December 12, 2016

RedHill Biopharma Announces Phase IIa 48-Week Final Results Further Supporting Potential of RHB-104 in Multiple Sclerosis

- **Thought to be autoimmune in nature, the multiple sclerosis (MS) inflammatory process is also consistent with an infectious disease; The CEASE-MS Phase IIa proof-of-concept (PoC), single-arm, open-label study was designed with a series of exploratory endpoints to evaluate the safety and potential efficacy of fixed oral-dose RHB-104 as an add-on therapy to interferon beta-1a in 18 patients treated for relapsing-remitting multiple sclerosis (RRMS); Patients underwent 24 weeks of RHB-104 add-on treatment and a 24-week follow-up treatment period with interferon beta-1a, without RHB-104**
- **Top-line final (48 weeks) results are consistent with the previously announced interim results suggesting meaningful positive safety and clinical signals upon 24 weeks of treatment with RHB-104 as an add-on therapy and support further clinical development**
- **The encouraging top-line final results from patients who completed the 48-week study period demonstrate marked improvement over historical self-control; The treatment effect of RHB-104 appears to be maintained after discontinuing RHB-104:**
  - **Annualized relapse rate (ARR) was 0.0 at both 24 and 48 weeks in the per-protocol (PP) population and 0.288 and 0.29, respectively, in the modified intent-to-treat (mITT) population, comparing favorably with previously reported pivotal studies of interferon beta-1a therapies Avonex® (0.67)[1] and Rebif® (0.87-0.91)[2]; Only five relapses were noted throughout the study, four of which occurred in a single subject**
  - **100% of the PP patient population were relapse free at both 24 and 48 weeks and 88% and 93% of the mITT patient population were relapse free at 24 and 48 weeks, respectively, comparing favorably with previously reported pivotal data on the use of Rebif® (75%) in comparison with Avonex® (63%) as standalone first-line therapies[3]**
  - **Expanded Disability Status Scale (EDSS) scores, a standard measure of MS disability, indicate the disease was stable during the treatment period and there was a signal of improvement; No increase in total EDSS scores was observed in any of the patients during the treatment phase**
  - **Combined unique active lesions (CUAs) noted on MRI were almost entirely T2 lesions; A reduction in total T2 lesion volume was observed at 24 and 48 weeks as compared to baseline, suggesting a decreased burden of disease and comparing favorably with previously reported Avonex®[4] and Rebif®[5] data; Furthermore, no clinically significant change was observed for total CUAs during the 24-week treatment period, which is supportive of a stable disease**
  - **RHB-104 appeared safe and well-tolerated, with no drug-related serious adverse events or other clinically relevant or unexpected adverse events**
  - **2016 U.S. and worldwide sales of multiple sclerosis therapies were estimated to exceed $12 billion and $18 billion, respectively**
  - **A first Phase III clinical study with RHB-104 for Crohn's disease is ongoing (the MAP US study), with an independent safety-focused data and safety monitoring board (DSMB) meeting on track by the end of the year and a second meeting expected in the second quarter of 2017, with an interim efficacy analysis of an option for early stop for success for overwhelming efficacy**

TEL-AVIV, Israel, Dec. 12, 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 announced the top-line final results from its CEASE-MS Phase IIa proof-of-concept (PoC) clinical study evaluating

fixed oral-dose RHB-104 in patients treated for relapsing-remitting multiple sclerosis (RRMS).

Ira Kalfus, MD, Medical Director of RedHill and the CEASE-MS study said, "We are very pleased with the final results from the CEASE-MS Phase IIa proof-of-concept study with RHB-104 for relapsing-remitting multiple sclerosis (RRMS). The findings from the study, including safety, clinical and MRI, support the therapeutic potential of RHB-104 as an add-on therapy in RRMS. The final results from patients who completed the 48-week study period demonstrate marked improvement over historical self-control, suggesting the treatment effect of RHB-104 is maintained after discontinuing RHB-104." **Dr. Kalfus added**: "Although designed as an exploratory proof-of-concept study in a very small patient population and not powered for efficacy, the study results demonstrate positive safety data and clinical signals, supporting additional studies to better investigate the therapeutic potential of RHB-104 in RRMS. The results of this study using targeted antibiotic therapy support the hypothesis that a bacterially-induced dysregulated immune system plays a role in the pathogenesis of multiple sclerosis. Importantly, a positive efficacy signal was seen in the reduction of total T2 lesion volume at 24 and 48 weeks compared to baseline. Moreover, despite the short duration of the study, EDSS scores at 24 weeks of treatment with RHB-104 were stable, with suggestion of improvement, and upon discontinuation of RHB-104, EDSS scores, while still stable, suggested a possible deterioration. Notably, no patients experienced a worsening in total EDSS while on treatment and a single patient experienced clinically relevant deterioration following treatment, further supporting the therapeutic potential of RHB-104 for the treatment of RRMS. RHB-104 was observed to be safe and well-tolerated with no clinically relevant or unexpected adverse events, reinforcing our confidence in this therapeutic candidate as we continue to advance the ongoing Phase III MAP US study with RHB-104 for Crohn's disease. Further analysis will drive next steps in the development path of RHB-104 for MS. We would like to thank the patients, investigators and clinical support staff who participated in this important study."

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease of the central nervous system (CNS) with an unknown multifactorial etiology. Thought to be autoimmune in nature, the MS inflammatory process is also consistent with an infectious disease. RHB-104 is a proprietary, orally administered, potentially groundbreaking antibiotic combination therapy with potent intracellular, anti-mycobacterial and anti-inflammatory properties. The completed CEASE-MS Phase IIa clinical study was a single-arm, open-label PoC study evaluating fixed oral-dose RHB-104 as add-on therapy to interferon beta-1a for the treatment of RRMS. This study followed positive pre-clinical research findings and provides clinical evidence of RHB-104's potential as a treatment for MS. The study was designed as an uncontrolled, non-powered, single-arm, open-label PoC study with the objective of evaluating the safety and potential efficacy of RHB-104 using a series of exploratory measures. The results presented in this press release remain subject to the Clinical Study Report (CSR), to be finalized.

Study Design and Baseline Characteristics

CEASE-MS was a 48-week study, where patients underwent 24 weeks of RHB-104 treatment and a 24-week follow-up treatment period with interferon beta-1a, without RHB-104 add-on. Interim results for this study were announced after the 24-week treatment phase was completed by all patients. All endpoints have been reassessed for the final data analysis using patients as their own control for analysis of interferon beta-1a treatment with and without add-on RHB-104 therapy.

18 patients suffering from RRMS were enrolled in the CEASE-MS study in two sites in Israel, of which 17 patients who completed dose escalation were included in the modified intent-to-treat (mITT) data set. One patient was withdrawn from the study due to prohibited concomitant medication usage. The patients had been treated with interferon beta-1a for an average of approximately five years prior to enrollment in the study, experienced at least one MS relapse within 12 months prior to enrollment or two MS relapses within 24 months prior to enrollment, and had an EDSS score of 6.0 or less at screening, with a mean of 3.06. The per-protocol (PP) analysis included ten patients, all of whom completed both the dose escalation and 48-week study period without any major protocol deviations.

Annualized Relapse Rate (ARR)

In the 24-week treatment period, patients in the study experienced an annualized relapse rate (ARR) of 0.0 in the per-protocol (PP) population and 0.29 in the mITT population. Notably, the ARR remained 0.0 in the PP population throughout the 24-week post-treatment period as well. This Phase II data using RHB-104 experimentally as an add-on therapy is encouraging in comparison with previously reported studies of FDA-approved standalone therapies like Avonex® and Rebif®.

The top-line final results from patients who completed the 48-week study period demonstrated marked improvement over historical self-control. The treatment effect of RHB-104 appears to be maintained after completion of treatment with RHB-104.

In the 24-week treatment period of the study, patients in the study experienced an ARR of 0.0 in the PP population and 0.288 in the mITT population. These results compare favorably with previously reported values for both interferon beta-1a therapies Avonex® and Rebif®. The pivotal study of Avonex® demonstrated an ARR of 0.67[6], and a different Avonex® study reported ARRs of 0.53 and 0.31 in patients with and without previous history of disease modifying therapy,

respectively[7]. The pivotal study of Rebif® demonstrated an ARR of 0.87 - 0.91 (a relapse rate of 1.73 - 1.82 over 2 years, 44 mcg or 22 mcg dose-dependent), respectively[8]. In separate studies, reported ARRs for Rebif® have ranged from 0.72 in the PRISMS-4 Long-Term Efficacy Study[9] and 0.39 as first line therapy in the CARE-MS I study[10].

Relapse During the Study

100% of the PP patient population was relapse free throughout the study, while 88% of the mITT patient population was relapse free during the 24 weeks of treatment with RHB-104 and 93% of the mITT patient population was relapse free in the 24 weeks following RHB-104 treatment. Two patients experienced relapses during the study. One between weeks four and eight of RHB-104 treatment, and another experienced four relapses from screening to completion of study. The latter patient was randomized inadvertently, as a relapse between screening and baseline visit should have been exclusionary. Nevertheless, while on RHB-104 treatment, this patient experienced a single relapse in the first four weeks of therapy, and then had two additional relapses following completion of treatment with RHB-104 (weeks 25-48). This suggests that this particular patient may have responded more favorably to treatment with RHB-104 as an add-on therapy.

Overall, the percentage of patients who were relapse free in this study, both on RHB-104 and upon completion of RHB-104 therapy, compares favorably with previously reported pivotal data on the use of Rebif® (75%) in comparison with Avonex® (63%) as standalone first-line therapies[11]. Notably, no patients receiving RHB-104 in the CEASE-MS study relapsed after treatment week 8 and almost all patients remained relapse free following completion of therapy (100% PP and 93% mITT).

Expanded Disability Status Scale (EDSS)[12]

Overall EDSS scores during the study were stable, with total scores during the treatment phase being suggestive of improvement and total scores during the follow-up phase being suggestive of deterioration. Deterioration during the period off RHB-104 was associated with a change in ambulation in one patient. Importantly, no increase in total EDSS scores was observed in any of the patients while on treatment and no patients experienced a decrease in total EDSS scores once off treatment. It should be noted that the 24 weeks on and off RHB-104 is a short period of observation for evaluation of EDSS score.

T2 Lesion Volume and MS Disease Burden

Burden of disease is defined as the total volume of all T2 lesions. T2 lesion load, expected to increase by approximately 11% per year in RRMS if untreated[13], is accepted as an indicator of response and progression in RRMS. Although not powered for efficacy, and conducted over a short period of time in a small number of patients, the CEASE-MS study results indicate a reduction in T2 lesion volume at 24 and 48 weeks of treatment with RHB-104 as compared to baseline, suggesting reduction in MS disease burden and comparing favorably with previously reported Avonex® and Rebif® data. In a previous study with Rebif® administered for 24 months as first-line treatment of RRMS, median T2 lesion burden was noted to decrease by 6.5% at 24 months[14], while patients treated with RHB-104 as an add-on therapy in the CEASE-MS study had a 3.37% decrease in median T2 lesion burden at 24 weeks and a 9.97% decrease in median T2 lesion burden at week 48. Improvement in T2 lesions on RHB-104 therapy was additive as mean T2 lesion burden decreased by 7.56% at 24 weeks and by 13.8% at 48 weeks in the CEASE-MS study with RHB-104 as an add-on therapy, compared with a 10.4% increase in Avonex® -treated patients at 12 months[15].

Combined Unique Active Lesions (CUAs)

MRI is useful in monitoring MS progression and MRI findings are generally accepted as a surrogate endpoint in MS trials. Combined unique active lesions (CUAs) are defined as active lesions on T1 post-gadolinium, T2 sequences, or both, avoiding double counting. A T2 lesion in this context is defined as a new or enlarging lesion or a lesion reappearing at a site of previous lesion resolution. CUAs served as the primary outcome measure of the CEASE-MS study. Among all patients followed for 48 weeks, only five active T1 post-gadolinium lesions were noted. CUAs in the study were almost entirely driven by changes in T2 lesions, and changes in total CUAs at weeks 24 and 48 were not clinically significant. An increase in the average percentage change from baseline was observed for total CUAs at weeks 24 and 48 yet, as noted above, a positive efficacy signal was seen in reduction of total T2 lesion volume at 24 and 48 weeks as compared to baseline. This apparent discrepancy between the average percentage change from baseline and the reduction of total T2 lesion volume is best explained by a combination of statistical fluctuation and definitional bias in this small study. Importantly, these MRI findings, along with the presence of only five active T1 post gadolinium lesions, are consistent with stable radiological and clinical disease.

Safety and Tolerability

Overall, RHB-104 was well-tolerated. There were no clinically relevant or unexpected adverse events reported in the study, and none of the five serious adverse events (SAEs) seen in the study were related to the study drug. As expected, almost all patients experienced chromaturia (abnormal coloration of the urine). Two subjects withdrew from the study due to adverse events of metallic taste and nausea/vomiting.

Cytokine Levels

Cytokine analysis contribution was generally difficult to assess due to absence of control, the very small patient population and heterogeneity in observed values.

Mycobacterium avium subspecies paratuberculosis (MAP) Status

Development of the RedHill MAP diagnostic is ongoing. It is expected that evaluation of MAP status, using samples collected and stored as part of the completed CEASE-MS study, will be performed in conjunction with the development of the diagnostic test.

RedHill continues to advance the development program for a commercial companion diagnostic test 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 University of Central Florida (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.

About Multiple Sclerosis:
Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease of the central nervous system with an unknown etiology, believed to be multifactorial. A dysfunctional immune system in MS patients causes recurrent inflammatory attacks on the central nervous system (CNS), leading to neurological disability. Diffuse inflammatory and demyelinating lesions, also known as plaques, are the main pathological finding in MS neural tissue. The lesions are primarily found in the spinal cord, optic nerves, brainstem, and periventricular white matter. The symptoms of MS are dictated by the location of the lesions within the CNS. Geographic variation in MS distribution, which cannot be solely explained by population genetics, supports the notion that environmental factors also hold etiological importance. There is currently no known cure for MS and available treatments are mainly intended to manage or prevent relapses or reduce symptoms. In 2015, there were estimated to be over 900,000 diagnosed patients with MS worldwide. Approximately 85% of MS patients initially exhibit relapse-remitting disease. The 2016 U.S. and worldwide sales of MS therapies were estimated to exceed $12 billion and $18 billion, respectively[16].

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, orally-administered, potentially groundbreaking 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 has also completed a 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 (the CEASE MS study). Top-line final results from the CEASE MS study suggest meaningful positive safety and clinical signals upon 24 weeks of treatment with RHB-104 as an add-on therapy and support further clinical development.

About RedHill Biopharma Ltd.:
RedHill Biopharma Ltd. (NASDAQ/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 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 a completed 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 and (vii) **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.

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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[2] 1.73 - 1.82 over 2 years; PRISMS Study Group: Lancet 1998; 352: 1498-504.

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[16] GlobalData PharmaPoint report, 2015.

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