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RO7049389, a core protein allosteric modulator, demonstrates robust anti-HBV activity in chronic hepatitis B patients and is safe and well tolerated

Edward Gane[1], Angela Liu[2], Man-Fung Yuen[3], Christian Schwabe[1], Qingyan Bo[2], Sudip Das[4], Lu Gao[2], Xue Zhou[2], Yifan Wang[2], Eoin Coakley[5], Yuyan Jin[2]

[1]Auckland Clinical Studies, Auckland, New Zealand; *[2]Roche Innovation Center Shanghai, Shanghai, China*; *[3]Unversity of Hong Kong, Medicine, Hong Kong, China*; *[4]Roche Products Limited, Shire Park, United Kingdom*; *[5]Roche Innovation Centre New York, New York, United States*

Email: sudip.das@roche.com

Background and Aims: RO7049389 is a small molecule, Class I HBV core protein allosteric modulator (CpAM). It induces formation of abnormal hepatitis B virus (HBV) core aggregates resulting in defective capsid assembly thereby suppressing HBV replication. In the AAV-HBV mouse model, robust HBV DNA declines (≈3.0 $\log_{10}$ copies/ml) were observed over 56 days of dosing.

Method: The ongoing Phase I study investigates the safety, tolerability, pharmacokinetics (PK), and anti-HBV activity of RO7049389. Study Part 1 evaluates the safety and PK of single ascending doses (SAD) of RO7049389/placebo (5 dosing cohorts from 150-2000mg) and multiple ascending doses (MAD) (5 dosing cohorts from 200-800mg BID x 14 days) in healthy volunteers (HVs). Study Part 2 also interrogates the anti-HBV effects of RO7049389 in untreated chronic HBV (CHB) patients (4 planned cohorts BID x 28 days).

Results: 75 HVs have been dosed in this study. Across the dosing range, RO7049389 was rapidly absorbed and eliminated from plasma. A trend of greater than dose-proportional increases in exposure from 150 to 1000 mg, and approximately dose-proportional increases from 1000 to 2000mg were observed in SAD cohorts. Accumulation of RO7049389 in MAD cohorts was minimal or none.

A blinded safety evaluation demonstrated that RO7049389/placebo in HVs was well tolerated in the SAD and MAD cohorts. In Part 1, a total of 55 adverse events (AEs) were reported in 36/75 HVs. In Part 2, a total of 14 AEs were reported in 3/7 patients. All AEs were reported as being mild in intensity with only five being considered as related to RO7049389, these were: nausea, abdominal discomfort, rash and 2 cases of headache. No serious AEs or AEs leading to drug discontinuation were reported and no clinically significant changes in ECG parameters, vital signs, or laboratory safety test results were observed.

Six CHB patients completed 28 days dosing period of RO7049389 at a dose of 200mg BID. Robust and continued HBV DNA declines from pre-dosing levels were observed, with median (maximal) decline being 2.7 (3.4) $\log_{10}$ IU/ml and below the limits of detection in 3/6 patients. No on-treatment virologic rebound was observed.

Conclusion: The RO7049389 appears to be safe, generally well tolerated and demonstrates robust anti-HBV activity over 28 days of dosing in patients with CHB.