



RedHill Biopharma's Opaganib Demonstrates Complete Inhibition of SARS-CoV-2

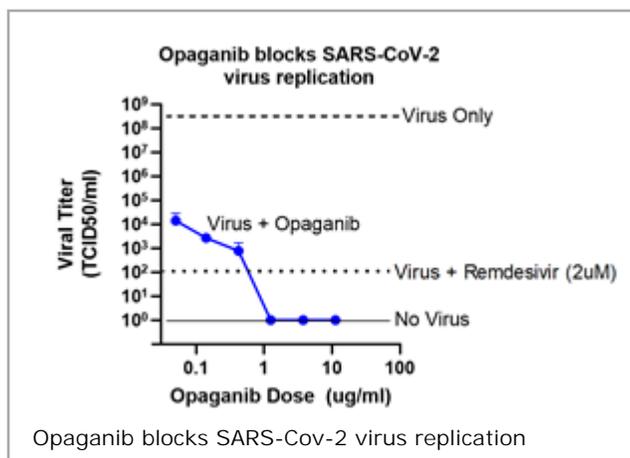
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Opaganib completely inhibited SARS-CoV-2 viral replication as measured after three days incubation in an in vitro model of human bronchial tissue, comparing favorably with remdesivir, the positive control in the study

Opaganib is uniquely positioned as an orally-administered potential COVID-19 treatment combining potent antiviral and anti-inflammatory mechanisms of action, targeting a host cell component and minimizing likelihood of resistance

Global Phase 2/3 and U.S. Phase 2 clinical studies ongoing with opaganib for severe COVID-19 pneumonia

RedHill's second COVID-19 drug candidate, RHB-107 (upamostat), a novel serine protease inhibitor, strongly inhibited SARS-CoV-2 viral replication in the same model, further supporting planned initiation of a Phase 2/3 U.S. outpatient study later this year



TEL AVIV, Israel and RALEIGH, N.C., Sept. 08, 2020 (GLOBE NEWSWIRE) -- [RedHill Biopharma Ltd.](#) (Nasdaq: [RDHL](#)) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced that opaganib¹ demonstrated potent inhibition of SARS-CoV-2, the virus that causes COVID-19, achieving complete blockage of viral replication in an *in vitro* model of human lung bronchial tissue. Opaganib is a first-in-class, orally-administered, sphingosine kinase-2 (SK2) selective inhibitor with dual anti-inflammatory and anti-viral activity that targets a host cell component, unaffected by viral mutation, thus minimizing the likelihood of resistance. Opaganib is currently being evaluated in global Phase 2/3 and U.S. Phase 2 clinical studies for the treatment of severe COVID-19 pneumonia.

Working in collaboration with the University of Louisville Center for Predictive Medicine, opaganib was studied in a 3D tissue model of human bronchial epithelial cells (EpiAirway™) which morphologically and functionally resembles the human airway and is similar to the model used to discover SARS-CoV-2². This study was designed to evaluate the *in vitro* efficacy of opaganib in inhibiting SARS-CoV-2 infection and included a positive control of remdesivir, a drug with known antiviral activity.

Results from this study showed a clear and compelling antiviral effect of opaganib against SARS-CoV-2. Opaganib demonstrated the most potent activity compared to all compounds tested, including the positive control, remdesivir. Treatment of cells infected with SARS-CoV-2 resulted in a dose-dependent inhibition of virus production without compromising cell membrane integrity, a measure of cell viability and drug safety, further demonstrating opaganib's promising potential for treating patients with COVID-19.

A graphic accompanying this announcement is available at <https://www.globenewswire.com/NewsRoom/AttachmentNg/e60ced55-ca9d-4648-81cb-907be7571136>

Opaganib at 1mg/ml (a pharmacologically relevant concentration) completely inhibited viral replication as measured after three days of incubation. This potent opaganib activity compares favorably with remdesivir data as the active control in the RedHill study which is consistent with published remdesivir data³. Data from the study is planned to be submitted to a peer-reviewed journal.

"Opaganib's previously demonstrated anti-inflammatory activity, combined with our now proven specific anti-SARS-CoV-2 viral activity, provides a

unique dual mechanism of action with the potential to greatly benefit COVID-19 patients by inhibiting the key drivers of disease progression - viral replication and lung inflammation,” said **Mark L. Levitt, M.D., Ph.D., Medical Director at RedHill**. “These compelling data, using a physiologically relevant human respiratory tissue model, demonstrate opaganib’s potential to strongly inhibit SARS-CoV-2 viral replication, validating the hypotheses underlying our ongoing global Phase 2/3 and U.S. Phase 2 clinical studies and further supporting their rationale. Accordingly, we are accelerating progress toward our goal of generating a robust data package to potentially support emergency use authorizations for COVID-19.”

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 recently received approval in Israel and has been approved in the United Kingdom, Italy, Russia and Mexico, with further expansion progressing.

In parallel, the randomized, double-blind, placebo-controlled U.S. Phase 2 study ([NCT04414618](#)) with opaganib in patients with severe COVID-19 pneumonia is more than 50% 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.

In addition to opaganib, RedHill’s in-vitro study evaluated the antiviral activity of its Phase-2 stage investigational drug, RHB-107 (upamostat), a serine protease inhibitor active against a number of human serine proteases, with results demonstrating potent inhibition of SARS-CoV-2 viral replication. A U.S. Phase 2/3 study with RHB-107 in an outpatient setting is planned to be initiated later this year.

“Host cellular proteases play a critical role in the process of SARS-CoV-2 entry into cells, specifically responsible for activating the SARS-CoV-2 spike (S) protein, which is a prerequisite for the fusion of viral and host cell membranes during viral entry,” said **Terry F. Plasse MD, Medical Director at RedHill**. “RHB-107 demonstrated excellent antiviral activity, with viral replication being strongly inhibited in a dose-dependent manner at pharmacologically relevant concentrations. As with opaganib, RHB-107 (upamostat) is orally bioavailable and therefore potentially suitable for both inpatient and out-patient settings.”

The results from the preclinical studies of opaganib and RHB-107 are preliminary and were provided to the Company by an independent third-party following an initial independent analysis and remain subject to additional review and analysis of the data and potentially supportive experiments.

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 coronavirus (COVID-19).

Preclinical data have demonstrated both anti-inflammatory and antiviral activities of opaganib, with the potential to reduce lung inflammatory 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* studies⁴ 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 published². 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 without requiring mechanical ventilation, whereas 33% of the matched case-control group required 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 RHB-107 (upamostat)

RHB-107 is a proprietary, first-in-class, orally-administered potent inhibitor of several serine proteases, with demonstrated antiviral and potential tissue-protective effects. This combined antiviral and potential tissue-protective action make it a strong candidate for evaluation as a treatment for COVID-19 infection. In addition, RHB-107 has potential in targeting cancer, inflammatory lung diseases and gastrointestinal diseases, and has undergone several Phase 1 studies and two Phase 2 studies, demonstrating its clinical safety profile in over 300 patients. RedHill acquired the exclusive worldwide rights to RHB-107, excluding China, Hong Kong, Taiwan and Macao, from Germany’s Heidelberg Pharmaceuticals (formerly WILEX AG) for all indications.

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 adults⁵, **Talicia®** for the treatment of *Helicobacter pylori* (*H. pylori*) infection in

adults⁶, and **Aemcolo**[®] for the treatment of travelers' diarrhea in adults⁷. 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.

The results from the preclinical studies of opaganib and RHB-107 are preliminary and were provided to the Company by an independent third party following an initial independent analysis and remain subject to additional review and analysis of the data and potentially supportive experiments. Such review and analysis may result in findings inconsistent with the results disclosed in this release and may not be replicated in future pre-clinical or clinical trials. Accordingly, investors should not rely on the results described in this release as definitive proof of the antiviral effect of opaganib against SARS-CoV-2 and whether in fact opaganib will be an effective treatment of SARS-CoV-2.

*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 RHB-107 will not be successful, if conducted at all; the risk the antiviral activity in the in vitro study will not be demonstrated in clinical trials; the risk of a delay in receiving data to support applying for 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 in additional countries and that it will not be successful; the risk that the Company will not initiate the Phase 2/3 study in COVID-19 with RHB-107 or that it will be delayed; the risk that other COVID-19 patients treated with opaganib will not show any clinical improvement; the risk that clinical trials with opaganib in 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; 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 or the development of a commercial companion diagnostic for the detection of *Mycobacterium avium* subspecies *paratuberculosis* (MAP); (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 (Yeliva)[®], ABC294640) is an investigational new drug, not available for commercial distribution.

² Na Zhu et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020;382:727-33.

³ Pruijssers AJ et al. Remdesivir Inhibits SARS-CoV-2 in Human Lung Cells and Chimeric SARS-CoV Expressing the SARS-CoV-2 RNA Polymerase in Mice. *Cell Reports*. Vol 32, Issue 3, 107940, July 21, 2020.

⁴ Xia C. et al. Transient inhibition of sphingosine kinases confers protection to influenza A virus infected mice. *Antiviral Res.* 2018 Oct; 158:171-177.

⁵ 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.

⁶ Full prescribing information for **Movantik**[®] (naloxegol) is available at: www.Movantik.com.

⁷ Full prescribing information for **Talicia**[®] (omeprazole magnesium, amoxicillin and rifabutin) is available at: www.Talicia.com.

⁷ Full prescribing information for Aemcolo[®] (rifamycin) is available at: www.Aemcolo.com.



Source: RedHill Biopharma Ltd.