RedHill Biopharma Receives U.S. Patent Allowance Covering Opaganib and RHB-107 Combination

November 4, 2020

Notice of Allowance received for combination of RedHill's novel orally-administered investigational drugs, opaganib and RHB-107, for treatment of solid tumor cancers; patent expected to extend IP protection until 2036

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Combination of opaganib and RHB-107 demonstrated potent antitumor effect and tumor regression in recent cholangiocarcinoma pre-clinical study

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RedHill plans to add third cohort evaluating this combination to its ongoing Phase 2a study of opaganib in advanced cholangiocarcinoma, subject to FDA discussions

TEL AVIV, Israel and RALEIGH, N.C., Nov. 04, 2020 (GLOBE NEWSWIRE) -- RedHill Biopharma Ltd. (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced that it has received a Notice of Allowance from the United States Patent and Trademark Office (USPTO) for a new patent application related to the use of two of RedHill's proprietary investigational compounds, opaganib (Yeliva ®, ABC294640) and RHB-107 (upamostat)[1], for the treatment of solid tumor cancers. The patent is expected to extend IP protection for the combination until 2036.

Findings from a recent pre-clinical study evaluating the antitumor effect of opaganib and RHB-107 on cholangiocarcinoma (also known as bile duct cancer) patient-derived xenografts demonstrated that treatment with opaganib and RHB-107, individually and in combination, resulted in tumor regression. Moreover, the combination of both drugs was found to be more potent and well tolerated in the animal models. These findings were presented at the American Association for Cancer Research (AACR) annual meeting earlier this year[2].

"It is becoming increasingly evident that cancers are dependent on a number of altered molecular pathways and can develop diverse mechanisms of resistance to therapy with single agents," **said Danielle T. Abramson, Ph.D., VP, Intellectual Property & Research at RedHill.** "This application is part of a growing patent portfolio that expands patent protection for our oncology program through 2036. We are very pleased with the additional IP protection for the novel combination of opaganib and RHB-107, which follows promising findings on the potent synergistic antitumor activity of this combination."

RedHill is conducting a Phase 2a study evaluating the activity of opaganib in advanced, unresectable intrahepatic, perihilar and extrahepatic cholangiocarcinoma (NCT03377179). Enrollment has been completed for the first cohort of 39 patients, evaluating the activity of orally-administered opaganib as a stand-alone treatment. Preliminary data from this cohort indicated a signal of activity in a number of subjects with advanced cholangiocarcinoma, and in light of these data, input from key opinion leaders and preclinical research that had been conducted at Mayo Clinic, RedHill initiated enrollment for a second cohort, evaluating opaganib in combination with hydroxychloroquine, an anti-autophagy agent. Given the encouraging pre-clinical data, RedHill plans to add an additional cohort to the ongoing Phase 2a study in cholangiocarcinoma, evaluating opaganib in combination with RHB-107, subject to discussions with the U.S. FDA.

About Opaganib (ABC294640, Yeliva®)
Opaganib, a new chemical entity, is a proprietary, 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, potentially minimizing the likelihood of viral resistance. Opaganib has also shown anticancer activity and has the potential to target 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 severe 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[3] 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, patients with COVID-19 (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 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 RHB-107 a strong candidate for evaluation as a treatment for COVID-19. A U.S. Phase 2/3 study with RHB-107 in an outpatient setting is planned to be initiated later this year. 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 and infectious diseases. RedHill promotes the gastrointestinal drugs, **Movantik®** for opioid-induced constipation in adults with non-cancer pain[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 investigational development programs include: (i) **RHB-204**, with a planned 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 will not succeed in adding a third cohort to its ongoing Phase 2a clinical study in patients suffering from advanced cholangiocarcinoma, in which the Company expects to evaluate the efficacy of opaganib in combination with RHB-107; as well as other risks and uncertainties associated with (i) the initiation, timing, progress and results of the Company's research, manufacturing, pre-clinical 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 pre-clinical studies or clinical trials or the development of a commercial companion diagnostic for the detection of 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 commercial products; (v) the Company's ability to successfully commercialize and promote Talicia ®, and Aemcolo® and Movantik®; (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 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, pre-clinical 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 experiences using investigative drugs under the Company's Expanded Access Program; (xiv) competition from other companies and technologies within the Company's industry; and (xv) the hiring and maintaining employment of executive managers. 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) and RHB-107 (upamostat, WX-671) are investigational new drugs, not available for commercial distribution.

[2] Faizal ZA et al. Abstract 3078: Effects of upamostat and opaganib on cholangiocarcinoma patient derived xenografts. Cancer Res August 15 2020 (80) (16 Supplement) 3078; DOI: 10.1158/1538-7445.AM2020-3078

[3] 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.

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

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

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

Source: RedHill Biopharma Ltd.