Brazil Approves RedHill Biopharma's Phase 2/3 COVID-19 Study with Opaganib

September 22, 2020

The ongoing global Phase 2/3 study with orally-administered opaganib in patients with severe COVID-19 is approved in Italy, the UK, Russia, Israel, Mexico and Brazil; 16 clinical sites initiated globally to date

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In parallel, the opaganib U.S. Phase 2 study, with 8 active clinical sites, is approximately 75% enrolled and expected to be completed in the coming weeks

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Opaganib completely inhibited SARS-CoV-2 viral replication in an in vitro human lung cell model, comparing favorably with remdesivir, the positive control in the study

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Opaganib demonstrated dual anti-inflammatory and antiviral activity and targets a host cell component, unaffected by viral mutation, thus minimizing the likelihood of resistance

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Global emergency use authorization applications planned, subject to positive clinical results

TEL AVIV, Israel and RALEIGH, N.C., Sept. 22, 2020 (GLOBE NEWSWIRE) -- RedHill Biopharma Ltd. (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced approval from the Brazilian Health Regulatory Agency (ANVISA) for its ongoing global Phase 2/3 study evaluating opaganib[1] in patients hospitalized with severe COVID-19 pneumonia. Opaganib is a first-in-class, orally-administered, sphingosine kinase-2 (SK2) selective inhibitor with demonstrated dual anti-inflammatory and antiviral activity that targets a host cell component, unaffected by viral mutation, thus minimizing the likelihood of resistance.

Gilead Raday, RedHill's Chief Operating Officer, said: "In recently announced preclinical results, opaganib demonstrated its ability to stop SARS-CoV-2 viral replication in its tracks - preventing its ability to spread and cause damage to other cells which, together with its potent anti-inflammatory mechanism, supports the rapid progress of our global Phase 2/3 and U.S. Phase 2 studies. Brazil continues to experience a significant number of COVID-19 cases and its addition is expected to further accelerate the global Phase 2/3 study with opaganib."

The ongoing global multi-center, randomized, double-blind, parallel-arm, placebo-controlled Phase 2/3 study (NCT04467840) evaluating opaganib for the treatment of patients with severe COVID-19 pneumonia continues to enroll with a target of up to 270 patients requiring hospitalization and treatment with supplemental oxygen. The study has been approved in Brazil, Israel, United Kingdom, Italy, Russia and Mexico, with further expansion ongoing and progressing rapidly.

In parallel, the randomized, double-blind, placebo-controlled U.S. Phase 2 study (NCT04414618) with opaganib in patients with severe COVID-19 pneumonia is approximately 75% enrolled, with enrollment set to be completed in the coming weeks. Recently, a pre-scheduled independent Safety Monitoring Committee recommended that the study continue without change. The study, which is not powered for statistical significance, is set to enroll up to 40 patients requiring hospitalization and supplemental oxygen.

The Company is in discussions with U.S. government agencies around potential funding to support the rapid advancement of opaganib toward potential emergency use approval.

About Opaganib (ABC294640, Yeliva®)
Opaganib, a new chemical entity, is a proprietary, first-in-class, orally-administered, sphingosine kinase-2 (SK2) selective inhibitor with anticancer, anti-inflammatory, and antiviral activities, targeting multiple oncology, viral, inflammatory, and gastrointestinal indications.

Opaganib received Orphan Drug designation from the U.S. FDA for the treatment of cholangiocarcinoma and is being evaluated in a Phase 2a study in advanced cholangiocarcinoma and in a Phase 2 study in prostate cancer. Opaganib is also being evaluated in a global Phase 2/3 study and a U.S. Phase 2 study for the treatment of COVID-19.

Preclinical data have demonstrated both anti-inflammatory and antiviral activities of opaganib, with the potential to reduce inflammatory lung disorders, such as pneumonia, and mitigate pulmonary fibrotic damage. Opaganib demonstrated potent antiviral activity against SARS-CoV-2, the virus that causes COVID-19, completely inhibiting viral replication in an *in vitro* model of human lung bronchial tissue. Additionally, preclinical *in vivo* studies[2] have demonstrated that opaganib decreased fatality rates from influenza virus infection and ameliorated *Pseudomonas aeruginosa*-induced lung injury by reducing the levels of IL-6 and TNF-alpha in bronchoalveolar lavage fluids.

Opaganib was originally developed by U.S.-based Apogee Biotechnology Corp. and completed multiple successful preclinical studies in oncology, inflammation, GI, and radioprotection models, as well as a Phase 1 clinical study in cancer patients with advanced solid tumors and an additional Phase 1 study in multiple myeloma.

Under a compassionate use program, COVID-19 patients (as classified by the WHO ordinal scale) were treated with opaganib in a leading hospital in Israel. Data from the treatment of these first patients with severe COVID-19 with opaganib have been published[2]. Analysis of treatment outcomes suggested substantial benefit to patients treated with opaganib under compassionate use in both clinical outcomes and inflammatory markers as compared to a retrospective matched case-control group from the same hospital. All patients in the opaganib-treated group were discharged from hospital on room air without requiring intubation and mechanical ventilation, whereas 33% of the matched case-control group required intubation and

mechanical ventilation. Median time to weaning from high-flow nasal cannula was reduced to 10 days in the opaganib-treated group, as compared to 15 days in the matched case-control group.

The development of opaganib has been supported by grants and contracts from U.S. federal and state government agencies awarded to Apogee Biotechnology Corp., including from the NCI, BARDA, the U.S. Department of Defense and the FDA Office of Orphan Products Development.

The ongoing studies with opaganib are registered on www.ClinicalTrials.gov, a web-based service by the U.S. National Institute of Health, which provides public access to information on publicly and privately supported clinical studies.

About RedHill Biopharma

RedHill Biopharma Ltd. (Nasdaq: RDHL) is a specialty biopharmaceutical company primarily focused on gastrointestinal diseases. RedHill promotes the gastrointestinal drugs, **Movantik®** for opioid-induced constipation in adults[3], **Talicia®** for the treatment of *Helicobacter pylori (H. pylori)* infection in adults[4], and **Aemcolo®** for the treatment of travelers' diarrhea in adults [5]. RedHill's key clinical late-stage development programs include: (i) **RHB-204**, with a planned pivotal Phase 3 study for pulmonary nontuberculous mycobacteria (NTM) infections; (ii) **opaganib (Yeliva®)**, a first-in-class SK2 selective inhibitor targeting multiple indications with a Phase 2/3 program for COVID-19 and Phase 2 studies for prostate cancer and cholangiocarcinoma ongoing; (iii) **RHB-104**, with positive results from a first Phase 3 study for Crohn's disease; (iv) **RHB-102** (**Bekinda®**), with positive results from a Phase 3 study for acute gastroenteritis and gastritis and positive results from a Phase 2 study for IBS-D; (v) **RHB-107**, a Phase 2-stage first-in-class, serine protease inhibitor, targeting cancer and inflammatory gastrointestinal diseases and is also being evaluated for COVID-19 and (vi) **RHB-106**, an encapsulated bowel preparation. More information about the Company is available at www.redhillbio.com.

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, the risk that the Company's Phase 2/3 study evaluating opaganib will not be successful; the risk that the antiviral activity of opaganib shown in the preclinical human lung cell model will not be demonstrated in clinical trials; the risk of a delay in receiving data to support emergency use applications; the risk that the U.S. Phase 2 clinical study evaluating opaganib will not be successful and the risk that completion of enrollment for this clinical study will be delayed; the risk that the Company will not initiate the Phase 2/3 study for opaganib in certain geographies, will not expand this study to additional countries and that it will not be successful; the risk that other COVID-19 patients treated with opaganib will not show any clinical improvement; the risk that clinical trials with opaganib in Brazil, Israel, the U.S., Italy, Russia, the UK, Mexico or elsewhere for the treatment of COVID-19, if conducted at all, will not show any improvement in patients; the risk of a delay in applying for emergency use authorizations, if at all; the development risks of early-stage discovery efforts for a disease that is still little understood, including difficulty in assessing the efficacy of opaganib for the treatment of COVID-19, if at all; intense competition from other companies developing potential treatments and vaccines for COVID-19; the effect of a potential occurrence of patients suffering serious adverse events using opaganib under compassionate use programs, as well as 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, and the timing of the commercial launch of its commercial products and ones it may acquire or develop in the future; (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 and type 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 and Talicia®; (v) the Company's ability to successfully commercialize and promote Movantik®, Talicia® and Aemcolo®; (vi) the Company's ability to establish and maintain corporate collaborations; (vii) the Company's ability to acquire products approved for marketing in the U.S. that achieve commercial success and build and sustain its own marketing and commercialization capabilities; (viii) the interpretation of the properties and characteristics of the Company's therapeutic candidates and the results obtained with its therapeutic candidates in research, preclinical studies or clinical trials; (ix) the implementation of the Company's business model, strategic plans for its business and therapeutic candidates; (x) the scope of protection the Company is able to establish and maintain for intellectual property rights covering its therapeutic candidates and commercial products and its ability to operate its business without infringing the intellectual property rights of others; (xi) parties from whom the Company licenses its intellectual property defaulting in their obligations to the Company; (xii) estimates of the Company's expenses, future revenues, capital requirements and needs for additional financing; (xiii) the effect of patients suffering adverse events using investigative drugs under the Company's Expanded Access Program; and (xiv) competition from other companies and technologies within the Company's industry. 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 March 4, 2020. All forward-looking statements included in this press release are made only as of the date of this press release. The Company assumes no obligation to update any written or oral forward-looking statement, whether as a result of new information, future events or otherwise unless required by law.

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[1] Opaganib is an investigational new drug, not available for commercial distribution.

[2] Xia C. et al. Transient inhibition of sphingosine kinases confers protection to influenza A virus infected mice. Antiviral Res. 2018 Oct; 158:171-177. Ebenezer DL et al. Pseudomonas aeruginosa stimulates nuclear sphingosine-1-phosphate generation and epigenetic regulation of lung inflammatory injury. Thorax. 2019 Jun;74(6):579-591.

[3] Full prescribing information for Movantik® (naloxegol) is available at: www.Movantik.com.

[4] Full prescribing information for Talicia® (omeprazole magnesium, amoxicillin and rifabutin) is available at: www.Talicia.com.
[5] Full prescribing information for Aemcolo® (rifamycin) is available at: www.Aemcolo.com.

Source: RedHill Biopharma Ltd.