netupitant, with palonosetron (Aloxi); and Rolapitant an NK-1 receptor antagonist, developed by Tesaro.

Distribution agreement: according to RedHill's business model, the marketing and distribution of RHB-102 will be executed by the Company's own sales force in the US, and by third parties (i.e. Pharmaceutical companies / distributors) outside the US. Our valuation is based on Red Hill's attaining similar marketing and distribution agreements, both inside and outside of the US. We take into consideration a non-US deal valued at $20 million. We assume RedHill will be entitled to receive royalties of 20% from the product's net revenues.

Capitalization rate: See Appendix C.

The valuation of RHB-102 is a risk-adjusted net present value (rNPV) capitalization to the net present value. The valuation includes weighting of several scenarios, based upon the main assessments described above. The valuation parameters are summarized in the following table.

Main valuation parameters for RHB-102

Territory	Current development stage	Regulatory approval success rate	Launch	Patent period
US	NDA submission-ready	90%	2020	2035
ROW		90%	2021	

Total market per product ($'000)	**400,000**
Market Growth (CAGR)	**2.0%**
Company share from Market (Peak Sales)	**18.0%**
Royalties to RedHill	**20.0%**
Royalties to original developer	**8.0%**

Given the aforementioned parameters, we estimate the total value of this program at approximately $24.5 million
(see "Company Valuation" for additional details).

RIZAPORT® (RHB-103): a fast dissolving thin film formulation of rizatriptan for the treatment of migraine

Background

A migraine is a neurovascular condition (affecting neurons and blood vessels) characterized by localized, pulsating headache which lasts between 4 and 72 hours. The pain is commonly accompanied by nausea, vomiting, and photophobia and phonophobia (sensitivity to light and sound, respectively). Migraines can be debilitating events that render the sufferer virtually ineffective and unable to function. It is estimated that global prevalence of migraine is 14.7%, meaning 1 in 7 people do suffer from this condition[20]. For the most part, migraines affect people between the ages of 18 and 50 and can be chronic or seasonal, depending on levels of stress and hormonal changes, amongst other factors.

The cause of migraines remains unknown, but abnormal brain activity has been implicated in their onset. It is believed that rapid changes in brain chemicals cause vasodilation (the expansion of blood vessels) in the brain, which then presses on surrounding nerves, forcing them to change their electric activity and to cause pain (Figure 10). As migraines are vascular ailments, the pain is often throbbing, pulsating and localized around the eye area or on the sides of the brain. In general, migraine medications on the market target vasodilation, by constricting the dilated blood vessels.

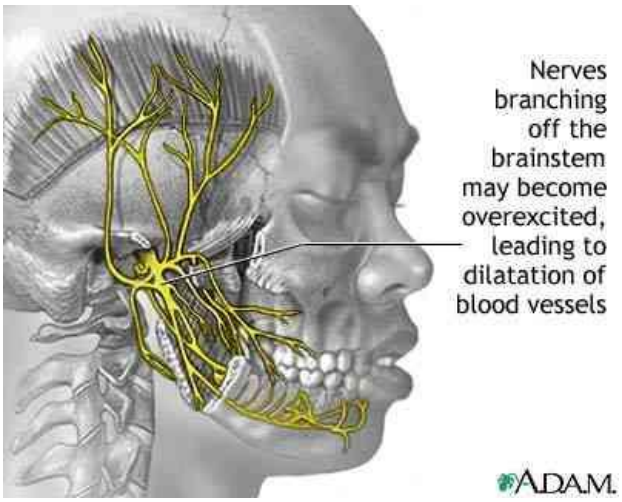


Figure 10: The proposed underlying mechanism of migraine, linking vascular and neuronal changes. (Source: ADAM)

Insofar the proposed triggers of abnormal brain activity that causes migraines have been numerous, ranging from hormonal changes and genetic causes to stress and fatigue. Gender is a defining factor for migraine sufferers: women are at least 5 times more likely to suffer from migraines than men. Approximately 70% of migraineurs have a first-degree relative suffering from migraines, suggesting substantial genetic roots to the disorder. Approximately 2% of migraine sufferers have chronic migraines, which affect them for 15 or more days per month.

The International Headache Society (IHS) has classified migraines into two major types: migraines with aura, and migraines without aura. An aura is a certain migraine-associated sensation which occurs as a result of neuronal excitation in the brain. Most commonly, the aura manifests itself in the form of bright light flashes or brief visual disturbances. The aura Phase can last between 15 minutes to one hour, prior to the headache Phase. Approximately 10% of migraine sufferers experience auras.

Migraines without aura occur in 90% of migraine sufferers, and have a more rapid onset than aura migraines due to lack of a “warning Phase”. The importance of a pre-migraine warning for migraine sufferers is not negligible: the nausea and vomiting stage can follow a migraine onset as closely as 10-15 minutes behind, leaving little time to orally administer medication. Diagnosis of migraines is a fairly recent practice and has not achieved optimal geographic coverage.

It is known that a migraine remains undiagnosed and undertreated in at least 50% of patients, and less than 50% of migraineurs sought a physician’s help for their headache[21].

[20] https://www.migrainetrust.org. Accessed on 28th June 2017
[21] Burch, R. C., Loder, S., Loder, E. and Smitherman, T. A. (2015), The Prevalence and Burden of Migraine and Severe Headache in the United States: Updated Statistics From Government Health Surveillance Studies. Headache: The Journal of Head and Face Pain, 55: 21–34

Market, Standard of care and Unmet Need

Approximately 15% of the global adult population is believed to be suffering from migraines, and the disease is more prevalent in the developed world. The incidence of a migraine is highest in North America, where over 60% of all migraine medication is sold, followed by Europe, Japan, and South America.

The majority of migraine sufferers are not satisfied with their current treatment highlighting, so there is a need for new therapies. Most migraine patients self-medicate with over-the-counter medication and do not seek medical help.

In 2017, the global migraine therapeutics market was valued at $2.16 billion. This market is expected to grow towards the end of the decade at a compounded annual growth rate of 15%, and to eventually reach $4.96 billion by 2022 (Evaluate Pharma). Drivers for the market's predicted expansion include an increase in the numbers of migraine patients (due to increased diagnosis rates), as well as in the sales volume (number of treatment units sold across the globe) of migraine drugs.

Because the exact causes of a migraine are not known, acute treatment is the therapy of choice for the majority of migraine sufferers. If detected early, a mild migraine can be prevented with standard over-the-counter pain medication, such as ibuprofen and aspirin. For moderate-to-severe migraine, prescription medication is needed, and, depending on how far the migraine has progressed, mode of administration can vary among oral, intravenous and suppository. Alternative administration methods to oral pills are mostly used when nausea and vomiting occur once a migraine has advanced, making the ingestion of pills difficult.

In cases of chronic migraines, antidepressants, blood pressure medicines, and seizure medicines can be prescribed for longer-term use as a prophylactic treatment. Botulinum toxin injections (Allergan's Botox) into the head and neck area have also recently become a popular prophylactic treatment for migraines, as they work by constricting blood vessels over longer terms.

The vast majority of migraine sufferers self-medicate at home. The agents which are used to treat an acute migraine include 5-hydroxytryptamine 1B/1D (5-HT 1B/1D) receptor agonists (e.g., triptans), dopamine receptor antagonists (phenothiazines, metoclopramide), ergot derivatives (dihydroergotamine), intravenous nonsteroidal anti-inflammatory drugs (NSAIDs), and opioid drugs (Table 7). There have been advancements in this sphere in recent years: nasal spray formulations have allowed the speed of headache relief to reach 15-20 minutes (vs. 30-60 minutes for oral tablets administration). Subcutaneous injections of sumatriptan have been able to achieve relief times of 10-15 minutes, but have not taken up a major market share due to the inconvenience of this mode of drug delivery.

The migraine market is highly competitive and new drugs aim at providing faster or easier drug delivery, such as nasal sprays, needleless injections, oral thin films and sublingual tablets. Triptans are the class of drug most commonly prescribed for the acute treatment of a migraine.

Leading and most recently approved Migraine drugs

Trade Name (generic name)	Company	Administration mode	Speed of Action (min)	Price per treatment ($)*	Patent Expiry
Triptans					
Maxalt (rizatriptan)	Merck	Oral tablet, ODT**	30-60	263	Expired (Dec 2012)
Zecuity	Teva	Injection	10-15	NA	NA. Halted sales in June 2016
Sumatriptan nasal powder	OptiNose	Delivered intranasally with an inhaler device		542 (6 spray vial)	March 2020
Imitrex (sumatriptan)	GSK	Oral tablet, Nasal spray, SC Injection	30-60 (tablet) 20 (spray) 10 (injection)	435 (oral 50mg 6 tablets) 654 (6 spray vial) 1056 (0.5 ml 5s)	Expired
Sumavel DosePro (sumatriptan)	Zogenix	Needle-free injection device	10-15	394 (0.5 ml 6s dose)	2025
Treximet (sumatriptan + naproxen)	GSK/Pozen	Oral tablet	30-60	640	2025
Zomig (zolmitriptan)	AstraZeneca	Oral tablet, Nasal spray	30-60	643 (branded oral tablets) 442 (6 spray vial)	Expired (Nov 2012)
Zolmitriptan Rapidfilm (zolmitriptan)	APR/Labtec	Polymeric film strip	15	N/A	2029
Frova (frovatriptan)	Vernalis	Oral tablet	30-60	530	2013-2015
Relpax (eletriptan)	Pfizer	Oral tablet	30-60	374	2017
Axert (almotriptan)	J&J/Lundbeck/ Almirall	Oral tablet	30-60	307	2015
Nonsteroidal anti-inflammatory agents					
Cambia (diclofenac)	Nautilus Neuroscience	Sachets dissolvable in water	15-20	615 (6 packets)	2026
Ergot derivatives					
Migranal (dihydroergotamine)	Novartis	Nasal spray; IV, SC, IM injections	30	4054 (4 spray vial)	Expired
Opioids					
Amidone, Dolophine (methadone)	various	Oral, rectal, IV injection, sublingual	30-45	5	Expired
Dopamine receptor antagonists (for treatment of nausea and vomiting)					
Reglan (metoclorpamide)	Schwarz Pharma	Oral	30-40	20	Expired

SC – subcutaneous; IV – intravenous; IM – intramuscular

* Price per treatment specifies price per 6 tablets unless indicated otherwise. Price points reference: RedBook

** Orally disintegrating tablet (Maxalt-MLT).

Despite a large array of drugs that target a migraine, significant unmet need remains in this therapeutic area. Longer-acting medications are desirable, as currently only about half of triptan medications are able to provide a 24-hour relief to migraine patients. Prophylaxis of migraines also remains a pressing issue, although it is not likely to be resolved before more is known about this ailment's mechanism of action. Finally, the speed of relief is of crucial

importance in migraine cases. Migraine onset is normally very rapid, averaging 15 minutes, and nausea and vomiting, once triggered, can prevent treatments that require swallowing altogether.

RIZAPORT® (RHB-103)

RIZAPORT® is an oral thin-film formulation of a leading migraine compound, rizatriptan, intended for the treatment of acute migraines (Figure 11). Rizatriptan was exclusively marketed under the name Maxalt by Merck until December 30, 2012, following which production of generic versions of rizatriptan by at least five generic companies commenced.

Figure 11: Thin film of RIZAPORT
Source: InteGenx Corp

RIZAPORT® is based on a technology called "VersaFilm", patented by the Canadian company called IntelGenx Corp.

RIZAPORT® is being developed as part of a co- development and commercialization agreement between RedHill and IntelGenx. VersaFilm allows the production of thin film strips that dissolve rapidly in the mouth and is designed to facilitate the drug's absorption through the oral mucosa and into the bloodstream. This mode of delivery is particularly convenient for patients whose migraine has advanced into the nausea/vomiting stage, or for patients who have trouble swallowing tablets with water.

It is important to note that rizatriptan (Maxalt) has been documented on several occasions to be consistently more effective than its triptan competitors[22][23]. A 2006 study found that 61% of migraine patients gave substantial preference to 10mg rizatriptan wafers (ODT) over other oral triptans based on their rapid headache relief alone[24]. As this drug is now generic, rizatriptan is likely to achieve more substantial prescription volumes in the future.

Clinical Data

RedHill advanced the clinical development of RIZAPORT® through the 505(b)(2) bioequivalence regulatory pathway since the only active pharmaceutical ingredient it contains is rizatriptan, which is approved for migraine therapy.

Having obtained an IND approval from the FDA and a CTA approval from the Canadian Health Authority in April 2012, a bioequivalence trial was conducted in Canada with RIZAPORT® on 24 volunteers. In the trial, the pharmacokinetic profile of RIZAPORT® was compared to the reference drug – Maxalt MLT. As seen in Figure 12, RIZAPORT® exhibited bioequivalence to the reference drug.

[22] Gerth, W. C et al. "Patient Satisfaction with Rizatriptan versus Other Triptans: Direct Head-to-head Comparisons." International Journal of Clinical Practice 55.8 (2001): 552-56
[23] Lipton, Richard B et al. "Effect of Rizatriptan and Other Triptans on the Nausea Symptom of Migraine: A Post Hoc Analysis." Headache: The Journal of Head and Face Pain 41.8 (2001): 754-63
[24] Láinez, Miguel JA. "Rizatriptan in the Treatment of Migraine." Neuropsychiatric Disease and Treatment 2.3 (2006): 247-59

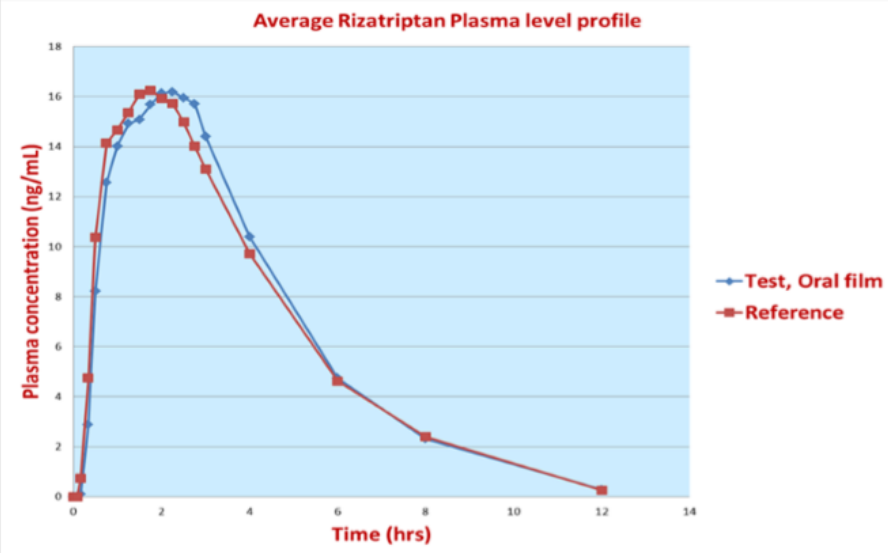


Figure 12: Plasma distribution of a single dose of RIZAPORT® vs. Maxalt MLT.
(Source: RedHill Company Presentation)

Consequently, RedHill filed an NDA for RIZAPORT® with the FDA in March 2013. Following a Complete Response Letter (CRL) received by RedHill in February 2014 mentioning issues related to third party manufacturing, packaging, and labeling, the Company is planning a re-submission of the NDA to the US FDA in during Q3 2017. Based on the bioequivalence study results and addressed issues of third-party chemistry, CMC, packaging and labeling, we anticipate a high probability of an FDA marketing approval.

In Europe, RIZAPORT® was approved in October 2015 by Germany's BfArM and in April 2017 by the Ministry of Health of Luxembourg under the European Decentralized Procedure. Grupo Juste S.A.Q.F (now Exeltis Healthcare, S.L.) is expecting to launch RIZAPORT® in H2 2017 in Spain, and Pharmatronic Co. will launch RIZAPORT® in South Korea (no financial details available). This agreement gives the potential for expansion into other territories in Latin America and the Middle East.

Another commercialization agreement was signed in December 2016 with Pharmatronic. This strategic partnership will facilitate geographic expansion into South Korea, with the launch expected in Q1 2019.

Pipeline Competition

There are many migraine drug candidates at different stages of drug development. They have novel mechanisms of action, more patient-friendly formulation or are new therapeutic targets. The majority of the pipeline is targeted at an acute migraine, whilst the rest is focused on prophylaxis of a chronic migraine. Effective new approaches are being developed for the treatment of an acute migraine. They target calcitonin gene-related peptide (CGRP) or serotonin (5-hydroxytryptamine, 5-HT1F) receptors. Additional therapies targeting the transient receptor potential vanilloid (TRPV1) receptor, glutamate and GABAA receptors are being investigated, however with limited success observed in clinical trials. The following table summarizes the leading migraine drug candidates in the pipeline (Phase III drugs mentioned only).

Leading drug candidates in the migraine pipeline

Drug	Company	Development stage	Anticipated market entry	Remarks
Triptan-based therapeutics				
NVD-201 (Sumatriptan Oral Spray)	SUDA	Phase II/III	NA	Oral spray formulation of sumatriptan with fast-onset at a lower dose compared to sumatriptan tablets
M 207 (zolmitriptan)	Zosano Pharma	Phase III	NA	A novel formulation of zolmitriptan, administered via the Company's proprietary transdermal delivery system.
Non-Triptan-based therapeutics				
Levadex/ Semprana (dihydroergotamine mesylate)	Allergan	Pre-registration	2017	Orally inhaled formulation of dihydroergotamine (DHE) (Novartis's Migranal)
Lasmiditan (COL-144, LY573144)	Eli Lilly	Phase III	2018	Oral 5-HT1F receptor agonist with no vasoconstrictor activity
Erenumab AMG334	Novartis/ Amgen	Phase III	N/A	Selective CGRP receptor antagonist.
Galcanezumab (LY2951742)	Eli Lilly	Phase III	N/A	An antibody that binds to CGRP, inhibiting its vasodilator effect. Injectable therapy
Ubrogepant (MK- 1602)	Allergan/ Merck	Phase III	N/A	Oral small molecule CGRP drugs

Many triptan drugs including sumatriptan, almotriptan, frovatriptan and rizatriptan went off patent during the last couple of years, which further drove the saturation of the already-rich triptan pipeline with both generic versions, and products with improved formulations and modified administration modes.

Non-triptan therapies can also be expected to emerge at a steady pace. These therapies do not currently offer superior relief to triptans, but they target the approximatetly 30% of migraine sufferers who do not respond well to triptans.

Summary of the competitive analysis

The most direct competition for RIZAPORT® will originate from drugs targeting the acute migraine niche, and in particular from faster-acting oral reformulations of sumatriptan, rizatriptan, almotriptan, and frovatriptan. Several generic versions of rizatriptan are being manufactured, including a generic version for Maxalt-MLT by Mylan; as of yet, however, RedHill's reformulation of Maxalt is expected to be the first rizatriptan thin film reformulation to reach the market after Maxalt's patent expiry. Another orally dissolving thin film strip (ODFS) formulation of rizatriptan is developed by MonoSol Rx in collaboration with Dr Reddy's Laboratories.

RIZAPORT's® market share will depend on ease of use compared to competing formulations (those currently marketed, as well as novel pipeline triptan delivery therapies, including oral film and spray products), as well as with inexpensive rizatriptan generics and with other novel treatments. RIZAPORT® advantages lie in an effective route of administration, ease of use, and superior adherence rates. It is likely to be the first thin film triptan to reach the US market.

Healthcare pricing pressures across the globe are likely to sway the market towards cheaper medications. As triptan generics are likely to be low-cost medications, the decision to prescribe a certain triptan, to include it in the Essential Drugs List, or to gain a high tier ranking among insurance payers may essentially come down to treatment cost. The cost of producing RIZAPORT® is low, thus allowing competitive pricing strategy to be put in place.

RHB-103 Program valuation

The main valuation parameters for RHB-103 for the treatment of migraine are:

Regulatory progress: RedHill has filed an NDA for RIZAPORT® with the FDA in March 2013. Following a Complete Response Letter (CRL) received by RedHill in February 2014 mentioning issues related to third party manufacturing, packaging and labeling, the Company is planning a re-submission of the NDA to the US FDA in Q3 2017. RIZAPORT® has been approved in Europe. We assume the FDA will approve RIZAPORT® in 2018.

Market parameters: RHB-103's target market is based on the current triptan market size (approximately $2.2 billion). Since this drug candidate is patent protected only in the US, we only take US-related sales (65% of the Company's global market) into consideration. We estimate the maximal share of RHB-103 to be 3% of this competitive and saturated market.

Distribution agreement: according to RedHill's business model, the marketing and distribution of RHB-103 will be executed by third parties (i.e. pharmaceutical companies/distributors). Our valuation is based on RedHill's attaining similar marketing and distribution agreements both inside and outside of the US. Our research revealed only one reference deal with published financial data - Pozen's and Desitin Arzneimittel's agreement for commercialization of MT 400 (similar to Pozen's marketed drug - Treximet) in the EU, which included upfront and milestone payments of up to $3 million, along with unspecified royalties from sales. We take into consideration a US distribution agreement valued at $8 million, comprising an upfront payment and sales-based milestone payments. We assume RedHill will be entitled to receive royalties of 20% from the product's net revenues.

Capitalization rate: See Appendix C.

The valuation of RHB-103 is a risk-adjusted net present value (rNPV) capitalization to the net present value. The valuation includes weighting of several scenarios, based upon main assessments described above. The valuation parameters are summarized in the following table.

Main valuation parameters for RHB-103

Territory	Current development stage	Regulatory approval success rate	Launch	Patent period
US	FDA review	80%	2018	2035

Total market per product ($'000)	**1,420,000**
Market Growth (CAGR)	**2.7%**
Company share from Market (Peak Sales)	**3.0%**
Royalties to RedHill	**20.0%**
Royalties to original developer	**40.0%**

Given the aforementioned parameters, we estimate the total value of this program at approximately $15.3 million
(see "Company Valuation" for additional details).

Donnatal and EnteraGam

RedHill has, thus far, successfully implemented a "standard" drug development strategy, with a business model that is based on licensing out its IP. While continuing its IP strategy, the Company has decided to also set up a sales organization in the US market that will drive revenues from selling the two drugs described below.

Donnatal®

Donnatal® (Phenobarbital, Hyoscyamine Sulfate, Atropine Sulfate, Scopolamine Hydrobromide) is a proprietary oral prescription drug composed of established compounds namely anticholinergic and barbiturate. Its mode of action involves slowing the natural movements of intestinal muscles, and acting on the brain as a mild sedative. Donnatal® comes in two formulations: immediate release tablets and immediate release elixir (syrup). Donnatal® is used as an adjunctive therapy in the treatment of irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis (inflammation of the small bowel). It may also be used as adjunctive therapy in the treatment of duodenal ulcer.

In December 2016, RedHill entered into a three-year co-promotion agreement with Concordia Pharmaceuticals Inc. for promotional rights for both formulations of Donnatal®. RedHill will exclusively promote this drug in some territories in the US. The revenues generated from sales will be shared based on an agreed split; the agreement did not include any upfront or milestone payments. Concordia's sales of Donnatal® reached $64.5 million in 2016. The sales were affected comparing to previous years due to the appearance of non-FDA approved illegal copy of Donnatal®. Concordia received a favorable jury verdict against Method Pharmaceuticals and is currently pursuing the undismissed lawsuit

RedHill has assembled an experienced gastrointestinal commercial team in the US and initiated promotion of Donnatal® and EnteraGam® in June 2017. The opportunity within the IBS market is significant as it is shown to be highly underserved, and its market size is estimated to exceed $2.3 billion by 2020.

EnteraGam

EnteraGam® (a serum-derived bovine immunoglobulin/protein isolate, SBI) is a commercially-available medical food, intended for the dietary management of chronic diarrhea and loose stools due to specific intestinal disorders, such as irritable bowel syndrome with diarrhea (IBS-D) and inflammatory bowel disease (IBD).

EnteraGam® is a fine powder which can be mixed with liquid or soft food and must be administered under medical supervision. EnteraGam ® is not absorbed systemically, that is, it only works in the gastrointestinal tract. It rebalances the microbial flora, manages gut barrier function and increases the uptake and utilization of nutrients.

Its mode of action involves binding toxic substances released by bacteria, preventing them from penetrating the lining of the intestine and causing complications (EnteraGam®website).

RedHill has a license agreement with Entera Health Inc. ("Entera Health"), granting RedHill exclusive US rights to EnteraGam®. Under the terms of the agreement, RedHill will pay Entera Health royalties based on net sales generated from the sale of EnteraGam® by RedHill.

Donnatal and EnteraGam Program valuation

We assume Donnatal sales similar to 2016 sales of $139 million and EnterGam sales based on $594 per package price (orange book data, 2017). We based our sales prediction on a population of 15 million suffering from bowel syndrome and a 2% market share. Our forecast is until 2029, based on market dynamics and patents period. NPV of sales of these two drugs are estimated at $132.6 million. We are reducing marketing and sales expenses to support sales within our unallocated cost as this sales force will distribute RedHill's **entire GI&I platform**. Thus, the NPV of this program is based on revenues' estimation only.

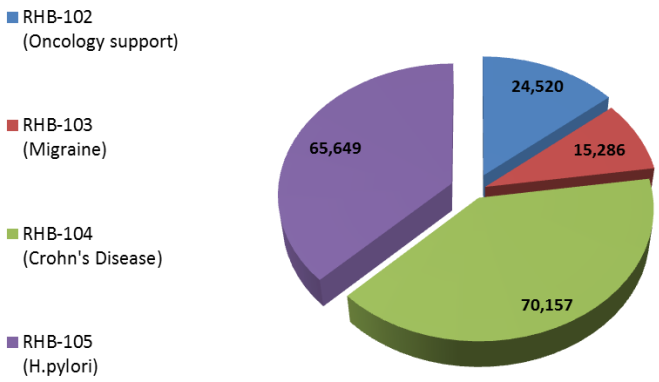
For additional programs (not included in RedHill's pipeline valuation), see Appendix D

Valuation Summary

Pipeline Analysis Summary

We conclude our pipeline interim analysis with a total value of $175.6 million. This value is for RedHill's main indications. We do not include RHB-106 in our valuation since Salix has been acquired by Valent and sales are currently unknown.

Pipeline analysis (000K)



Technological Platform Valuation

RedHill's product pipeline is supported by the Company's broad business and technological grounds. Valuation of RedHill's "technological basis" is in fact a valuation of the company's "residual value". This valuation was conducted using the Feed Rate methodology that is common in the field of life sciences, rather than using the conventional terminal value, normally used by non- Life-Science companies, for the following reasons:

- The terminal value reflects a kind of steady state in the company's sales with a certain fixed growth rate (g) based upon past data. This is not the case for Life Science companies, where the terminal value derives from projects in development.
- The terminal value for companies usually constitutes between 70-80% of the company's worth. In contrast, in Life Science companies, the main share of the value is attributed to income generated during several years

following product launch (for the most part, about 6-10 years), after which a certain decline occurs (expiration of the patent, competing products, etc.).

The technological platform valuation is based on the average number of new projects that the company can yield annually. Estimating the capitalization value of future projects is based on pre-clinical and clinical development aspects, assessment of unallocated costs, and a higher capitalization rate than the one used during the forecast years, due to the uncertainty of the company's future projects[25]. In RedHill, we see the company's technological platform as the management's ability to produce additional worthy technology acquisitions, and incorporating them into the company's product pipeline.

Main technology platform valuation points:

- We assume one new project every three years with an average value of $43.9 million (equal to the average value of the current pipeline programs)
- Unallocated costs are mainly G&A and sales costs, with a similar share from the project's value as in the current pipeline programs
- We estimate unexpected costs to be 10% of the average value
- Statutory tax rate of 23%
- The capitalization rate is higher than the one used in the pipeline valuation, reflecting the increased uncertainty
- It is assumed that the "platform" generates projects for n years: in our valuation, and based on the average patent period, n=13 years. We therefore subtract from the technological platform value all projects generated after n years (the exceeding projects).

The following formula reflects the value of the technology:

$$\mathrm{V(tech)} = \frac{(fVproject - (1+r)costs)}{r} * 1 - \frac{1}{(1+r)\text{^n}}$$

Main valuation parameters of the technological platform

Average # of New Projects per Year	0.33
Project Value (000K)	**43,903**
Unallocated Costs (000K)	-5,260
Unexpected Costs (000K)	-4,390
Tax	23%
Capitalization	25.6%
Terminal Technology Value (000K)	**33,954**
Technology Value - 2017-2029 (000K)	**1,748**
Technology Value (000K)	**32,206**

[25] Bogdan & Villiger, "Valuation in Life Science - Practical Guide", 2008, Second Edition.

Equity Value

Non-operational assets/Liabilities and unallocated costs

Unallocated costs include two "layers" – the first is a basic layer in which RedHill needs to operate the pipeline and technology platform; the second is specific to its new business model of forming a US-based sales force where RedHill to market and sell drugs in in the US.

Thus, the unallocated costs of the Company (not associate with a specific drug or indication) are primarily future G&A costs, calculated with an annual growth rate of 5%. Initial G&A costs are based on the average costs of 2015 and 2016, assuming same cost structure.

The Company's business model is based on its sales force in the US. Thus unallocated costs include COGS, marketing and sales expenses (25% expenses from sales revenues) and a 10% revenues share assumption from total drugs' revenues (Donnatal and EnteraGam). We evaluate these unallocated costs as $ 187.1 million.

As of March 31, 2017, the Company has non-operational assets (cash) of approximately $61 million with an estimated annual burn rate of $40 million for 2017 ($31 million in 2016).

Tax - The balance of carry forward losses as of December 31, 2016 is $71 million. These tax loss carry forwards have no expiration. We assumed with our tax model, carry forward tax losses will be used by the Company in the upcoming years from 2025.

We present below the equity valuation elements:

Equity value

Pipeline Analysis		rNPV (000K)
102	Oncology	24,520
103	Migraine	15,286
104	Chrohn`s	70,157
105	H.pylori	65,649
Donnatal & EnteraGam	GI&I	132,618
Unallocated Costs		-187,074
Terminal Technology Value		**32,206**
Enterprise Value		**153,362**
Non-operational assets/liabilities		60,729
Equity Value		**214,091**

Business Model Analysis

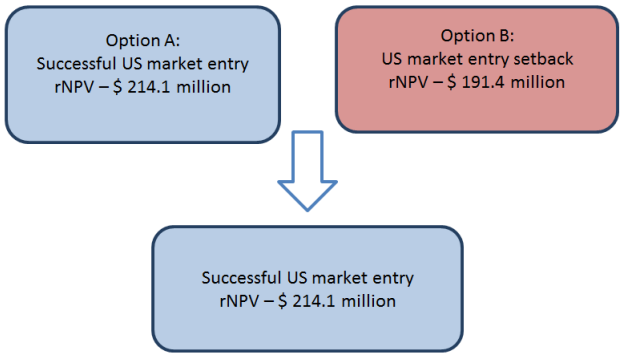
As discussed above, RedHill's business model in the US has recently changed. On the one hand, this strategic turning point may be a leap forward as this move is elevating the Company within the value chain and positioning it as a market player in the GI&I market place rather than a development company. On the other hand, it may result in an unsuccessful entry.

We conducted an economic analysis of these two scenarios:

- Scenario A: a successful entry to the US market as a "big-pharma" company for GI&I - our primary assumption
- Scenario B: a setback in this turning point.

We have implemented several changes to our analysis regarding Scenario B, including that the business model in the US will be based on an out-licensing deal while the company will lose two years of sales and marketing expenses.

At this point of time, we view RedHill's position as consistent with Scenario A



Given the aforementioned parameters, we estimate RedHills' equity value at $214.1 million / NIS 762.2 billion.

Sensitivity Analysis

In the table below we present RedHill's price target in relation to the capitalization rate. We set a range of 0.5% change from our CAPM model (as presented in Appendix D) as the stock range.

Sensitivity analysis - Capitalization rate vs. Target price

Cap. rate	Price Target (NIS)
19.6%	4.61
20.1%	**4.52**
20.6%	**4.44**
21.1%	**4.36**
21.6%	4.29

We estimate the price target in the range of NIS 4.36 - NIS 4.52, with a mean of NIS 4.44. Thus, 1 ADS (Each ADS represents 10 ordinary shares) is equal to $0.125[26]

[26] Calculation is NIS 4.44 divided by 10 ordinary shares, i.e. NIS 0.444 (44.4 Agorot) divided by 3.56 NIS/$ = $ 0.125

Relative Advantages

Investment Thesis and Price Forecast Risks

Biotech companies, particularly those at the research and development stage, are relatively high-risk companies. Key risks that may affect RedHill include:

The risk of delay/postponement of marketing regulatory approval decisions

In order for RedHill to market or out license its products, it is necessary for them to receive marketing approval from regulatory agencies, such as the FDA (in the US) and EMA (in the EU). Our estimates regarding time to market are based on the assumption that these products will successfully complete Phase II- and III clinical trials without significant delays. Failure to fulfill the clinical endpoints of these experiments will force the Company to conduct additional clinical trials or abandon the development of certain projects. We consider this to be the main risk factor for the Company's activity at this stage.

Risks involved in obtaining sources of financing and stock trading

As a biotech company in the research and development stage, without minimal revenue from sales, the Company will be required to conduct fundraising prior to becoming profitable, unless early licensing deals are made. Failure to raise funds, or fundraising under conditions that are not beneficial to the Company, may affect its worth. In addition, the low level of tradability may deter some investors from buying the Company's stock.

General risks related to similar companies

The value of small companies in the biotech field could, to a relatively high degree, be affected by publications not related directly to their activities. Such publications may be connected with competitors, macrotrends in the healthcare sector, political events, etc.

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Management:[27]

Dror Ben-Asher , CEO

Dror Ben-Asher, Co-Founder of RedHill, was previously with ProSeed Capital, a European corporate finance boutique. Mr. Ben-Asher is a graduate of the University of Oxford (M.Jur.) and completed LL.M. studies at Harvard University. At Harvard, Mr. Ben-Asher was also a Fulbright Scholar focusing on the pharmaceutical industry and markets, an Olin Fellow for Law, Economics and Business, and an Economics Teaching Fellow at Harvard's Economics Department. Dror Ben-Asher received an LL.B. with distinction (First Class Honours) from the University of Leicester.

Reza Fathi PhD , Senior VP R&D

Prior to joining RedHill, Dr. Fathi served as Director of Research Operations at XTL Biopharmaceuticals. He was previously at VivoQuest, PharmaGenics, Metrigen, Enzo Biochem and the Harvard Institute of Chemistry and Cell Biology. Dr. Fathi graduated from Rutgers University (Ph.D. and Post-Doctoral Fellow) and Texas Tech University (BSc).

Gilead Raday , Chief Operating Officer

Gilead Raday previously served as interim CEO of Sepal Pharma, and as a director at TK Signal and Morria Biopharmaceuticals. He is a graduate of the University of Cambridge (M.Sc in Bioscience Enterprise) and the Hebrew University of Jerusalem (M.Sc Neurobiology, BSc Mathematics and Biology).

Adi Frish , Senior VP Business Development and Licensing

Adi Frish brings extensive business development and transactional experience to RedHill. Prior to joining RedHill, he served as VP Business Development at Medigus (TASE: MDGS). Mr. Frish was previously a partner at Y. Ben-Dror & Co. He is a graduated of Bar Ilan University (LL.M.) and Essex University (LL.B. with Honors).

Micha Ben Chorin , CFO

Mr. Ben Chorin has over 20 years of financial management experience with specific expertise in financing, M&A and international operations. He was a member of the team that built GVT (currently Telefonica Brazil). Most recently, Mr. Ben Chorin served as CFO of Pyramid Analytics and he previously served as CFO of Starhome B.V. Mr. Ben Chorin holds an M.A. and a B.A. from Tel-Aviv University and is a Certified Public Accountant.

[27] http://www.redhillbio.com/management-team

Guy Goldberg , Chief Business Officer

Prior to joining RedHill, Guy Goldberg served as Senior Vice President of Business Operations at Eagle Pharmaceuticals, a specialty injectable drug development company, based in New Jersey. Previously, Mr. Goldberg was a member of the investment team at ProQuest Investments, a healthcare focused venture capital firm. He previously served as a consultant at McKinsey & Company and holds a B.A. in Economics and Philosophy from Yale University and a J.D. from Harvard Law School.

Appendices

Appendix A - Financial Reports

Profit and Loss Statement	$000s				
	2013	**2014**	**2015**	**2016**	**Q1-2017**
Total Revenues	12	7,014	3	101	0
Cost of Revenue	0	1,050	0	0	0
Net Revenue	12	5,964	3	101	0
Net Research and development expenses	8,100	12,700	17,771	25,241	8,137
General and administrative expenses	2,684	4,011	4,134	5,403	1,315
Selling, Marketing and BD expenses	0	0	0	0	605
Other income	0	100		0	0
Other expenses	0	0	100	0	45
Operating loss	**10,772**	**10,647**	**22,002**	**30,543**	**10,102**
Financial income	158	319	1,124	1,548	1,556
Financial expenses	14	383	212	375	50
Other financial income (expenses), net	144	64	912	1,173	1,506
Loss and comprehensive loss	10,628	10,711	21,090	29,370	8,596

Balance Sheet			$000s		
Current assets	**2013**	**2014**	**2015**	**2016**	**Q1-2017**
Cash and cash equivalents	11,851	5,892	21,516	53,786	29,624
Bank deposits	19	17,053	36,622	55	15,609
Financial assets at fair value through profit or loss	243	0	0	12,313	15,351
Prepaid expenses and receivables	488	3,074	2,372	1,661	2,675
Total current assets	12,601	26,019	60,510	67,815	63,259
Non-current assets					
Bank deposits	81	78	134	137	145
Fixed assets	103	146	124	165	151
Intangible assets	1,555	2,615	6,060	6,095	6,050
Total non-current assets	1,739	2,839	6,318	6,397	6,346
Total assets	**14,340**	**28,858**	**66,828**	**74,212**	**69,605**
Current liabilities					
Accounts payable and accrued expenses	2,415	1,720	3,514	3,356	3,786
Payable in respect of intangible asset purchase	0	0	2,000	2,000	2,000
Total current liabilities	2,415	1,720	5,514	5,356	5,786
Non-current liabilities					
Derivative financial instruments	0	2,125	1,237	6,155	4,873
Total non-current liabilities	0	2,125	1,237	6,155	4,873
Total Liabilities	**2,415**	**3,845**	**6,751**	**11,511**	**10,659**
Equity					
Ordinary shares	174	240	343	441	455
Additional paid-in capital	43,144	65,461	120,621	150,838	156,415
Warrants	1,867	1,528	1,057	1,057	0
Accumulated deficit	33,260	42,218	61,944	89,635	97,924
Total Equity	11,925	25,011	60,077	62,701	58,946
Total liabilities and equity	**14,340**	**28,856**	**66,828**	**74,212**	**69,605**

Appendix B - 505(b)(2) Approval Route

The clinical development of RedHill's drug candidates is advanced through the US FDA's 505(b)(2) regulatory pathway. This pathway is applicable for development of drugs that are based on modifications of existing, approved drugs. In this section, we discuss the nature of the 505(b)(2) pathway and how it affects RedHill's drug development strategy.

Clinical development programs of innovative drugs are advanced through the FDA's 505(b)(1) New Drug Application (NDA) process, which typically requires pre-clinical studies and massive clinical trials. In addition to the high costs and prolonged development timeline associated with the 505(b)(1) pathway, clinical development attrition rates of innovative drugs are high, with an industry-wide success average of approximately 10% from beginning of clinical development to FDA approval.

The 505(b)(2) regulatory pathway is defined in the Federal Food Drug and Cosmetics Act as "an NDA containing investigations of safety and effectiveness that are being relied upon for approval and were not conducted by or for the applicant". These applications differ from the 505(b)(1) NDA in that they allow a sponsor to rely, at least in part, on the FDA's findings of safety and/or effectiveness for a previously approved drug (the "reference drug")[1]. Therefore, The 505(b)(2) approval process can be utilized for drug candidates that present limited modifications of previously approved drugs.

Such modifications may include:

- Alternative formulations and new dosage strengths
- Changes in route of administration
- Modified release dosage forms (extended-release, sustained-release)
- Minor changes to an active ingredient (altered salt, ester complex, etc.)
- Alternative therapeutic indication that has not been previously approved for a listed drug
- A new combination product in which the active ingredients have been previously approved individually.

The 505(b)(2)approval route was designed to encourage innovation and to eliminate costly and time-consuming duplicative clinical studies by relying on a reference drug for safety and efficacy information. Only a small amount of new clinical data is required to establish comparability to the reference drug and provide data necessary to ensure that differences from the reference drug do not compromise safety and effectiveness. This means that the clinical development required to achieve FDA approval usually includes a fraction of the number of clinical trials, at lower costs and reduced development risks.

Drugs approved through the 505(b)(2) route usually qualify for three years of market exclusivity in the US (compared to 5 years in the 505(b)(1) route). Exceptions to the market exclusivity period, which can be based on the extent of the change to the original drug, the type of clinical data included in the NDA, and the target indication (orphan or pediatric for example), may provide 5 or 7 years of market exclusivity. The European counterpart of Section 505(b)(2) is Article10(3) of Directive 2001/83/EC. Applications for well-established drugs are afforded one year of market exclusivity only. To obtain full protection of eight years in the EU, developers are required to submit full dossiers for drugs not well-established in the community.

Summary of primary differences between the 505(b)(1) and 505(b)(2) regulatory pathways

	505(b)(1)	505(b)(2)
Drug development		
Discovery	2-5 years	<1-3 years
Pre-clinical	1-3 years	<1-2 years
Clinical	7-10 years	2-5 years
Cost of clinical development	$50-500 million	$1-10 million
Regulatory aspects		
Full efficacy/safety reports	Yes	Sometimes
Extensive stability data	Yes	Sometimes
Review Classification & Timeline	6 months (Priority Review) / 10 months (Standard Review)	6 months
Market Exclusivity Period	5 years (NCE) / 7 years (Orphan Drug)	3 years (standard) / 5 years (NCE) / 7 years (Orphan Drug)

Appendix C - Capitalization Rate

Cost of equity capital (ke) represents the return required by investors. The capitalization rate is calculated using the CAPM (Capital Asset Pricing Model). It is based on a long-term 20-year T-bond with a market risk premium, and based on Professor Aswath Damodaran's (NY University) commonly used sample (www.damodaran.com). As of December 31, 2016, the Israeli market risk is estimated at 6.69%.

A three-year market regression Beta is 1.19, according to a sample of 411 companies representing the US biotechnology sector. RedHill has no loans or any other rate-carrying liabilities, which are considered non-operational liabilities. In order to reach the relative CAPM, we used an unleveraged beta of this sample, which is higher than a leveraged beta, due to high rate of cash versus debt. The implied CAPM is 10.4%.

CAPM model (ke) is estimated as follows:

$ke = rf + \beta(rm-rf) + P$

RedHill is a small cap company, in which marketability and size premiums need to be considered. Duff and Phelps data research in the years 1963-2012 indicates that a 10.24% premium needs to be added to the CAPM for small cap companies. We therefore estimate the company's CAPM to be 20.6%.

CAPM Model		Value	Source
Long-term (20 years) T-bond	R(f)	2.4%	US Department of the Treasury
Market risk premium	R(m)- R(f)	6.69%	based on Professor Damodaran's sample (31/12/16)
Beta unleveraged	β	1.19	Beta sample of 411 Drugs (Biotechnology) firms (31/12/16)
Cost of Capital	ke	10.4%	
Size Premium		10.24%	Duff and Phelps data
CAPM	CAPM	**20.6%**	

Appendix D – Additional Clinical Trials

RHB-106: bowel preparation prior to gastrointestinal procedures

Background

Over the past decade, the number of diagnostic and therapeutic colonic investigation procedures has been on a rise, accompanied by advances in techniques and equipment. Colonoscopy has become fundamental in the investigation and monitoring of a number of bowel conditions, such as colonic polyps and inflammatory bowel diseases, and is a principal method in many national colon cancer screening programs, as they have been shown to help reduce the incidence of colon cancer (Figure 13).

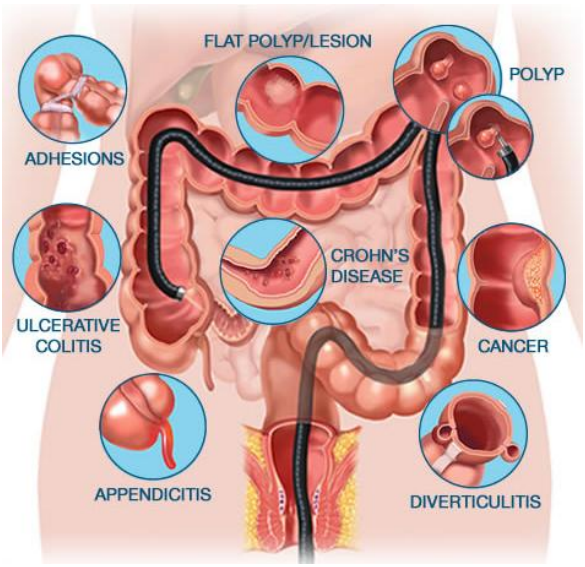

Figure 13: *The colonoscope is inserted into rectum and advanced through colon*
Source: www.colorectalcentre.co.uk

A successful colonoscopy requires visualization of the entire mucosal surface of the colon, thus complete cleaning of the large intestine is essential prior to this procedure. Similarly, radiological investigations and surgical procedures in the gastrointestinal (GI) tract require a preceding complete bowel evacuation. Effective bowel preparation is predominantly important in the diagnosis of colon cancer, which can be challenging to detect, and for flat colonic lesions that can be easily missed. Moreover, inadequate bowel preparation may lead to the termination of a scheduled colonoscopy, hence requiring repetition of the procedure and putting patients at unnecessary risk and discomfort. For those reasons, the quality of GI cleansing is highly influential on the quality, difficulty, speed, and completeness of the GI-associated procedure. Despite the above mentioned, poor bowel preparation is the most common reason for colonoscopy failure, usually attributable to inadequate adherence of patients to bowel preparation requirements, typically due to tolerability issues with the product or the regimen.

Market, standard of care and unmet needs

An estimated 30 million colonoscopies are performed every year worldwide with 15 million being carried out in the US and approximately 1.5 million in Korea[24]. They are mostly performed as a preventive procedure for colorectal cancer detection among adults beginning at age 50 but also to detect any changes to the bowel lining including ulcers, colon polyps, tumors, and areas of inflammation or bleeding. The worldwide market potential for colonoscopies is estimated at 30-40 million, as reimbursement for colorectal cancer screening is being promoted and approved in a growing number of countries. According to a market research report by EvaluatePharma, the global market of products used for gastrointestinal preparation was estimated at approximately $216 million in 2016.

All bowel preparation regimens require exclusion of high residue foods for at least 48 hours and a diet of clear fluids only for 16-24 hours before the examination. In addition to this dietary restriction, patients are usually given a laxative, with several available treatment options that can be primarily segmented to osmotic laxatives and stimulant laxatives (see the table below).

Osmotic laxatives attract and retain water in the intestinal lumen, thus increasing the pressure inside the gut and softening the stool. These laxatives may cause dehydration and depletion of electrolytes.

Stimulant laxatives irritate the intestinal lining and stimulate peristaltic action, which increases muscle contractions in the intestinal wall and enhances the forward motion of intestinal contents. Like osmotic laxatives, stimulant laxatives promote accumulation of water and electrolytes in the intestines[25].

Leading marketed laxatives used for bowel preparation

Product type	Trade names	Mechanism of action	Average wholesaler price ($)	Remarks
Osmotic laxatives				
Polyethylene glycol - Electrolyte Lavage Solution (PEG-ELS) or Low-volume PEG-ELS with ascorbic acid	MoviPrep, Golytely,	Non-absorbable isosmotic solutions that pass through the bowel without absorption	~25-82	- Large volumes (2-4 L) are required - Unpalatable taste - Above issues are associated with reduced compliance
SF-PEG-ELS	NuLYTELY; Trilyte	Non-absorbable isosmotic solutions that pass through the bowel without absorption. The mechanism of action is dependent on the osmotic effects of sulfatefree (SF) PEG-ELS	~27	- More palatable, less salty, more effective colonic cleansing than PEG-ELS - Large volumes (2-4 L) are required
Magnesium Citrate	Generic (OTC)	Increases water in the GI tract and stimulates peristalsis.	~2.5	- Commonly used in conjunction with Sodium picosulfate or PEG.
Sodium phosphate (tablets)	OTC available Visicol, OsmoPrep. Brand name removed.	Hyperosmotic agent - draws large volumes of water into the colon.	~151	- Can cause severe electrolyte disturbances - an adequate oral intake of water is essential. - Use of this product has decreased due to issues with renal insufficiency that led to a severe warning by FDA
Stimulant laxatives				
Bisacodyl	Bisalax, Dulcolax	Stimulates peristalsis and promotes water and electrolyte accumulation within the colon	~20-30	- Easy to use - Can cause electrolyte disturbances. - Commonly used in conjunction with other products (usually PEG) - Bisacodyl can cause abdominal cramping and has been associated with ischemic colitis
Sodium picosulfate	Durolax SP, Picolax/PrepoPik	Stimulates peristalsis and promotes water and electrolyte accumulation within the colon	~95	- Hydrolyzed by bacteria in the colon to produce the same active agent as Bisacodyl. - PrepoPik is the first product containing this agent to be approved by the US FDA (July 2012)

Polyethylene glycol (PEG) is an osmotic laxative which is currently the gold standard for cleansing the colon. Recent versions of this product are given as an iso-osmotic solution (PEG-ELS), in order to reduce the fluid and electrolyte imbalance that was caused by previous non-ELS versions. This preparation is often poorly tolerated because patients

are required to drink 4 liters of this salty tasting fluid, and the marketed flavored versions offer little help. 5% to 15% of patients do not complete the preparation because of poor palatability and/or large volume. PEG preparations can cause volume-related symptoms such as nausea, bloating and abdominal pain. In an attempt to improve patient tolerance, low volume PEG solutions were developed. In these products a lower volume of PEG solution (2 liters) is administered in conjunction with bisacodyl tablets and/or magnesium citrate.

Sodium phosphate tablets are highly effective bowel preparation products; however, due to serious adverse events they are not recommended. Deaths and severe side effects related to the use of phosphate preparations have been reported, prompting the FDA to release a severe warning regarding the use of the over-the-counter Fleet Phospho-Soda product and the prescription versions of the drug (Visicol and OsmoPrep) were required to display "black box" warnings indicating the associated risks.

Bisacodyl and **sodium picosulfate** are stimulant laxatives that are hydrolyzed by bacteria in the colon to produce the same active ingredient 4,4'-dihydroxy-diphenyl-(2-pyridyl) methane. They increase the frequency and force of peristalsis. Bisacodyl is generally used in combination with low volume PEG preparations. Laxatives that use sodium picosulfate as the active ingredient have been available outside the US since 1980 in sachet form that also contains magnesium citrate (under the trade names Pico-salax, Picolax and Picoprep), and as generic sodium picosulfate tablets (Cremalax, Colax and more). In July 2012 Picolax (sodium picosulfate and magnesium citrate sachets) has been approved by the FDA as a bowel cleanser in preparation for colonoscopy under the trade name Prepopik (Ferring Pharmaceuticals).

Prepopik comes as two powder mixture packets that are mixed with water to generate a low volume (5 ounces/150ml) drink, taken at two separate times. This new product demonstrated non-inferiority to 2 liters PEG-ELS plus bisacodyl tablets in two Phase III studies, and significantly lowers the volume of liquid patients must drink compared to this comparator. However, patients that use Prepopik must consume additional fluids during and after use, in order to reduce the risk of fluid and electrolyte imbalance.

Despite its importance, the quality of bowel preparation prior to colonoscopy is currently suboptimal, and rates of adequate prepping, which are associated with colonoscopy effectiveness, have changed little over the last 10 years. There is still a need in the market for a tolerable product with palatable taste that requires minimal drinking volumes and simple administration instructions, while causing minimal side effects and electrolyte abnormalities.

RHB-106

RHB-106 is a bowel preparation capsule of sodium picosulfate indicated for bowel preparation prior to GI interventions, such as colonoscopy and surgical procedures. As mentioned earlier, sodium picosulfate is a stimulant laxative that works by stimulating the nerve endings in the walls of the colon and rectum, thus causing the muscles in the intestinal wall to contract more often and with increased force. Those muscle contractions move the contents of the intestine through the colon to the rectum so that the bowel can be emptied. Sodium picosulfate is activated by the natural bacteria in the colon, so it is inactive until it reaches the intestine.

RHB-106 was acquired by RedHill from Giaconda along with the acquisition of RHB-104 and RHB-105 and is intended for further clinical development by RedHill under the 505(b)(2) regulatory pathway.

RHB-106's worldwide exclusive rights were out-licensed to Salix Pharmaceuticals in February 2014 along with rights to other purgative developments. Salix Pharmaceuticals was acquired by Valeant in 2015 and there is no clarify on further development plans.

Clinical data

While RHB-106 was developed by Giaconda, a Phase IIa clinical study was conducted in Australia to assess its safety and tolerability in comparison to other bowel preparation products. In this study, sodium picosulfate was administered in capsule form, with and without hypertonic solution, and in sachet form (powder – mixed with water prior to administration), and was compared to the standard PEG preparation (3 liters of Glycoprep).

The study's results indicated that sodium picosulfate tablets were significantly more tolerable to patients compared to all other preparations (Figure 14A). The safety profile of all three sodium picosulfate preparations was comparable and better than the standard PEG preparation, and no significant changes were observed in the biochemical profiles (electrolytes) in either treatment.

Out of the different bowel preparations tested, the efficacy of sodium picosulfate capsules combined with a hypertonic solution was greater than sodium picosulfate capsules alone and Glycoprep, but efficiency differences were small (Figure 14B).

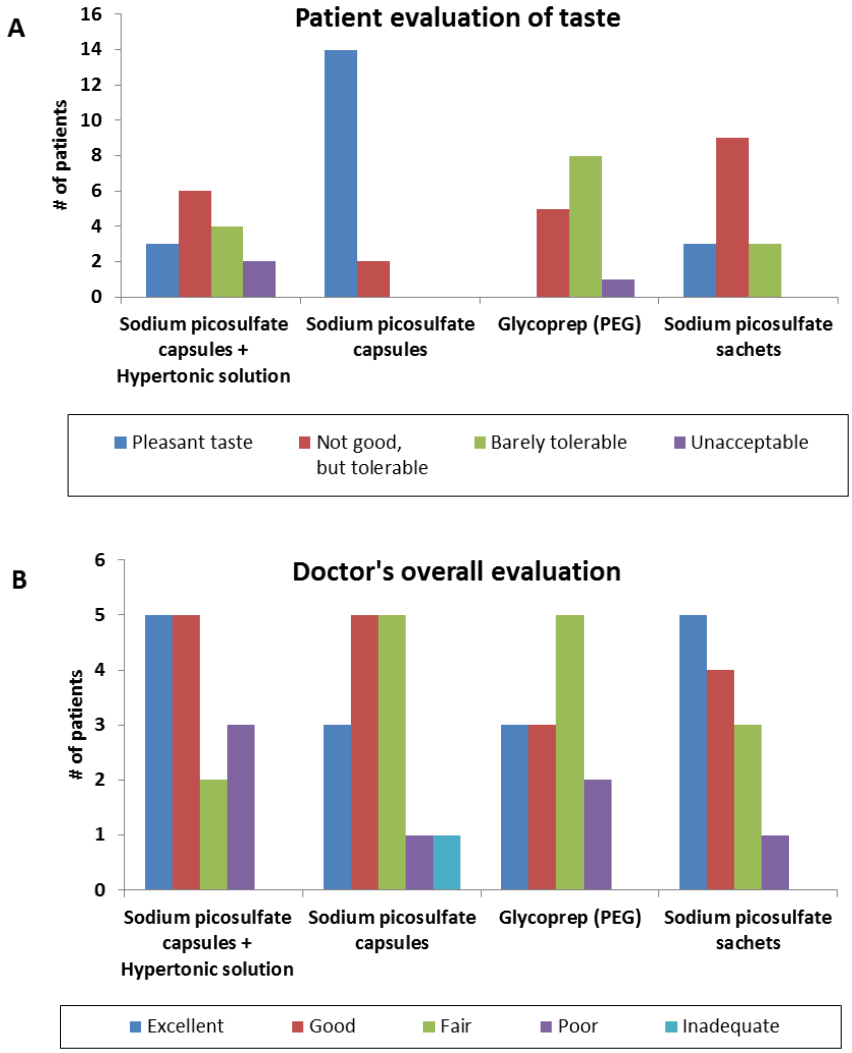

Figure 14: *Patients' and Doctors' evaluations of Sodium Picosulfate preparations for bowel preparation.(A) Tolerability marks provided by patients, based on taste and ease of treatment completion.(B) Efficiency marks of the different preparations as provided by Doctors.*
(Source: Adapted from a Giaconda poster)

Pipeline Competition

At the time of the preparation of this report, we did not find any new bowel preparation products under development.

Summary of the competitive analysis

Since RHB-106 is administered as a capsule, it does not share the disadvantages of bowel preparation formulations currently used in the US, such as the requirement to drink large amounts of liquids and unpalatable taste. However, the efficacy and safety profile of this product will have to be further tested and compared to the latest gold standards. Should RHB-106 prove to have comparable efficacy and safety to such products, the convenience of its administration could set it apart from its competitors.

RHB-106 is currently in the formulation stage. In order to offer a clear benefit to patients while providing clinical efficacy, RHB-106 will have to be administered as a capsule only (without any accompanying solution) with a reasonable dosing protocol (i.e. minimal number of capsules).

Importantly, sodium picosulfate tablets have been commonly used outside the US for years, thus we predict that RHB-106's main market would be the US market.

YELIVA®: first-in-class sphingosine kinase-2 selective inhibitor for multiple indications

Background

Sphingosine-1-phosphate

Sphingosine-1-phosphate (S1P) is a membrane-derived lysosphingolipid. It is produced in mammalian cells by phosphorylation of sphingosine by two enzymes called sphingosine kinases (SphK1 and SphK2). After completion of the phosphorylation process, S1P is exported out of cells via specific transporters. S1P can bind to five G protein-coupled receptors called S1P receptors (S1PRs) initiating various signaling pathways (Figure 15). It is known to be a critical regulator of many biological processes. It plays a pivotal role in multiple cellular signaling systems as well as controlling of immune cell trafficking. S1P has been also shown to be associated with cell survival and suppression of apoptosis and was shown to regulate allergic responses, cytokine and adhesion molecule expression, lymphocyte differentiation and endothelial barrier integrity, to name few processes. Therefore, S1P has been implicated in various disorders, including cancers, osteoporosis as well as inflammatory diseases such as atherosclerosis and diabetes. Multiple studies are being carried out to establish whether S1P might be therapeutically targeted either via inhibiting its biosynthesis, preventing its export out of cells or by blocking its signaling pathway activity.

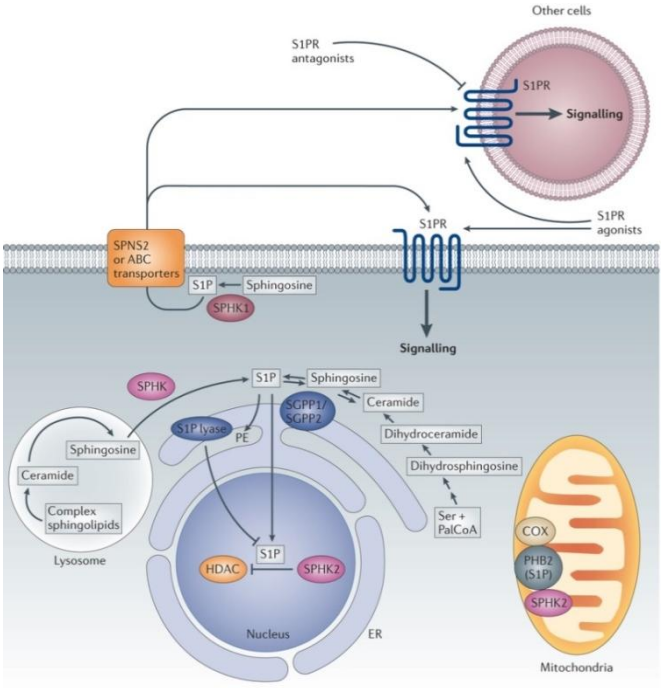

Figure 15: S1P protein biosynthesis, export, degradation and signaling.
Source: Targeting the sphingosine-1-phosphate axis in cancer, inflammation and beyond. Kunkel, G.T et al Nature Reviews Drug Discovery12, 688–702 (2013)

In addition, there are multiple studies showing the effect of SphKs enzymes on cells. SphK1 was shown to promote survival of cells and was proved to be inclined with various cancer types. By contrast, Sphk2 inhibits cell growth and enhances apoptosis, however, there is an only scarcity of cancer studies showing the connection between SphK2 and cancer[28].

YELIVA®

YELIVA® (ABC294640) is a first-in-class orally-administered sphingosine kinase-2 (SphK2) inhibitor that prevent the formation of sphingosine 1-phosphate (S1P). As previously mentioned, it is unclear whether the SphK2 enzyme is directly associated with cancer. However, it was shown that S1P can be reduced by downregulation of SphK2. Since S1P was shown to promote cancer growth and proliferation and it affects TNFα signaling and cytokine production, YELIVA® may hypothetically indirectly inhibit all those biological processes. The drug is currently developed for the treatment of solid tumors such as pancreatic, and cholangiocarcinoma, refractory or relapsed multiple myeloma, hepatocellular carcinoma, refractory/relapsed diffuse large B-cell lymphoma (DLBCL), Kaposi sarcoma and prostate cancer and as a radioprotectant to prevent mucositis in head & neck cancer patients undergoing therapeutic radiotherapy.

RedHill in-licensed YELIVA® from Apogee Biotechnology for all indications in March 2015 prior to which Apogee Biotechnology conducted multiple pre-clinical studies as well as a successful first-in-human Phase I clinical study with gastrointestinal cancer patients (pancreatic, colorectal cancers, cholangiocarcinoma, and other solid tumors). This study investigated maximum tolerated dose (MTD), the dose limiting toxicities (DLTs) and safety of YELIVA®. The study as well determined the PK and PD properties and assessed antitumor activity of YELIVA®. The analysis of S1P levels was measured as well and it was confirmed that after administration of YELIVA® there was a rapid and prominent decrease in levels of S1P. The results were published in June 2016.

Clinical Data

There are numerous, supported by research grants, clinical studies being conducted or planned to be initiated with YELIVA® for multiple indications. Most are in the initial stages, primarily Phase I/II studies.

Clinical studies with YELIVA®

Study	Initiation date	Patients number	Status	Indication
Open-label, dose escalation study conducted at Duke University, supported by a $2 million NCI grant	09/2016	Up to 77 (who have previously been treated with proteasome inhibitors and immunomodulatory drugs)	Phase Ib/II	Refractory or relapsed multiple myeloma
Efficacy and safety study with Medical University of South Carolina, supported by an NCI grant	10/2016	Up to 39 (who have experienced tumor progression following treatment with first-line single-agent sorafenib (Nexavar®))	Phase II	Advanced hepatocellular carcinoma
Safety and tolerability study with preliminary evaluation of efficacy of the drug	06/2015, protocol amended 11/2016	Up to 33	Phase I/II	Refractory/relapsed diffuse large B-cell lymphoma and Kaposi's sarcoma

[28] Maceyka M, Harikumar KB, Milstien S, Spiegel S. SPHINGOSINE-1-PHOSPHATE SIGNALING AND ITS ROLE IN DISEASE. Trends in Cell Biology. 2012;22(1):50-60. doi:10.1016/j.tcb.2011.09.003

Evaluation of YELIVA® as a radioprotectant to prevent mucositis	Q3/2017	TBC	Phase Ib	Radioprotectant in cancer patients (head and neck cancer) undergoing therapeutic radiotherapy
Efficacy and safety study	H2/2017	TBC	Phase II	Ulcerative colitis
A single-arm study evaluating response rate after administering YELIVA® as a single agent in cholangiocarcinoma patients.	Q3/2017	TBC	Phase IIa	Cholangiocarcinoma

Pipeline Competition

There are many potential molecules being investigated in vitro and in vivo studies targeting the S1P pathway. There are either S1P-specific antibodies leading to sequestration of S1P; small molecules such as VPC44116, VPC23019, and VPC25239 or W146 (3-amino-4-(3-hexylphenylamino)-4-oxobutylphosphonic acid) which are S1P receptor-directed reagents and small molecules that inhibit SphK activity such as:

- DMS (N,N-dimethylsphingosine) and sphinganine (D,L-threo-dihydrosphingosine);
- SK1-I (BML-258, (2R,3S,4E)-N-methyl-5-(4-pentylphenyl)-2-aminopent-4-ene-1,3-diol);
- SKi (SKI-II; 2-(p-hydroxyanilino)-4-(p-chlorophenyl) thiazole);
- B-5354c (natural product from a marine bacterium; SANK 71896);
- F-12509A (natural product from culture broth of a discomycete, Trichopezizella barbata; SANK 25395);
-S-15183a and S-15183b (natural products from culture broth of a fungus, Zopfiella inermis; SANK 15183);
- Amidine-based range of sphingosine analogues[29]

There are multiple drugs in clinical trials targeting the S1P axis. Gilenya (Novartis) is a sphingosine-1-phosphate receptor (S1PR) modulator that is approved for multiple sclerosis, demonstrates a proven efficacy in cancer models and is being investigated for multiple indications including amyotrophic lateral sclerosis; schizophrenia; chronic inflammatory demyelinating polyradiculoneuropathy and acute, non-infectious intermediate, posterior and panuveitis.

Siponimod (BAF312) by Novartis is an S1PR1 and S1PR5 modulator in Phase III for relapsing–remitting multiple sclerosis and in earlier clinical studies for polymyositis, dermatomyositis and hepatic impairments.

Ozanimod (RPC1063) was developed by Receptors and was acquired by Celgene. Ozanimod is a sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5) agonist for the therapy of relapsing multiple sclerosis (RMS) and ulcerative colitis (UC).

Ponesimod is a potent orally active, selective (S1P1) immunomodulatory developed by Actelion. It is in Phase III clinical trials for relapsing multiple sclerosis.

Summary of the competitive analysis

The most direct competitor for YELIVA® is either the first oral small molecule S1P receptor modulator - Fingolimod (Gilenya, Novartis) or still in late clinical trials BAF312 (Siponimod, Novartis).

Gilenya is used to treat relapsing forms of multiple sclerosis and reached $3.1 billion of net sales in 2016. Its patent is due to expire in 2019, hence Novartis has this follow-on programme, BAF312 (siponimod), with a similar mode of

[29] Sphingosine 1-phosphate signalling in cancer Pyne J.N, et al.Biochemical Society Transactions. Jan 19, 2012, 40(1)94-100

action. BAF312 is a Sphingosine-1-phosphate receptor modulator for the treatment of secondary progressive multiple sclerosis. This drug was shown in August 2016 to meet its primary endpoint of reducing the risk of three-month confirmed disability progression versus placebo in patients with secondary progressive multiple sclerosis. Novartis has planned filing date for 2019, although there are ongoing discussions with health authorities to agree on next steps.

YELIVA® has a distinctive mode of action and is the only drug on the market targeting SphK2. Direct competitors such as Gilenya was shown to have several adverse effects and can cause a dose-dependent decrease in leukocytes. This may affect the immune system that is already compromised in treated individuals, hence giving YELIVA® a differentiating advantage.

YELIVA® was also recently granted the Orphan Drug designation for the treatment of cholangiocarcinoma by the US Food and Drug Administration (FDA). It gives RedHill market exclusivity for 7 years upon approval for marketing.

MESUPRON

RedHill acquired worldwide exclusive development and commercialization rights (excluding China, Hong Kong, Taiwan and Macao) to Mesupron from a German-based WILEX AG in June 2014.

It is a proprietary orally administered, single capsule, first-in-class, protease inhibitor with several potential mechanisms of action to inhibit tumor invasion and metastasis, presents a new non-cytotoxic approach to cancer therapy.

It has several potential mechanism of action to inhibit tumor invasion, metastasis and tumor growth. This non-cytotoxic drug may provide a promising approach to cancer therapy.

Prior to its acquisition by RedHill, WILEX AG performed multiple clinical trials including Phase I and proof-of-concept Phase II studies with patients suffering from advanced pancreatic cancer as well as patients with metastatic breast cancer. Those studies evaluated the safety and tolerability profile of Mesupron.

In the Phase II study in non-metastatic pancreatic cancer, Mesupron was administered in capsule form with Gemcitabine (Gemzar®). 95 patients were enrolled into a study and results were published in 2010. The study's primary endpoint of overall response rate, progression free survival, time to first metastasis and overall survival rates were investigated. It was observed that 12-month overall survival was 48% higher in Mesupron 400 mg/day group compared to patients treated with Gemcitabine (Gemzar®) alone.

In the Phase II study in HER2-negative metastatic breast cancer, Mesupron was administered in capsule form in combination with Capecitabine (Xeloda®). 132 patients were enrolled into a study and results were published in 2012. The study's primary endpoint of overall response rate, progressions free survival and overall survival rates were investigated. It was observed that combinational therapy of Capecitabine (Xeloda®) and Mesupron increased objective response rate and median progression-free survival in the subgroup of patients who had received adjuvant chemotherapy (aggressive primary disease).

RedHill is planning to initiate Phase I/II clinical trial for patients receiving adjuvant chemotherapy for pancreatic cancer in Germany in H2/2017.

In addition, RedHill also started a collaboration with Department of Molecular Biology and Genetics, Aarhus University, Denmark to identify additional high-affinity molecular targets of Mesupron.

Ebola

Ebola virus disease (EVD) also known as Ebola hemorrhagic fever, is a very rare but often fatal infection caused by one of five strains of Ebola virus (Figure 16). The Ebola virus was first discovered in 1976, yet the most complex and largest outbreak occurred in 2014 in West Africa. In early 2016 a new Ebola flare-up occurred in Guinea, with 800 confirmed Ebola cases.

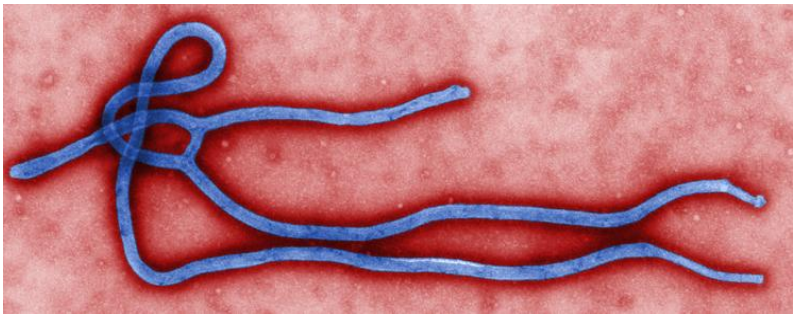

Figure 16: Ebola virus
Source: www.cdc.gov/vhf/ebola/

The Ebola natural hosts are fruit bats as well as chimpanzees, gorillas, monkeys, forest antelope, and porcupines. Humans get infected with the virus upon close contact with blood or other bodily fluids of infected animals. The fatality rate of those infected is estimated to be 50% but it can vary from 25 - 90%[30]. According to the Centers for Disease Control and Prevention, there have been 28,639 cases of EVD and 11,316 deaths up to March 2016.

There are currently no approved treatments or vaccines for Ebola, however, there are 19 potential new vaccines and drug therapies that are being developed and assessed in clinical trials (see the table below). One investigational vaccine (ChAd3-ZEBOV) is being developed by GSK in partnership with US National Institutes of Health's Vaccine Research Center (VRC). GSK acquired this Ebola vaccine from Okairos in May 2013.

Another experimental vaccine called VSV-EBOV is developed by Merck in partnership with NewLink Genetics and was shown in December 2016 to be safe and well tolerated in humans but more importantly was shown to be highly protective against the deadly virus. Clinical trials Phase II and Phase III are underway.

Janssen Pharmaceutical Companies in collaboration with Bavarian Nordic is also developing an Ebola vaccine regimen composed of two doses called Ad26-EBOV and MVA-EBOV (heterologous prime-boost). The results from clinical trial Phase I are available.

In addition, Novavax has developed a recombinant protein Ebola which was tested in Phase I human clinical trials in Australia. The study has shown that Ebola GP Vaccine is highly immunogenic and well-tolerated in humans.

The treatment of EVD is also complicated as there are no approved drugs available. Experimental therapies include using pre-existing medicines such as Favipiravir (Fujifilm/Toyama) and Brincidofovir (Chimerix), or novel products, like FX06, Zmab, TKM-100802 (siRNA) (Tekmira); ZMapp (MappBio) or MIL-77 (MabWorks). All those products are in early stages of development (Phase I/II of clinical trials)[31].

[30] http://www.who.int/mediacentre/factsheets/fs103/en/. Accessed on 03 April 2017
[31] http://www.who.int. Accessed on 03 April 2017

Ebola therapies pipeline (Source: Pharmaprojects)

Primary drug name	Synonyms	Company	Status	Mechanism of action
Favipiravir	Avigan	Toyama MediVector	Phase II	DNA-directed RNA polymerase inhibitor
Filovirus vaccine	MVA-BN filovirus vaccine, Bavarian Nordic MVA-BN-Filo, Bavarian MVA-mBN226B	Bavarian Nordic Johnson&Johnson	Phase III	Immunostimulant
Ebola vaccine,	BPSC-1001, V-920	NewLink Genetics Merck & Co.	Phase III	Immunostimulant
Ebola vaccine (monovalent)	Ad26.ZEBOV, Johnson & Johnson, Ebola vaccine, (monovalent), NIAID	Johnson&Johnson	Phase III	Immunostimulant
Larcaviximab	Ebola mAbs, Mapp, Biopharmaceutical, MB 003 + ZMAb, LeafBio, zMapp	Mapp Biopharmaceutical, Defyrus	Phase II	Immunostimulant
GS-5734	GS5734	Gilead Sciences, Ligand	Phase II	Unidentified pharmacological activity
GBV-006	GBV006	Globavir	Phase II	Unidentified pharmacological activity
Ebola Zaire vaccine	Ad5-EBOV, Ebola adenovirus vector vaccine, Tianjin CanSino,	Tianjin CanSino Biotechnology	Phase II	Immunostimulant
Ebola Zaire vaccine (monovalent)	cAd3-EBO Z, Ebola Zaire vaccine (monovalent), GSK GSK-3390107A, VRC-EBOADC076-00-VP	Okairos	Phase II	Immunostimulant
Ebola virus therapy	NA	Genzyme	Phase II	Interferon beta 1 agonist
rVSV-Ebola vaccine	Ebola virus vaccine	Profectus BioSciences	Phase I	Immunostimulant
REGN3470-3471-34 79	Ebola mAbs, Regeneron	Regeneron	Phase I	Immunostimulant
Modified vaccinia Ankara-Ebola Zaire vaccine	ebola vaccine	Emergent BioSolutions	Phase I	Immunostimulant
Galidesivir	BCX-4430	BioCryst Pharmaceuticals	Phase I	RNA directed RNA polymerase inhibitor
Ebola vaccine	INO-4212	Inovio, AstraZeneca, GeneOne Life Science	Phase I	Immunostimulant
Ebola vaccine (bivalent, Sudan and Zaire strains)	cAd3-EBO	Okairos	Phase I	Immunostimulant
Ebola vaccine (2014 Makona strain)	Ebola GP vaccine	Novavax	Phase I	Immunostimulant
ANP-015	ANP015	ANP Technologies	Phase I	Unidentified pharmacological activity
Ad26.Filo vaccine	Ad26.Filo vaccine, NIAID, filovirus vaccine (multivalent),NIAID/J&J	Johnson & Johnson	Phase I	Immunostimulant

RedHill has signed an agreement with National Institute of Allergy and Infectious Diseases (NIAID) in July 2016 to assess RedHill's proprietary experimental therapy for the treatment of Ebola virus disease. This orally-administered drug showed positive results in preliminary non-clinical studies. It is intended to be evaluated for survival outcome and assessed through comparison of viral loads and cytokine levels in active treatment arms and placebo arm. Since human efficacy studies cannot be easily conducted with EVD patients, this additional research is supposed to facilitate discussion with the FDA for the potential use of the Animal Rule pathway for approval of RedHill's product.

Appendix E - Team Bios

Kobi Hazan is the Lead Analyst at Frost & Sullivan Research & Consulting Ltd., a subsidiary of Frost & Sullivan in Israel. He has over 14 years of experience in capital markets, including research, analysis, investment advisory, and management. Mr. Hazan served as a Fund Manager for provident and mutual funds at Analyst Ltd. and, since 2012, he owns and manages the Amida Israel Fund, a hedge fund specializing in Israeli equities. Kobi holds an Economics and Management degree from The College of Management Academic Studies. He is licensed as an Investment Advisor in Israel.

Dr. Anna Cirmirakis joined Frost & Sullivan Transformational Healthcare team as a Healthcare consultant in February 2015. She works primarily with biotech, pharma and diagnostics companies on a wide range of strategic projects including product evaluation, market analysis as well as competitive intelligence. Prior to her role as a consultant she studied Human Genetics and she holds a PhD in biotechnology from University College London. Anna is a specialist in the field of monoclonal antibody production with keen interest in regenerative medicine, immunotherapies and biologics.

Dr. Tiran Rothman is an Analyst and Consultant at Frost & Sullivan Research & Consulting Ltd., a subsidiary of Frost & Sullivan in Israel. He has over 10 years of experience in research and economic analysis of capital and private markets, obtained through positions at a boutique office for economic valuations, as chief economist at the AMPAL group, and as co-founder and analyst at Bioassociate Biotech Consulting. Dr. Rothman also serves as the Economics & Management School Head at Wizo Academic College (Haifa). Tiran holds a PhD in Economics, MBA (finance), and was a visiting scholar at Stern Business School, NYU.

References

[1] Federal Food Drug and Cosmetic Act—Chapter V, Section 505(b)(2)

[2] https://www.crohnsandcolitis.org.uk/

[3] Martin Feller et al. Mycobacterium avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis. The Lancet Infectious Diseases 2007:607-613

[4] Robert J Greenstein. Is Crohn's disease caused by a mycobacterium? Comparisons with leprosy, tuberculosis, and Johne's disease. The Lancet Infectious Diseases 2003:507-514.

[5] Economou and Pappas. New Global Map of Crohn's Disease: Genetic, Environmental and Socioeconomic Correlations. Inflamm Bowel Dis 2007, 14 (5): 709–720.

[6] Gilaad G. Kaplan The global burden of IBD: from 2015 to 2025. Nature Reviews Gastroenterology & Hepatology 12, 720–727 (2015)

[6] Gohil K, Carramusa B. Ulcerative Colitis and Crohn's Disease. Pharmacy and Therapeutics. 2014;39(8):576-577

[7] Sandborn WJ. The Present and Future of Inflammatory Bowel Disease Treatment. Gastroenterology & Hepatology. 2016;12(7):438-441.

[8] Selby et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. Gastroenterology. 2007;132(7):2313-9

[9] Behr and Hanley. Antimycobacterial therapy for Crohn's disease: a reanalysis. The Lancet Infectious Diseases 2008, 8(6): 344.)

[10] National Cancer Institute (NCI) at the National Institute of Health (NIH), USA.

[11] WHO. Accessed on 14/03/2017. http://www.who.int/mediacentre/factsheets/fs297/en/)

[12] Maddix et al. Rifabutin: a review with emphasis on its role in the prevention of disseminated Mycobacterium avium complex infection. Ann Pharmaco ther 1994; 28: 1250–4

[13] Gisbert and Calvet. Review Article: Rifabutin in the Treatment of Refractory Helicobacter pylori Infection. Aliment Pharmacol Ther. 2012;35(2):209-221

[14] Graham et al.. A report card to grade Helicobacter pylori therapy. Helicobacter 2007; 12: 275–8.

[15] Borody et al. Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant Helicobacter pylori infection. Aliment Pharmacol Ther 2006; 23: 481–488)

[16] Chow CM, Leung AK, Hon KL. Acute gastroenteritis: from guidelines to real life. Clinical and experimental gastroenterology. 2010;3:97-112.

[17] Simmons K, Gambhir M, Leon J, et al. Duration of Immunity to Norovirus Gastroenteritis. Emerging Infectious Diseases. 2013;19(8):1260-1267. doi:10.3201/eid1908.130472.

[18] Credence Research, Inc. "Global Irritable Bowel Syndrome with Diarrhea Market — Growth, Share, Opportunities, Competitive Analysis, and Forecast, 2016–2022,".

[19] https://www.migrainetrust.org

[20] Burch, R. C., Loder, S., Loder, E. and Smitherman, T. A. (2015), The Prevalence and Burden of Migraine and Severe Headache in the United States: Updated Statistics From Government Health Surveillance Studies. Headache: The Journal of Head and Face Pain, 55: 21–34.

[21] Gerth, W. C et al. "Patient Satisfaction with Rizatriptan versus Other Triptans: Direct Head-to-head Comparisons." International Journal of Clinical Practice 55.8 (2001): 552-56

[22] Lipton, Richard B et al. "Effect of Rizatriptan and Other Triptans on the Nausea Symptom of Migraine: A Post Hoc Analysis." Headache: The Journal of Head and Face Pain 41.8 (2001): 754-63

[23] Láinez, Miguel JA. "Rizatriptan in the Treatment of Migraine." Neuropsychiatric Disease and Treatment 2.3 (2006): 247-59

[24] Facts: Colorectal Cancer and Population Screening. www.endoscape.com, Accessed on 17th of March 2017

[25] Bowel preparation before colonoscopy. Saltzman, John R. et al. Gastrointestinal Endoscopy, Volume 81, Issue 4 , 781 – 794.

[26] Maceyka M, Harikumar KB, Milstien S, Spiegel S. SPHINGOSINE-1-PHOSPHATE SIGNALING AND ITS ROLE IN DISEASE. Trends in Cell Biology. 2012;22(1):50-60. doi:10.1016/j.tcb.2011.09.003

[27] Sphingosine 1-phosphate signalling in cancer Pyne J.N, et al.Biochemical Society Transactions. Jan 19, 2012, 40(1)94-100.

[28] http://www.who.int/mediacentre/factsheets/fs103/en/. Accessed on 03 April 2017.

[29] http://www.who.int. Accessed on 03 April 2017.

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