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RedHill Biopharma Provides Progress Update on RHB-104 Phase III Crohn's Disease Program and Introduces Option for Early Stop...

RedHill Biopharma Provides Progress Update on RHB-104 Phase III Crohn's Disease Program and Introduces Option for Early Stop for Success in Q2/2017

- **An option for early stop for success for overwhelming efficacy has been introduced into the ongoing first Phase III study with RHB-104 for Crohn's disease (the "MAP US" study) and analysis is expected in the second quarter of 2017 as part of a second independent data safety and monitoring board (DSMB) interim safety and efficacy review; The introduction of an early stop for success option may provide an opportunity to significantly shorten the time for study completion**

- **An independent safety-focused DSMB meeting for the Phase III MAP US study is on track for the fourth quarter of 2016**

- **RHB-104 is a potential paradigm-changing treatment for Crohn's disease, targeting a suspected underlying bacterial infectious cause of the disease, *Mycobacterium avium subspecies paratuberculosis* (MAP)**

- **Ongoing work on RedHill's companion MAP diagnostic test has led to the successful identification of MAP DNA in blood samples from Crohn's disease patients; Further development work on the MAP companion diagnostic is in progress; RedHill has recently entered into a collaboration with Baylor College of Medicine - RedHill's third such MAP diagnostics collaboration with a leading U.S. university**

- **In order to enhance the overall robustness of the MAP US Phase III study, provide a more comprehensive assessment of RHB-104's treatment effect and bolster the likelihood of the study's success even further, RedHill is implementing several improvements to the study's protocol and introducing additional enhancements to the overall RHB-104 development program, including:**

    - **The total number of patients to be enrolled in the MAP US study has been increased from 270 to 410 in order to expand the collection of clinical data, including mucosal healing, and to compensate for early terminations; The increase is in line with historical power assumptions and remission rates of Phase III studies with approved Crohn's disease drugs**

    - **Overall 90% power has been maintained and sample size calculations have been modified to reduce the detectable effect from 21% to 15%, reflecting a more clinically expected treatment effect; Furthermore, with this modified sample size, more precise estimates of the treatment effect can be ascertained; No changes are planned to the primary endpoint of remission, defined as CDAI (Crohn's Disease Activity Index) of less than 150 at week 26**

    - **With 219 of the targeted 410 patients already enrolled in the MAP US study, the second independent DSMB meeting is expected in the second quarter of 2017, when the first 205 patients will have completed 26 weeks of study participation; This independent DSMB review will include safety and interim efficacy analysis, with evaluation of an early stop for success under pre-specified efficacy criteria, providing an opportunity to significantly shorten the time to study completion in the event of overwhelming efficacy and potentially expediting the data locking process, once the study is fully completed**

- **The modifications to the statistical design allow for sequential tests to be made; If the pre-specified statistical significance threshold is met at the interim analysis in the second quarter of 2017, the study could be stopped for efficacy or inefficacy; Should the pre-specified threshold not be met in the interim analysis, the study is planned to continue through randomization of all 410 patients and follow-up at 26 weeks, with final efficacy testing performed using a two-sided p-value of 0.049**

- **The increase in the number of patients in the MAP US study is also intended to allow for collection of significantly more colonoscopic mucosal healing data, supporting future potential marketing applications and reflecting and adhering to the most recent FDA and EMA guidance**

- **A third safety-focused independent DSMB meeting is planned for when 75% of the 410 patients will have completed 26 weeks of study participation**

- **In order to improve patient retention and further expedite recruitment, RedHill is preparing to initiate an open-label extension study, offering all patients who complete 26 weeks of study drug administration and remain out of remission (CDAI > 150) the opportunity to receive treatment with RHB-104 for a 52-week period**

- **To further expedite recruitment and expand data collection in Europe, RedHill is increasing the number of European sites by adding approximately 30 new sites in up to four additional European countries, more than doubling the current number of European sites in the MAP US study**

- **In the coming months, RedHill intends to initiate two additional ex-U.S. small-scale open-label clinical studies with RHB-104, each with up to 20 Crohn's disease patients, to provide additional supportive clinical data to potential future marketing applications, as well as evaluate RHB-104's efficacy in newly diagnosed and treatment-naïve Crohn's disease patients and as an add-on therapy to current standard of care**

- **RedHill will remain blinded to the interim and ongoing results from the Phase III study; No changes are planned to the MAP US Phase III study's primary endpoint or 90% power; Assuming enrollment of all 410 planned subjects, completion of patient recruitment is expected by the end of 2017**

- **RedHill maintained a debt-free balance sheet with $47.7 million in cash and cash equivalents at the end of the second quarter of 2016; The cash burn resulting from the changes outlined above in the third quarter of 2016 was insignificant; The expected total impact of cash burn resulting from the expanded recruitment and the initiation of the open-label extension study up until the second independent DSMB meeting and the option for early stop for success in the second quarter of 2017, is approximately $6 million**

- **Two recent non-clinical studies by researchers from the University of Central Florida (UCF) College of Medicine suggest that RHB-104 capsule proprietary formulation should be more effective in eradicating MAP infection than regimens with multi-individualized antibiotics and that RHB-104 active components at minimum inhibitory concentrations provide synergistic anti-MAP growth activity compared to individual or dual combinations**

- **RedHill will host a conference call and webcast to discuss the updates on the RHB-104 Phase III development program today, Thursday, October 6th, 2016, at 8:30 am EDT; Please visit the Company's website for dial-in information and webcast access:http://ir.redhillbio.com/events.cfm**

TEL-AVIV, Israel, Oct. 06, 2016 (GLOBE NEWSWIRE) -- RedHill Biopharma Ltd. (NASDAQ:RDHL) (TASE:RDHL) ("RedHill" or the "Company"), a biopharmaceutical company primarily focused on development and commercialization of late clinical-stage, proprietary, orally-administered, small molecule drugs for gastrointestinal and inflammatory diseases and cancer, today provided an update on the RHB-104 Phase III Crohn's disease development program, planned enhancements to the MAP US first Phase III study and expected milestones, including an option for early stop for success for overwhelming efficacy.

Ira Kalfus, MD, Medical Director at RedHill Biopharma, noted: "The increased number of patients and new open-label program reflect the strong and growing interest we have had from our current investigators who see the potential benefit of RHB-104 and the value of participating in this important study." **Dr. Kalfus further stated:** "We do not expect these

changes to significantly impact timelines and the addition of an interim analysis for early stop for success, expected in the second quarter of 2017, may in fact substantially shorten time to study completion."

Professor David Graham, MD, M.A.C.G., internationally-renowned researcher and physician at the Baylor College of Medicine and the lead investigator of the RHB-104 MAP US Phase III study, said:"Crohn's disease is a chronic inflammatory condition with a devastating impact on patient's overall health and quality of life. With the cause of the disease remaining unknown, current standard of care therapies offer only to control the disease symptoms by suppressing the immune system. RHB-104 targets a specific pathogen believed to be the cause of the disease and thus presents a new approach to treating Crohn's disease. If the RHB-104 MAP US Phase III study is successful, it could completely change the treatment paradigm with therapy being based on the etiology of this disease."

"We are introducing an option for early stop for success, expected in the second quarter of 2017, providing a new near-term catalyst and an opportunity to considerably speed up the study's timelines, without compromising its integrity," **said Dror Ben-Asher, RedHill's CEO.** "RHB-104 is one of RedHill's three ongoing gastrointestinal Phase III flagship programs in the U.S., along with RHB-105 for *H. pylori* infection and BEKINDA® for gastroenteritis and gastritis. RHB-104 is a potential ground-breaking therapy for the treatment of Crohn's disease and a potential blockbuster, if approved. Given the important unmet medical need in Crohn's disease, the large commercial opportunity it presents and the clinical data already accumulated, we are determined to optimally position this study for success**.** The purpose of this update is to provide a detailed and transparent report of RedHill's RHB-104 Crohn's disease program and the important actions we are taking to further enhance the program and the ongoing Phase III study protocol, while maintaining the same endpoints and powering and keeping cash burn in check." **Mr. Ben-Asher added:** "We are very pleased with the current recruitment pace of the MAP US Phase III study and we are taking additional steps to accelerate recruitment even further. The changes introduced to the study's protocol are intended to expand the analyzable data to support future potential marketing applications and further bolster the study's likelihood of success. We are excited about the significant progress achieved with RHB-104, including the successful identification of MAP DNA in blood samples from Crohn's disease patients as part of our diagnostic development program. Our hope is to address the strong unmet medical need in Crohn's disease by potentially changing the treatment paradigm for patients suffering from this debilitating and painful disease."

Professor Thomas Borody, MD, a leading innovator of therapeutic approaches for gastrointestinal diseases, inventor of the original anti-MAP combination, which included the RHB-104 actives (Myoconda), as well as the first patented triple antibiotic therapy for *H. pylori*peptic ulcer disease, and a member of RedHill's Advisory Board, said: "I have been treating patients in my clinic with the anti-MAP combination of antibiotics for over 20 years and have seen remarkable results, with many patients achieving complete and lasting remission over time. It is very exciting to see RedHill continue to progress RHB-104 through advanced clinical development. The similarities between Crohn's disease in humans and Johne's disease in cattle, the strong science pointing to MAP as the infective suspected cause of Crohn's disease and my extensive experience in treating patients with these antibiotics, all lead me to believe that RHB-104 has the potential to become a ground-breaking treatment for Crohn's disease. I am therefore hopeful that RedHill's RHB-104 Phase III program will succeed in demonstrating the relationship between MAP and Crohn's disease and, if successful, help provide Crohn's patients with a new, safe and effective treatment option."

Professor Colm O'Morain, MD, internationally-renowned researcher and physician, former Dean of Healthcare Sciences at Trinity College Dublin, past president of the United European Gastroenterology Federation (UEG) and advisor to RedHill, said: "Crohn's disease incidence in Europe is one of the highest in the world and has increased in several European countries over the past few decades. Patients suffering from Crohn's disease are limited in their therapeutic options, with existing therapies targeting only symptomatic relief and accompanied by major potential side effects. The expansion of the European leg of the MAP US Phase III study is very encouraging, as this drug is targeting the suspected cause of the disease, rather than only disease symptoms. I hope that the expansion of the MAP US study in Europe will help advance the development of RHB-104 and provide additional European patients, who are in need of a new therapeutic alternative, the opportunity to receive treatment with this potential paradigm-changing new therapy."

RHB-104 Crohn's Disease Program and the Microbiome Revolution

RHB-104 is a proprietary and potentially groundbreaking antibiotic combination therapy in oral capsule formulation, with potent intracellular, anti-mycobacterial and anti-inflammatory properties. The development of RHB-104 is based on increasing evidence supporting the hypothesis that Crohn's disease and potentially other autoimmune diseases are related to *Mycobacterium avium subspecies paratuberculosis* (MAP) infection in susceptible patients. The development of RHB-104 is consistent with the growing awareness of the possibility that a bacterially-induced dysregulated immune system may contribute to the pathogenesis of various autoimmune diseases of unknown etiology.

RHB-104 and the Ongoing RHB-104 MAP US First Phase III Study for Crohn's Disease

RedHill is developing RHB-104 for the treatment of Crohn's disease, with an ongoing first Phase III study (the MAP US study). RHB-104 is also being developed for multiple sclerosis, with a Phase IIa proof of concept study recently completed in Israel (the CEASE-MS study). Final results from the Phase IIa study for multiple sclerosis are currently under analysis,

following encouraging top-line interim results.

The ongoing RHB-104 MAP US Phase III study for Crohn's disease is enrolling in up to 150 clinical sites in the U.S, Canada, Europe, Israel, Australia and New Zealand. Additional studies will likely be required to support a U.S. New Drug Application (NDA) for RHB-104.

The MAP US study is a randomized, double-blind, placebo-controlled first Phase III study intended to evaluate the safety and efficacy of RHB-104 in patients with moderately to severely-active Crohn's disease, defined as Crohn's Disease Activity Index (CDAI) between 220 and 450. Subjects enrolled in the study are randomized in a 1:1 fashion to receive RHB-104 or a placebo, with a primary endpoint of disease remission, defined as reduction in CDAI to less than 150 at week 26. Secondary and exploratory endpoints include, among others, state of response at week 26, maintenance of remission through week 52 and efficacy outcome measures in relation to the presence of MAP bacterial infection. Exploratory endpoints include endoscopic evaluation of mucosal healing.

219 subjects have already been randomized in the MAP US study, with a data and safety monitoring board (DSMB) meeting on track to take place in the fourth quarter of 2016. This independent DSMB meeting will focus on safety. RedHill will remain blinded to the interim and ongoing results from the Phase III study.

In order to further enhance the overall robustness of the MAP US Phase III study, provide a more comprehensive assessment of RHB-104's treatment effect, better evaluate the Crohn's disease population enrolled in the study, further improve recruitment pace, address retention and early terminations and bolster the likelihood of study success even further, RedHill is implementing several changes to the study's protocol and introducing additional enhancements to the overall RHB-104 development program, including:

- RedHill has increased the number of subjects planned to be enrolled in the study from 270 to 410, in order to enhance the study's overall robustness, account for early terminations and increase precision of estimates of efficacy.

  Overall, 90% power has been maintained and sample size calculations have been modified to reduce the detectable effect from 21% to 15%, reflecting a more clinically expected treatment effect. Furthermore, with this modified sample size, more precise estimates of the treatment effect can be ascertained. No changes are planned to the primary endpoint of remission at week 26.

  219 patients have already been enrolled in the MAP US study and an independent DSMB review, focused on safety, is on track for the fourth quarter of 2016. Two additional DSMB meetings are expected to take place in the MAP US study after 50% and after 75% of the 410 patients planned to be enrolled in the study will complete 26 weeks of study participation. The second independent DSMB meeting is expected in the second quarter of 2017, after the first 205 patients complete 26 weeks of study participation. Patient 205 was randomized in August 2016.

  The second DSMB meeting will include safety and interim efficacy analysis and could potentially provide the opportunity to expedite the data locking process for the final analysis, once the study is complete.

  Importantly, this independent DSMB meeting will evaluate the option of an early stop for success, according to a pre-specified statistical significance threshold for analysis requiring overwhelming efficacy of RHB-104 versus placebo in the primary endpoint (two sided p-value < 0.003). Potentially, this could shorten the time to study completion considerably without compromising its integrity. The modifications to the statistical design allow for sequential tests to be made using the O'Brien-Fleming spending function to determine the test boundaries. If the pre-specified threshold is met at the second DSMB meeting, the study could be stopped for efficacy or inefficacy. If the pre-specified threshold is not met during the interim analysis, the study is planned to continue through randomization of all 410 patients and follow-up at week 26, with final efficacy testing performed using two sided p-value of 0.049. Given the high thresholds for determining interim efficacy (or inefficacy) set by the pre-specified test boundaries using the O'Brien-Fleming method, RedHill expects to continue the MAP US Phase III study through completion of enrolment of all 410 patients and that the DSMB will not recommend an early stop.

  Taking into account the increase in the total number of patients in the study, and assuming the study is not stopped for success or inefficacy following the DSMB meeting in the second quarter of 2017, completion of recruitment is expected by the end of 2017.

The expansion of the MAP US study is also expected to improve the ability to capture more data related to mucosal healing with endoscopic testing, an exploratory endpoint in the MAP US study. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have stressed the increasing importance of mucosal healing data in Crohn's disease studies. Mucosal healing is a voluntary exploratory endpoint in the MAP US Phase III study and the additional imaging data from this study, as well as from two planned ex-U.S. small-scale clinical studies with RHB-104, will potentially add to the understanding of RHB-104's therapeutic effect and may support future potential marketing applications.

- In order to improve patient retention, further expedite recruitment and expand the safety and efficacy data set of RHB-104, RedHill plans to initiate an open-label extension study for all patients who have completed 26 weeks of treatment in the MAP US study and failed to achieve remission at week 26, the study's primary endpoint. Patients with a Crohn's Disease Active Index (CDAI) score of greater than 150 at week 26 will be offered the opportunity to receive treatment with active drug (RHB-104) for a 52-week period. This study is considered separate from the MAP US study results and data collected will be supplemental to the MAP US study data.

- To further expedite recruitment and expand data collection in Europe, RedHill is increasing the number of European sites in the MAP US study by adding approximately 30 new sites in up to four additional European countries, more than doubling the current number of sites in Europe.

- In support of future potential marketing applications, RedHill also plans to initiate two additional open-label, ex-U.S. clinical studies of up to 20 Crohn's disease patients each to further evaluate the safety and efficacy of RHB-104, including generation of additional efficacy data in newly diagnosed and treatment-naïve Crohn's disease patients and as an add-on therapy to current standard-of-care. In addition, an extensive pharmacokinetic (PK) program is ongoing, including a population PK (pop PK) study which is being conducted as part of the MAP US study along with previously completed food effect and drug-drug interaction studies.

- RedHill maintained debt-free balance sheet with $47.7 million in cash and cash equivalents at the end of the second quarter of 2016. The expected cash burn resulting from the changes outlined above in the third quarter of 2016 was insignificant. The expected total cash burn impact resulting from the expanded recruitment and the initiation of the open-label extension study, up until the second independent DSMB meeting and the option for early stop for success in the second quarter of 2017, is approximately $6 million.

Mycobacterium avium subspecies paratuberculosis (MAP) - Johne's and Crohn's diseases

MAP is a slow-growing, Gram-positive bacterium which is the causative agent of Johne's disease, a severe enteritis that afflicts cattle and other ruminant animals. Heinrich Albert Johne first characterized the condition in 1895 when he demonstrated the presence of acid fast microorganisms in intestinal mucosa of cattle with enteritis[1]. Nearly two decades later, T. K. Dalziel identified a human enteritis similar to Johne's disease yet distinctly different from tuberculosis, another acid fast organism[2]. At the same time, F. W. Twort succeeded in cultivating a new mycobacterium which produced experimental enteritis formally designated *mycobacterium avium paratuberculosis*[3] and the veterinary disease was renamed paratuberculosis. In 1932, Burril Crohn reported on the disease that bore his name similarly describing a non-tuberculous granulomatous regional ileitis[4].

Johne's disease is a chronic granulomatous disease that primarily affects the ileum. It is characterized by progressive weight loss and chronic diarrhea, resulting in wasting and eventual death. Initial clinical signs typically arise after maturity and the birth of first calf following a healthy appearing prolonged incubation period of two to ten years[5]. Infected animals may shed up to one million infectious doses of MAP in their feces per day[6] and it is estimated that over 90% of U.S. dairy herds[7] and roughly 5-10% of U.S. dairy cattle are infected[8].

Crohn's disease shares many similarities with Johne's disease. They both were first described as occurring in the ileum, and like Johne's disease, Crohn's disease presents as a disease of the young. Typical onset of Crohn's disease is between the ages of 15-25 and it is characterized by chronic, recurrent abdominal pain, diarrhea, weight loss and failure to thrive. Pathologically, granulomatous inflammation of the intestinal wall is seen in both Crohn's disease and Johne's disease as is a cobblestone appearance of the intestinal mucosa, which is pathognomonic of Crohn's disease in humans. The principal pathological changes found in the intestine, such as thickening of the ileum and ulcerations of the mucosa, usually with

underlying nodules of lymphoid tissue, have been observed in both Johne's disease and Crohn's disease.

In humans, MAP is an intracellular pathogen that resides in monocytes and macrophages and may persist for months in a dormant spheroplast form without a cell wall. This makes detection by standard staining methods difficult. MAP takes up to six months to grow and requires a highly specialized media, further confounding its identification. *Mycobacterium paratuberculosis* is a Gram-positive, acid-fast, non-spore forming and non-motile bacteria with a straight or curved rod shape. Within macrophages, MAP drops its cell wall, the component of the bacterium that takes up the characteristic acid stain and enhances the ability of the mycobacterium to resist host defenses. The lipid-rich cell wall is believed to determine many of the properties of the organism, such as virulence and resistance to extracellular degradation. In addition, without the cell wall, the bacterium is no longer 'acid fast' and cannot be detected microscopically. Recent studies have demonstrated the capacity of MAP to undergo a morphologic change to become spore-like. The spore morphotype survives heat and may lead to increased persistence in hosts and the environment[9,10].

There is currently no FDA-approved commercial diagnostic test for MAP. However, recent advances in diagnostic technology have led to increasingly higher identification of MAP, with studies demonstrating high prevalence of MAP in Crohn's disease patients[11].

Clinical Study History - MAP and Crohn's disease

In the summer of 1998, the Paratuberculosis Awareness and Research Association issued a plea to the United States Government to investigate the relationship between the cattle pathogen, MAP, and the devastating human condition known as Crohn's disease. In 1999, the U.S. National Institute of Allergy and Infectious Disease (NIAID), part of the National Institutes of Health (NIH), published a research agenda which targeted research into the relationship between infection and Crohn's disease, with particular reference to infection with MAP.

Since the 1998 NIH / NIAID-sponsored conference on MAP in Crohn's disease, there have been numerous studies published in peer-reviewed journals regarding MAP detection in human blood, tissues and stool samples taken from Crohn's disease patients demonstrating a strong relationship between Crohn's disease and MAP.

The resemblance of intestinal pathology in Johne's disease to Crohn's disease was more recently identified and studied by Professor Thomas Borody[12], an innovator of therapeutic approaches to treating gastrointestinal tract diseases. Professor Borody pioneered anti-MAP therapy approximately 20 years ago and has since treated over 300 Crohn's disease patients with the same antibiotics as are used in RHB-104. Professor Borody has published results from several of his studies, including a retrospective analysis of 12 Crohn's disease patients demonstrating complete remission in half of those treated with anti-MAP therapy[13]. Pharmacia Corporation ("Pharmacia"), which was later acquired by Pfizer Inc., licensed the product from Professor Borody and conducted a large 213 patient study which, until RedHill's current study, had been the largest study ever done with anti-MAP therapy in Crohn's disease. Unfortunately, the Pharmacia study design left it significantly underpowered and led to its missing its primary endpoints, although the active arm was better than placebo throughout study drug administration (16 weeks, 52 weeks and 104 weeks)[14]. A reanalysis of the study conducted by McGill University researchers Drs. Marcel A. Behr, MD, and Professor James A. Hanley, PhD, and published in the Lancet Infectious Diseases[15] found that flaws in the study design led not only to an analysis of incremental benefit instead of maintenance of benefit, but also to the introduction of bias in the treatment groups as well. Correcting for these concerns, Drs. Behr and Hanley demonstrated that anti-MAP therapy was significantly more efficacious than placebo with a persistent treatment effect of approximately 16% from week 16 through week 104. According to the Behr and Hanley reanalysis, the Pharmacia study demonstrated a 66% vs. 50% treatment effect favoring anti-MAP therapy at 16 weeks (p=0.02). This was maintained through 52 weeks, with results of 40% vs. 22% (p=0.003) and through 104 weeks with 30% vs. 14% (p=0.005), favoring anti-MAP therapy.

In 2010, following publication of the Lancet article, RedHill acquired the worldwide exclusive rights to RHB-104 from the Sydney, Australia-based company, Giaconda. RedHill has since initiated an extensive R&D program and significantly advanced the development of RHB-104, which included an improved reformulation of the active ingredients in higher doses in an all-in-one single oral capsule, clinical PK studies, a development program for a companion diagnostic for MAP and discussions with the FDA and additional regulatory agencies to clarify the potential regulatory path for approval.

A recent non-clinical study conducted at the University of Central Florida (UCF) College of Medicine's Burnett School of Biomedical Sciences compared the minimum inhibitory concentrations of RHB-104 proprietary all-in-one oral capsule with an RHB-104 analog of the three antibiotics dissolved individually for eradication of MAP infection, as well as other organisms. The study was designed to evaluate the synergistic properties of the RHB-104 all-in-one formulation of three antibiotics and was described by the researchers in an article titled "*A single capsule formulation of RHB-104 demonstrates higher anti-microbial growth potency for effective treatment of Crohn's disease associated with Mycobacterium avium subspecies paratuberculosis"* which has been accepted for publication in the peer-reviewed journal Gut Pathogens[16]. The article concludes that the RHB-104 proprietary formulation of three antibiotics in a single oral capsule results in potent synergistic anti-microbial activity far exceeding the treatment efficacy of multi-individually dissolved drugs. The study strongly suggests

that the proprietary RHB-104 capsule formulation should be more effective in eradication of MAP infection than regimens with multi-individualized antibiotics.

This study follows a previous publication by researchers from the University of Central Florida (UCF) College of Medicine's Burnett School of Biomedical Sciences, which was also published in Gut Pathogens under the title "*RHB-104 triple antibiotics combination in culture is bactericidal and should be effective for treatment of Crohn's disease associated with Mycobacterium paratuberculosis"*[17]. The results described in this article demonstrated that the RHB-104 active components, in their individual concentrations or in dual combinations, were not as effective compared to the triple combination of RHB-104, at minimum inhibitory concentration levels, against all microorganisms. The authors concluded that the triple combination of RHB-104 active components at minimum inhibitory concentration (MIC) provided synergistic anti-MAP growth activity compared to individual or dual combinations of the drugs and, consequently, administration of RHB-104 is considered favorable and should lead to tolerable dosage that is desirable for long-term treatment of Crohn's disease.

RedHill's MAP Diagnostics Development Program

RedHill continues to advance the development program for a commercial companion diagnostic for the detection of MAP bacteria in Crohn's disease patients.

Results to date include initial validation of RedHill's platform PCR (polymerase chain reaction) detection methodology licensed from UCF and developed by Professor Saleh A. Naser, a leading investigator in the field of *Mycobacterium avium subspecies paratuberculosis* (MAP) and its association with Crohn's disease. Further testing of the methodology at three different U.S. laboratories has successfully identified MAP DNA in blood samples drawn from patients with Crohn's disease outside of the MAP US study. Further optimization of the processes for rapid detection of MAP is currently in progress.

The development of the commercial companion diagnostic is an extension of RedHill's RHB-104 Phase III development program. RedHill has also recently initiated a third U.S. university collaboration with Baylor College of Medicine intended to further advance the efforts to develop a companion diagnostic for MAP. RedHill had previously acquired the rights to two separate patented technologies from the laboratory of Professor Saleh A. Naser at the UCF College of Medicine's Burnett School of Biomedical Sciences and from the University of Minnesota.

Critical to the successful development of a companion diagnostic will be ensuring that any future commercial test is accurate and reproducible. RedHill believes that PCR (polymerase chain reaction) technology is the most promising approach currently available and is focusing its efforts in that direction.

There is currently no validated, FDA-approved, commercially available method of detecting the presence or absence of MAP in patients suffering from Crohn's disease and other diseases. The development of a companion diagnostic is expected to contribute to the understanding of the role of MAP infection in Crohn's disease and potentially other inflammatory diseases.

RedHill's RHB-104 Phase IIa Multiple Sclerosis Program

RHB-104 is also under development for relapsing-remitting multiple sclerosis (RRMS). Top-line final results from the Phase IIa CEASE-MS study with RHB-104 for RRMS are expected in the fourth quarter of 2016, following the recently announced last patient follow-up visit in the study. In the first 24 weeks, patients enrolled in the CEASE-MS study received treatment with RHB-104 as an add-on therapy to interferon beta-1a and were then evaluated for an additional 24-week follow-up period during which they were treated with interferon beta-1a alone. Top-line interim results announced in March 2016, after completion of the 24-week treatment period, demonstrated positive safety and efficacy signals, including an encouraging relapse-free rate, Expanded Disability Status Scale (EDSS) scores and MRI results, which support further clinical development.

RHB-104 - Strong Patent Protection

RedHill has built a robust patent portfolio, including protection of the RHB-104 formulation and method-of-use through 2032. RedHill's formidable patent portfolio covering its oral antibiotic combination therapy includes more than 25 patents in various countries including the U.S., Australia, Canada, Japan and multiple European countries with additional patent claims being pursued worldwide.

RHB-104 is composed of three active pharmaceutical ingredients (APIs) and RedHill has been working with various manufacturers to obtain secure and reliable sourcing of these active components. In some cases, this has required the development of proprietary manufacturing processes, which RedHill believes may be an added source of protection for RHB-104.

RedHill will host a conference call and webcast call today, October 6th, 2016 at 8:30 a.m. EDT, to review the RHB-104 development program and the planned changes to the MAP US Phase III study. Please visit the Company's website for dial-in information and webcast access:http://ir.redhillbio.com/events.cfm

About RHB-104:

Currently in a first Phase III study for the treatment of Crohn's disease (the MAP US study), RHB-104 is a proprietary and potentially groundbreaking oral antibiotic combination therapy, with potent intracellular, anti-mycobacterial and anti-inflammatory properties. RHB-104 is based on increasing evidence supporting the hypothesis that Crohn's disease is caused by *Mycobacterium avium subspecies paratuberculosis* (MAP) infection in susceptible patients. Clinical trials conducted with earlier formulations of RHB-104 include an Australian Phase III study conducted by Pharmacia/Pfizer. RedHill has conducted several supportive studies with the current formulation of RHB-104 and a long-term population pharmacokinetic (pop-PK) study is ongoing as part of the Phase III MAP US study. RHB-104 is covered by several issued and pending patents. RedHill is also conducting the CEASE-MS Phase IIa, proof-of-concept clinical study, evaluating RHB-104 as an add-on therapy to interferon beta-1a in patients treated for relapsing-remitting multiple sclerosis (RRMS), with top-line interim results announced and top-line final results expected in the fourth quarter of 2016.

About RedHill Biopharma Ltd.:

RedHill Biopharma Ltd. (NASDAQ:RDHL) (TASE:RDHL) is a biopharmaceutical company headquartered in Israel, primarily 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. RedHill's current pipeline of proprietary products includes: (i) **RHB-105 -** an oral combination therapy for the treatment of *Helicobacter pylori* infection with successful results from a first Phase III study; (ii) **RHB-104 -** an oral combination therapy for the treatment of Crohn's disease with an ongoing first Phase III study and an ongoing proof-of-concept Phase IIa study for multiple sclerosis; (iii) **BEKINDA®(RHB-102) -** a once-daily oral pill formulation of ondansetron with an ongoing Phase III study for acute gastroenteritis and gastritis and an ongoing Phase II study for IBS-D; (iv) **RHB-106 -** an encapsulated bowel preparation licensed to Salix Pharmaceuticals, Ltd.; (v) **YELIVA(™) (ABC294640) -** a Phase II-stage, orally-administered, first-in-class SK2 selective inhibitor targeting multiple oncology, inflammatory and gastrointestinal indications; (vi) **MESUPRON -** a Phase II-stage first-in-class, orally-administered uPA inhibitor, targeting gastrointestinal and other solid tumors; (vii) **RP101 -** currently subject to an option-to-acquire by RedHill, RP101 is a Phase II-stage first-in-class, orally-administered Hsp27 inhibitor, , targeting pancreatic and other gastrointestinal cancers; (viii) **RIZAPORT® (RHB-103) -** an oral thin film formulation of rizatriptan for acute migraines, with a U.S. NDA currently under discussion with the FDA and marketing authorization received in Germany in October 2015; and (ix) **RHB-101 -** a once-daily oral pill formulation of the cardio drug carvedilol.

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements may be preceded by the words "intends," "may," "will," "plans," "expects," "anticipates," "projects," "predicts," "estimates," "aims," "believes," "hopes," "potential" or similar words. Forward-looking statements are based on certain assumptions and are subject to various known and unknown risks and uncertainties, many of which are beyond the Company's control, and cannot be predicted or quantified and consequently, actual results may differ materially from those expressed or implied by such forward-looking statements. Such risks and uncertainties include, without limitation, risks and uncertainties associated with (i) the initiation, timing, progress and results of the Company's research, manufacturing, preclinical studies, clinical trials, and other therapeutic candidate development efforts; (ii) the Company's ability to advance its therapeutic candidates into clinical trials or to successfully complete its preclinical studies or clinical trials; (iii) the extent and number of additional studies that the Company may be required to conduct and the Company's receipt of regulatory approvals for its therapeutic candidates, and the timing of other regulatory filings, approvals and feedback; (iv) the manufacturing, clinical development, commercialization, and market acceptance of the Company's therapeutic candidates; (v) the Company's ability to establish and maintain corporate collaborations; (vi) the Company's ability to acquire products approved for marketing in the U.S. that achieve commercial success and build its own marketing and commercialization capabilities; (vii) the interpretation of the properties and characteristics of the Company's therapeutic candidates and of the results obtained with its therapeutic candidates in research, preclinical studies or clinical trials; (viii) the implementation of the Company's business model, strategic plans for its business and therapeutic candidates; (ix) the scope of protection the Company is able to establish and maintain for intellectual property rights covering its therapeutic candidates and its ability to operate its business without infringing the intellectual property rights of others; (x) parties from whom the Company licenses its intellectual property defaulting in their obligations to the Company; (xi) estimates of the Company's expenses, future revenues capital requirements and the Company's needs for additional financing; (xii) competitive companies and technologies within the Company's industry; and (xiii) the impact of the political and security situation in Israel on the Company's business. More detailed information about the Company and the risk factors that may affect the realization of forward-looking statements is set forth in the Company's filings with the Securities and Exchange Commission (SEC), including the Company's Annual Report on Form 20-F filed with the SEC on February 25, 2016. All forward-looking statements included in this Press Release are made only as of the date of this Press Release. We assume no obligation to update any written or oral forward-looking statement unless required by law.

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