RedHill Biopharma's Oral Opaganib Reduces Mortality by 70% Given on Top of Remdesivir and Corticosteroids in Severe COVID-19

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Updates on Regulatory Discussions and Plans in Multiple Countries
Prespecified analysis of Phase 2/3 opaganib data in severe COVID-19 patients showed a significant, 70.2% mortality benefit with opaganib by Day 42 when given on top of the best available standard-of-care (SoC), remdesivir and corticosteroids (6.98% mortality in the opaganib arm versus 23.4% for placebo, p-value=0.034)
A second prespecified analysis showed that opaganib also delivered a significant 34% benefit in 'time to recovery by Day 14', with 37.4% of opaganib-treated patients reaching this event versus 27.9% of patients treated with placebo + SoC (p-value=0.013)
These additional prespecified mortality and recovery analyses, along with previously announced data showing opaganib's improved median time to SARS-CoV-2 viral RNA clearance, further strengthen the positive outcomes in the Phase 2/3 study post-hoc analysis. All data is being shared with regulators
Opaganib data submissions initiated in Q4/21, initial guidance on potential path to approval received from the EU's EMA, the U.S. FDA, UK's MHRA and others, discussions ongoing
Based on regulatory feedback and external advice received from other territories, potential emergency and marketing authorization applications planned in H1/2022

TEL AVIV, Israel and RALEIGH, N.C., Feb. 7, 2022 /PRNewswire/ -- RedHill Biopharma Ltd. (NASDAQ: RDHL) (“RedHill” or the “Company”), a specialty biopharmaceutical company, today announced results from two recently completed prespecified analyses from the oral opaganib (ABC294640) Phase 2/3 study in hospitalized severe COVID-19. The
first analysis showed that opaganib significantly reduced mortality when given to patients who received remdesivir and corticosteroids, the best available standard-of-care (SoC) for hospitalized patients. A second analysis further showed that opaganib delivered a significant benefit in time to recovery, defined as achieving a score of 1 or less on the WHO Ordinal Scale by Day 14. The Company is advancing regulatory discussions in multiple countries, with potential emergency and marketing authorization applications being planned for certain countries in the first half of 2022.

The prespecified mortality analysis, undertaken for all patients from the Phase 2/3 study who were receiving remdesivir and corticosteroids at baseline, demonstrated a significant 70.2% mortality benefit for opaganib-treated patients, with a mortality rate of 6.98% (n=3/43) for the opaganib arm + SoC versus 23.4% (n=11/47) for placebo + SoC by Day 42 (p-value=0.034).

The second prespecified analysis showed opaganib delivered a significant 34% benefit in time to recovery, defined as achieving a score of 1 or less on the WHO Ordinal Scale by Day 14, with 37.4% of opaganib-treated patients (n=86/230) reaching this event versus 27.9% of patients (n=65/233) treated with placebo + SoC (p-value=0.013, Hazard Ratio 1.49).

"These prespecified analyses, along with the recent data showing opaganib's improved median time to viral RNA clearance, provide strong support for the promising results observed in the Phase 2/3 study post-hoc analysis. Oral opaganib has now shown an ability to reduce deaths, speed up recovery and clear viral RNA, all with a safety and tolerability profile similar to placebo. Strikingly, opaganib has delivered these benefits over and above the very best level of current standard-of-care, with patients receiving both remdesivir and corticosteroids," said Dr. Mark Levitt, RedHill’s Chief Scientific Officer. "The hospitalized moderate to severe COVID-19 patient group is estimated to represent more than 50% of all hospitalized COVID-19 cases and growing. The prevalence of Omicron, new emerging variants, loss of efficacy of existing drugs against such variants and the difficulty in stopping COVID-19 early enough in its course, despite the availability of new drugs, all point very clearly to the urgent need for new, preferably orally-administered, therapeutic options, unaffected by spike protein mutations, for this underserved and substantial patient population."

Regulatory progress continues to be made, with opaganib data submissions initiated in the fourth quarter of 2021 in the U.S., Europe, UK and additional countries. Discussions remain ongoing and initial guidance on a confirmatory study and potential path to approval has been received from the EU's EMA, the U.S. FDA, UK's MHRA and others. Based on regulatory feedback from other territories and external advice received, the Company is also planning
potential emergency and marketing authorization applications in certain such countries in the first half of 2022.

Oral opaganib was studied in a global Phase 2/3 study in hospitalized patients with severe COVID-19 pneumonia (NCT04467840). In a prespecified analysis of all Phase 2/3 study patients with a positive PCR at screening\(^2\) opaganib improved the median time to viral RNA clearance by at least 4 days, achieving viral RNA clearance in a median of 10 days, while the median for clearance was not reached by the end of 14-days treatment in the placebo arm (Hazard Ratio 1.34; nominal p-value=0.043, N=437/463). Additionally, results from a post-hoc analysis of data from 251 study participants requiring a Fraction of inspired Oxygen (FiO2) up to and including 60% at baseline (54% of the study participants) demonstrated that treatment with oral opaganib resulted in a 62% reduction in mortality as well as improved outcomes in time to room air, median time to hospital discharge, and likelihood of intubation and mechanical ventilation in this large group of hospitalized, moderately severe COVID-19 patients.

**About Opaganib (ABC294640)**

Opaganib, a new chemical entity, is a proprietary, first-in-class, orally-administered, sphingosine kinase-2 (SK2) selective inhibitor, with proposed dual anti-inflammatory and antiviral activity. Opaganib is host-targeted and is expected to be effective against emerging viral variants, having already demonstrated inhibition against variants of concern, including Delta. Opaganib has also shown anticancer activity and positive preclinical results in renal fibrosis, and has the potential to target multiple oncology, viral, inflammatory, and gastrointestinal indications.


Opaganib has also 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. Patient accrual, treatment and analysis in this study are ongoing.

Opaganib demonstrated potent antiviral activity against SARS-CoV-2, the virus that causes COVID-19, inhibiting viral replication of the original SARS-CoV-2 and variants tested to date in an in vitro model of human lung bronchial tissue. Additionally, preclinical in vivo studies have demonstrated opaganib's potential to decrease renal fibrosis, have shown decreased fatality rates from influenza virus infection, and amelioration of bacteria-induced pneumonia lung injury with reduced levels of IL-6 and TNF-alpha in bronchoalveolar lavage fluids\(^3\).

The ongoing clinical studies with opaganib are registered on [www.ClinicalTrials.gov](http://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 and infectious diseases. RedHill promotes the gastrointestinal drugs, Movantik® for opioid-induced constipation in adults[4], Talicia® for the treatment of Helicobacter pylori (H. pylori) infection in adults[5], and Aemcolo® for the treatment of travelers' diarrhea in adults[6]. RedHill's key clinical late-stage development programs include: (i) RHB-204, with an ongoing Phase 3 study for pulmonary nontuberculous mycobacteria (NTM) disease; (ii) opaganib (ABC294640), a first-in-class oral 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-107 (upamostat), an oral serine protease inhibitor in a U.S. Phase 2/3 study as treatment for symptomatic COVID-19, and targeting multiple other cancer and inflammatory gastrointestinal diseases; (iv) RHB-104, with positive results from a first Phase 3 study for Crohn's disease; (v) RHB-102, with positive results from a Phase 3 study for acute gastroenteritis and gastritis and positive results from a Phase 2 study for IBS-D; and (vi) RHB-106, an encapsulated bowel preparation. More information about the Company is available at www.redhillbio.com/twitter.com/RedHillBio.

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 and include the plan for potential emergency and marketing authorization applications in certain ex-U.S. countries in the first half of 2022. 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 the Phase 2/3 COVID-19 study for opaganib and its results may not be sufficient for regulatory applications, including emergency use or marketing applications, and that additional COVID-19 studies for opaganib are likely to be required by regulatory authorities to support such potential applications and the use or marketing of opaganib for COVID-19 patients, that emergency and marketing authorization applications in certain ex-U.S. countries will be delayed, that opaganib will not be effective against emerging viral variants, 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 18, 2021. 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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Category: R&D

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

[2] Positive PCRs at screening obtained for 437 out of 463 patients - remaining patients could not be included in this
prespecified analysis due to lack of PCR results at screening


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