RedHill BioPharma: A Highly De-risked And Undervalued Biopharma Company With A Deep Pipeline

Summary:

- RDHL is an Israeli-based clinical and commercial stage biopharmaceutical company with a large and diverse pipeline specializing in gastrointestinal (GI) indications and other inflammatory diseases.
- RDHL has many catalysts coming in September/October, including Phase 2 results in IBS-D, an NDA resubmission for migraine treatment, and an FDA meeting following a successful Phase 3 trial in acute gastroenteritis/gastritis.
- Long-term, RDHL also has promising Phase 3 trials in Crohn's Disease and *H. pylori* with estimated completion in mid-late 2018.
- Current uncertainty in the market seems to be due to investment in a recent acquisition and commercialization of three FDA-approved drugs, leading to the potential need for fundraising and thus dilution.
- With many late-stage assets that are de-risked due to similarities to approved treatments or previously completed trial data, RDHL has a high likelihood of success across various indications.

Investment Thesis:

RedHill BioPharma is developing technologies that are substantially de-risked, late-stage clinical assets that are largely previously-approved drugs that are either 1) new formulations or combination therapies, and/or 2) being used to treat unique indications. Many of its lead assets have been evaluated in clinical trials and have shown efficacy, including the compounds being tested in the Phase 2 IBS-D trial and Phase 3 Crohn's Disease trial. While there is some risk from their propensity to acquire or license commercial assets, we believe that these early efforts to commercialize and establish a presence in the US market will help RedHill as its pipeline approaches the commercial stage. Based on the strength and diversity of this pipeline, we see many opportunities at upside.

Company Overview:

RedHill BioPharma (NASDAQ: RDHL) is an Israeli-based biopharmaceutical company with both clinical and commercial stage products. It primarily tests pre-existing drugs in new inflammatory indications, focusing primarily on gastrointestinal (GI) indications such as Irritable Bowel Syndrome with Diarrhea (IBS-D), Crohn's Disease (CD), and acute gastroenteritis/gastritis. RDHL does not have a unique drug candidate that is not currently on the market. Instead, RDHL licenses or acquires previously approved products and creates unique combinations or formulations to use in unapproved indications. For its current commercially available drugs, RDHL has an exclusive US co-promotion deal with Confordia for Donnatal, a potential adjunctive therapy for IBS and acute enterocolitis available as an immediate release tablet and as a fast-acting liquid comprised of phenobarbital, hyoscyamine sulfate, atropine sulfate, and scopolamine. It also has an exclusive license from Entera Health for EnteraGam, a medical food comprised of serum-derived bovine immunoglobulin/protein isolate used to treat chronic diarrhea and loose stools in indications like IBS-D. Within the US, RDHL has not garnered much attention and is traded at very low volumes (under 100,000 shares per day as of September 15th), possibly because it is a company based overseas.

Pipeline:

Irritable Bowel Syndrome with Diarrhea (IBS-D)

IBS is a gastrointestinal (GI) disorder that features abdominal pain and altered bowel movements without a known pathological cause. IBS-D is IBS where the predominant symptom is diarrhea, with other symptoms including abdominal pain and bloating, urgency (the feeling that one has an incomplete ability to control defection), and often incontinence.

The dominant FDA-approved treatments in the IBS-D market are alosetron (Lotronex), rifaximin (Xifaxan), and eluxadoline (Viberzi). Xifaxan, an antibiotic, and Viberzi, a μ-opiod agonist that works on the enteric nervous system to control gut motility, were both approved by the FDA in 2015. Xifaxan has been shown to improve both abdominal pain and stool consistency in various clinical trials, but in the key TARGET clinical trials conducted for FDA approval, the difference in response rate was only 8-9% compared to placebo (a 32% fold increase), and treatment sometimes needed to be repeated to see efficacy. Viberzi also improves pain and stool consistency, but the difference in response rate is an unimpressive 10-12% above placebo, although it does represent a fold increase of roughly 60%. Also, Viberzi is not recommended for use in patients without a gallbladder due to hospitalizations and deaths due to pancreatitis.

Lotronex is a 5-HT_3 receptor antagonist that blocks vagal stimulation of the gut, which reduces gut motility and secretion, and was approved by the FDA for use in women in 2000. Although Lotronex shows a 23% improvement over placebo in response rate, it has had a complicated and mixed reception in the medical community, with Glaxo Wellcome willingly withdrawing Lotronex from the market after cases of ischemic colitis (IC) and serious complications of constipation (CoC) that in some cases resulted in death. Remarkably, due to popular demand, it was returned to the market at a lower dose in 2002 for use in women with chronic, refractory IBS-D symptoms lasting at least 6 months who have no GI abnormalities that could predispose them to IC or CoC. However, these restrictions, plus negative sentiment among clinicians has significantly reduced its use.

RDHL has formulated an alternative 5-HT_3 receptor antagonist, ondansetron, as a once-daily extended release oral tablet (BEKINDA, RHB-102) as a new treatment for IBS-D for a wider range of patients and the potential for fewer adverse events. Their current Phase 2 clinical trial will track 120 patients receiving one 12 mg tablet of bimodal release ondansetron or placebo (60:40 split) a day over 8 weeks in both men and women at or above 18 years of age (at least 35% of patients will be men). In accordance with the updated FDA guidelines, the primary endpoint is based on the average number of days a patient experiences messy stools or diarrhea related to a lack of control of bowel movements. This is represented by a Bristol Stool Type score of 6 or 7 (mushy or liquid stool), which is self-reported by the patients. More specifically, in order to be considered a weekly responder, the average number of days a patient experiences these stools in a given week must be reduced by at least 50% compared to their baseline. This needs to be met without increasing the weekly average of worst daily pain by more than 10%. To be considered an overall responder, a subject must be a weekly responder for equal to or greater than 50% of the weeks tested. To meet its endpoint, RDHL must demonstrate a statistically significant increase in overall responders in the treatment arm versus the placebo arm. Secondary endpoints look at pain reduction independent of stool improvement (a decrease in the weekly average of worst abdominal pain in the past 24 hours by 30% or more), overall responders for both pain and stool consistency, and an exploratory endpoint of urgency reduction.

Ondansetron is already approved for treatment of nausea and vomiting in cancer patients receiving cisplatinum chemotherapy with mild side effects. Furthermore, ondansetron has already shown efficacy in IBS-D patients when given three times a day at 4 mg doses, which is comparable to the 12

mg BEKINDA bimodal release tablets used by RDHL. In a 2016 randomized study of 120 IBS-D patients, ondansetron was shown to reduce Bristol Stool Score by -.9 from ~5 baseline to ~4 within a week (Figure 1), significantly reducing defecation, bloating, and urgency without significantly changing pain. Overall, 67% of patients reported adequate relief of symptoms on ondansetron compared to 14% on placebo. Furthermore, 80% of patients given ondansetron were considered stool consistency responders using the same FDA weekly stool consistency criteria as the current study, compared to 41% of patients given placebo, indicating a 39% relative improvement in response rate (p-value of <0.001). Although this study did not directly compare to Lotronex, it did note that adverse events were minimal and potentially better than what is reported with Lotronex due to the fact that ondansetron is 3-10X weaker in stimulation. A 1996 randomized study conducted in 50 IBS patients also showed that specifically in the IBS-D subset, stool consistency increased by at least one point over a two-week period based on an older 5-point stool consistency scale.

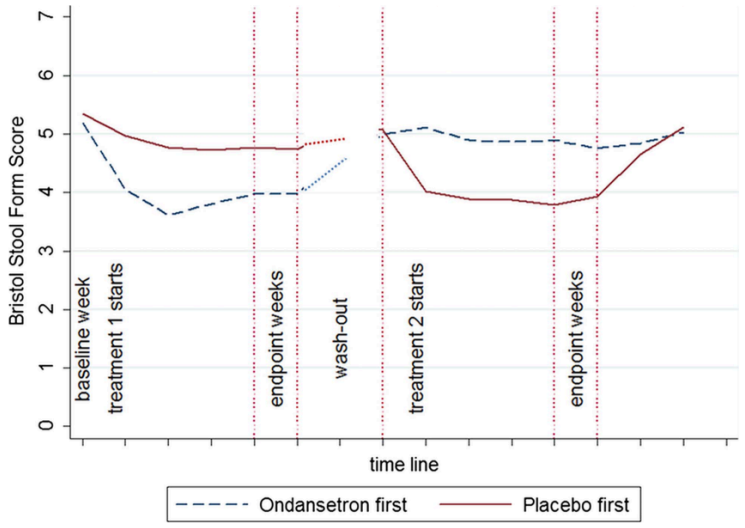

Figure 3 Time course for stool consistency during the two treatment periods. Time shown in weeks. Washout period was variable so the value during the last 7 days is shown as the first data point in the treatment period 2. The graph shows very little placebo effect with rapid onset of treatment effect on commencing ondansetron and loss of effect on discontinuing.

Figure 1. Ondansetron Improves Bristol Stool Consistency in IBS-D (from Garsed, et al.)

Crohn's Disease (CD)
CD differs from IBS in that CD has a known immune system component, featuring extensive chronic inflammation in response to food, commensal bacteria, and other material in the GI tract. Other symptoms overlap with IBS-D, including abdominal pain and persistent diarrhea. However, CD is a more severe condition compared to IBS.

CD treatment is highly variable, with no concrete standard of care. Many interventions focus on inhibition of the immune system/inflammation through treatment with corticosteroids and anti-TNFα antibodies like infliximab (REMICADE). Data from the ACCENT I Phase 3 trial showed that ~42% of enrolled patients failed to qualify as responders to REMICADE, and of responders, only 23-26% of patients achieved remission at 30 weeks. Furthermore, REMICADE and other anti-TNFα antibodies have also received a black box warning due to increased risk for a rare form of T-cell lymphoma in young patients as well as opportunistic infections like TB and fungal infections like histoplasmosis.

Otherwise, doctors prescribe antibiotics, suggest dietary changes, or as a last effort, resort to surgery to remove damaged portions of the intestinal tract, only providing temporary relief.

RDHL's RHB-104 is a triple-combination antibiotic targeting moderate to severe CD using clarithromycin, rifabutin, and clofazimine. This treatment regimen is based on the hypothesis that CD is caused by *Mycobacterium avium paratuberculosis* (MAP), a known cause of a disease with similar symptoms in cattle called Johne's disease. There is debate about the equivalency of the etiology of these two diseases. In a review of 23 peer-reviewed studies attempting to detect MAP in CD patients, 70% of them determined that MAP was detectable in at least 30-50% of patients, while 30% did not detect MAP in any CD patients. However, these results are complicated by the fact that MAP is a very slow-growing bacterium that in CD assumes a form without a cell wall and is therefore difficult to culture and detect in the laboratory.

Pfizer (NYSE: PFE) originally conducted a Phase 3 trial in Australia looking at the same combination of antibiotics in the treatment of CD. Although this trial achieved significant improvements at 16 weeks, they decided not to seek marketing approval due to a perceived lack of sustained response to treatment. This interpretation was made based on relapse rates among those in remission at the 16-week mark. However, the trial design and analysis has been subject to much criticism in retrospect. One response noted that dosing was unusual in the trial compared to clinical standards, with Pfizer using 30% less rifabutin, 50% less clarithromycin, and 50% less clofazimine. There were also compliance issues, and even among the patients that did comply, some were potentially given non-dissolving clofazimine for 10 months, as admitted by the authors. Neither of these factors were corrected or accounted for in the trial. Even with these issues, one paper showed that if you reanalyze the original trial data for remission, you could see significance at 52 and 104 weeks. In the original publication, Pfizer measured initial remission at 16 weeks and then measured the rate of relapse at 52 and 104 weeks within this subset of patients. However, if you look at overall remission, it remains superior to placebo through 104 weeks (Figure 2).

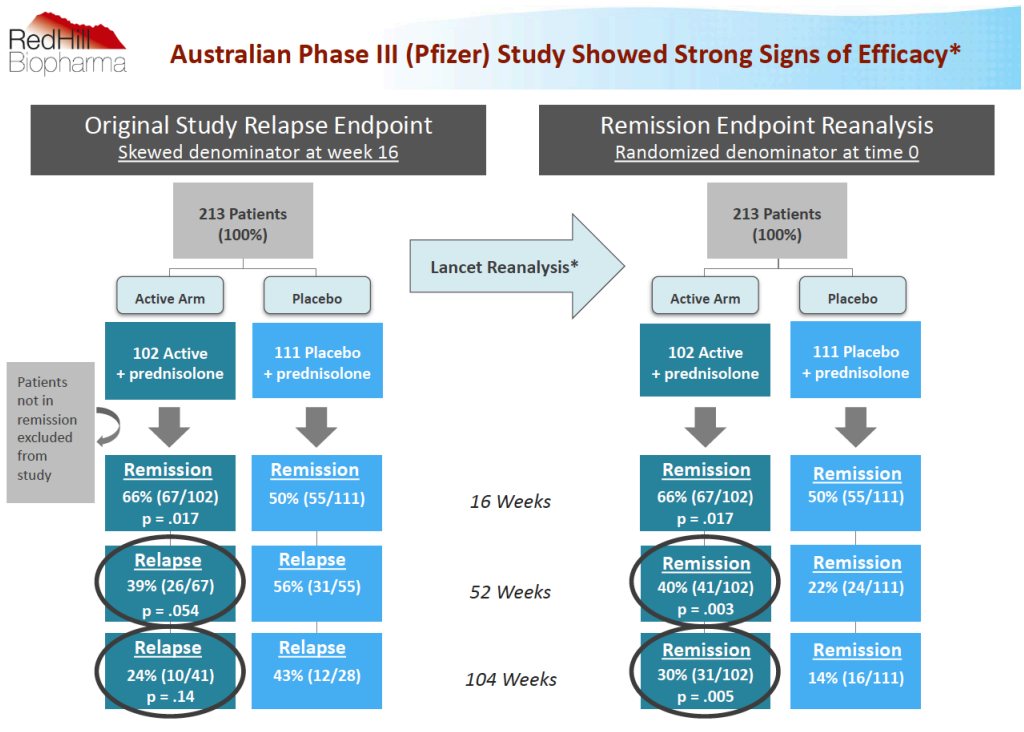

Figure 2. Original and Reinterpreted Results of Phase 3 Pfizer Trial in Crohn's Disease

RDHL's randomized, placebo-controlled Phase 3 trial accounts for many of the original problems in the Pfizer trial. Although RDHL is still using less rifabutin (450 mg/day vs. 600 mg/day recommended in original criticisms of the Pfizer trial, a 25% reduction), the doses for clofazimine are exactly the same as recommended (100 mg/day) and almost exactly the same for clarithromycin (950 mg/day vs. 1000 mg/day recommended) in its RHB-104 formulation. This formulation has been shown to be effective in a 2016 publication *in vitro* against MAP^+ cultures and other bacteria linked to CD such as *Listeria monocytogenes* and *Staphylococcus aureus* and more effective than an RHB-104 analog. Also, RDHL's primary endpoint is remission at 26 weeks (a Crohn's Disease Activity Index (CDAI) less than 150), closer to the original time point where Pfizer already saw statistically significant improvements. Secondary outcomes include general response at 26 weeks (CDAI reduction by at least 100 points), time to remission and response within 52 weeks, duration of remission and response through 52 weeks, and then maintenance of remission from 26 to 52 weeks. Various other outcomes are being measured, including changes in MAP blood status.

Although the interim efficacy analysis of the MAP US study in CD did not meet the early termination criteria (p-value of <0.003 showing overwhelming success in the first half of the targeted 410 patients enrolled), the DSMB unanimously agreed that the trial could continue. Another safety-focused DSMB meeting will be held once 75% of patients have completed the 26-week time point. Although we did not expect the trial to hit this p-value, the market might have hoped it would, leading to the recent decline in stock from a brief increase to $10.50/share. Estimated primary completion for the MAP US trial is in September 2017 with study completion in April 2018. There is also an extension open-label trial (MAP US2) that was initiated in March.

Acute Gastroenteritis/Gastritis
Acute gastroenteritis is an infection or irritation in the stomach or small intestine, while gastritis is limited only to the stomach. Both are primarily caused by viral infection and less commonly by bacterial infection. Treatment primarily focuses on symptom management.

To treat this indication, RDHL is using the same drug as in the IBS-D trials (BEKINDA, a re-formulated ondansetron). Ondansetron is already widely used in emergency departments without formal FDA approval for this indication in children and infants. The Phase 3 GUARD trial sought to test ondansetron in patients aged 12-85 years old with acute gastroenteritis or gastritis. The primary endpoint was defined by patients not vomiting or needing IV hydration or rescue medication within 24 hours of treatment. Phase 3 top-line results presented in June showed that it did successfully meet its primary endpoint in the Intent to Treat (ITT) population despite high positive outcome in the placebo group, showing a 21% fold increase in response rate (65.8% vs. 53.9%, an absolute difference of 11.9%, p value = .03). A Type B FDA meeting in October is expected to discuss these results and determine if another trial is needed prior to NDA filing.

Migraine
RIZAPORT, an oral, fast-dissolving thin film formulation of rizatriptan (a $5\text{-}HT_1$ agonist), is a drug being co-developed with IntelGenx Corp. as a treatment for acute migraines. It is an alternative formulation of the already-approved orally dissolving tablet of rizatriptan, MAXALT-MLT, owned by Merck (NYSE: MRK). RIZAPORT has already been approved for use in various countries in Europe, including Luxembourg and Germany, and commercialization agreements have been signed in Spain and South Korea. Initial NDA submission of RIZAPORT was turned down by the FDA apparently for chemistry, manufacturing, and controls (CMC) reasons associated with Apotex Pharmachem India Pvt. Ltd., the contract manufacturer of the active ingredient, but the drug itself has been shown to be bio-equivalent to MAXALT-MLT (found on slide 59 of the hyperlink) and has no safety concerns. NDA resubmission is expected in October 2017.

Helicobacter pylori (*H. pylori*)
H. pylori is a bacterium that is potentially present in half of people worldwide. For unknown reasons, only a subset of people with resident *H.pylori* develop complications, including peptic ulcers, gastritis, and stomach cancer. Traditionally, *H. pylori* has been treated with triple combination therapies comprising a proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole. However, due to increasing resistance to clarithromycin and metronidazole, this standard of care is becoming increasingly ineffective. One review determined that the incidence of clarithromycin resistance was 29.3% in America, while metronidazole was 44.1%.

RDHL wants to provide a new standard of care for *H. pylori* by swapping out clarithromycin or metronidazole with rifabutin in triple combination therapies, testing rifabutin with amoxicillin and the proton pump inhibitor omeprazole to create the RHB-105 formulation. Rifabutin has shown significantly lower rates of resistance in *H.pylori* (1.3% globally) among 2982 patients from 11 different studies. The first Phase 3 trial conducted showed 89.4% efficacy in eradicating *H. pylori* ($p<.001$) with no serious adverse events, which compared favorably to treatment with the standard of care efficacy of 63%. This observed efficacy is lower than the historical standard of care efficacy of 70%, but treatment with RHB-105 still would have exceeded this value. A confirmatory randomized and double-blind Phase 3 trial with an active comparator arm to high dose amoxicillin and omeprazole alone is currently being conducted with estimated completion is September 2018.

Risks
Initially, there were concerns about whether RDHL would be able to meet the stricter FDA guidelines for proving efficacy in the treatment of IBS-D compared to previously approved drugs. This concern was also discussed in the medical community according to the director of the Gastrointestinal Motility Program at Cedars-Sinai Medical Center, Mark Pimentel, MD, in a recent interview. However, we believe that RDHL will be able to meet this standard due to the fact that the 2016 study mentioned also used these criteria and showed a significant improvement in response rate relative to placebo at a value of 39%, which suggests it should also be very competitive in future trial comparisons to Lotronex and other standards of care.

Another concern is that for the CD trial, RDHL is not selecting patients based on MAP status. The original Pfizer trial also faced criticism for lacking screening. Although RDHL will monitor MAP status and could potentially do subset analysis on these patients, efficacy of treatment among the entire cohort can be drastically hindered if the percent that are MAP-positive is on the lower end (30%) as suggested by the previous review article. However, antibiotic treatment could still help CD patients regardless of MAP status if CD is being caused by another bacterial infection.

A large concern in the market also seems to be the potential risk of dilution, which is exacerbated by RDHL's effort to commercialize various products while simultaneously developing their own product candidates. In addition to Donnatal and EnteraGam, which RDHL has just started to sell, RDHL recently announced the acquisition and promotion of Esomeprazole Strontium Delayed-Release Capsules for treatment of gastroesophageal reflux disease (GERD) and other GI indications.

Lastly, for its Phase 3 acute gastroenteritis/gastritis asset, while it met its primary endpoint, the placebo effect observed in this background was particularly high. This result could impact the FDA's desire for another trial, which will be discussed at a Type B meeting in October. However, considering the support from the literature and current use of ondansetron off-label to treat this indication, we are still optimistic that RDHL will be able to move forward with approval.

Financials:
As of Q2 2017 discussed on an investor call on July 23rd, RDHL's current cash position is $51M, with operating costs at $9.7M, an increase of $4M from Q1 due to research and development expenses for its trials as well as marketing and business development to begin its sales presence in the US. RDHL has begun to generate revenue from two commercialized products, Donnatal and EnteraGam. Within a very small portion of Q2 (June 12th – 30th 2017), these two drugs generated $500,000 in revenue, but costs associated with this revenue were $300,000, leading to net revenue of $200,000. RDHL's market cap is ~$150M, with the stock trading around $9/share.

Market Evaluation:
With all indications combined, the market potential of RDHL far exceeds the current market cap.

The total IBS market globally is expected to increase in value from $589.6M in 2013 to $1.5B by 2023. Viberzi sold for $93.3M in 2016 and is projected to generate $236.9M in revenue by 2023. Xifaxan, another current treatment for IBS-D, generated $220M in Q3 2015 and $210M in Q4 2015, increasing from $148M from Q3 2014. Also, even in its limited target demographic of women with severe IBS-D, Lotronex generated $50M in annual revenue according to 2016 IMS market data. In 2016, RDHL's currently commercialized drug EnteraGam generated $5M in net sales in the US before the RDHL acquisition. Within the US, IBS affects 10-15% of adults, with IBS-D specifically accounting for 1/3 of these patients. Unadjusted mean annual all-cause costs per patient totaled to $13,038 in 2013, representing an incremental increase of $7,273 in medical costs and $1,494 in prescription costs compared to matched controls.

In 2012, GlobalData reported that in 2012, CD treatments reached ~$3.17B in global sales, with a projected increase to $4.2B in 2022. Also, in a review of various clinical and commercial treatments for CD, one group showed that projected sales of CD drugs like Stelara (owned by Janssen Biotech, a subsidiary of Johnson & Johnson (NYSE: JNJ)) to have peak sales of ~$400M, with currently approved treatments like Cimzia and Tyzabri costing $83,075 and $60,827 per 1-year treatment regimens, respectively.

Based on historical studies done by the CDC still cited today, *H. pylori* causes 80% of gastric ulcers and 90% of duodenal ulcers, which incurs a large healthcare cost. Credence Research recently projected that the global ulcer drug market was worth $4.63B in 2016, which is projected to grow to $5.92B by 2025. RDHL's internal analysis results in a similarly sized market, estimating the market at approximately $1.45 billion in the US and $4.83 billion globally in 2015.

Summary:
RDHL represents a strong investment opportunity at its current price due to the strength and diversity of its pipeline with many upcoming potential catalysts. In 2017 alone, near-term catalysts include Phase 2 results in September for IBS-D, an NDA re-submission in October for migraine, and a Type B meeting to discuss successful Phase 3 results in acute gastroenteritis/gastritis. This momentum will most likely continue into 2018 as we approach the release of Phase 3 results in CD and *H. pylori* clinical trials, arguably RDHL's biggest drivers. We are particularly excited for the *H. pylori* indication because of the high likelihood of success and the large market share it can potentially acquire as resistance becomes an increasingly troubling issue with the standard of care. Thus, although we feel that RDHL is likely to meet its near-term Phase 2 driver event with its IBS-D candidate, should it fail, it likely would provide a very nice entry point, and we would likely increase our RDHL position in our hypothetical model portfolio going into the 2018 RDHL driver events. Although RDHL has been pushing commercialization early with other products, we believe this will position RDHL well as its own products approach the commercial stage.

At AMP, we aim to differentiate ourselves with deeper analysis that leverages our years of scientific training and industry experience. Currently contributing are several PhDs and 1 MD.