A RANDOMIZED, PLACEBO-CONTROLLED, FIRST IN HUMAN PHASE I SINGLE ASCENDING DOSE (SAD) AND MULTIPLE ASCENDING DOSE (MAD) STUDY IN HEALTHY MALE VOLUNTEERS OF THE IMMUNOSTIMULANT 7HP349

Lionel Lewis*, 1William Shary, 2Siddhartha De, 3Peter Vanderslice, 4Yared Hailemichael, 5William Overwijk, 6Frank Lee, 7Upendra Marathi. 17 Hills Pharma & The Geisel School of Medicine at Dartmouth, Lebanon, NH, United States; 27 Hills Pharma LLC Texas Heart Institute, Houston, TX, United States; 3Texas Heart Institute, Houston, TX, United States; 4MD Anderson Cancer Center, Houston, TX, United States; 5Nextar, Houston, TX, United States; 6Frontage Clinical Services, Sacaucus, NJ, United States

Background 7HP349 is a first in class allosteric agonist of integrins α4β1 and αLβ2 which promotes both T-cell extravascular trafficking and antigen priming. In B16 and CT26 syngeneic models 7HP349 monotherapy has anti-tumor efficacy and enhanced anti-CTLA-4 and anti-PD-1 tumoricidal effects. 7HP349 has a very safe acute and chronic preclinical toxicity profile. We undertook a placebo-controlled Phase I SAD and MAD study with the objectives of determining (i) the safety and tolerability of oral 7HP349 (ii) the optimal pharmacokinetic dose (OPD).

Methods Four cohorts (1-4) of healthy male volunteers (n=8; 6 active;2 placebo) received single oral 7HP349/placebo doses of 50, 100, 200 or 300 mg after a standard breakfast. Two further cohorts [5&6 (n=8)] received 100 or 300 mg 7HP349/placebo daily for five days. Subjects were monitored for clinical and laboratory adverse events (AEs) during and up to 7 days post single dose and during and up to 10 days post multiple dosing and graded using 5.0 CTCAE criteria. Pharmacokinetic samples were collected pre-treatment and up to 96h post single and the last multiple dose. 7HP349 plasma concentrations were measured by LC-MS/MS, PK data was analyzed non-compartmentally.

Results Forty-eight healthy male volunteers median age 32 (range 21-44 y) were enrolled in the study, 36 received 7HP349 and 12 placebo. No 7HP349 related SAEs or clinical AEs were noted. Treatment emergent, reversible, non-clinically significant safety lab abnormalities were: SAD cohort 100 mg Gr 1 isolated ALT n=1/6; SAD Cohort 200 mg Gr 1 isolated ALT n=1/6 and Gr 1 isolated amylase/lipase n=1/6; SAD Cohort 300 mg Gr 1 ALT =1/6; MAD cohort 100 mg Gr 1 isolated ALT n=1/8; MAD cohort 300 mg Gr 1 AST/ALT & Gr 1 isolated amylase/lipase n=1/8 and Gr 1 AST/ALT n=1/6. Similar out of range lab values were seen in a minority of placebo-treated subjects (1-2/12). 7HP349 mean PK parameters [(n=6; (±SD)] are detailed in table 1.

Conclusions Oral 7HP349 at single and multiple doses (daily x 5) up to 300 mg was safe and very well tolerated. 7HP349 mean terminal T1/2 ranged from 20.6-34.6 h, with no accumulation and non-linear PK at the highest doses. Planned studies combining 7HP349 dosed at 100 mg and 300 mg/day x 5 (at a monotherapy safety margin of >10x) have the potential to augment immune checkpoint blockade without additional toxicity.

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Trial Registration NCT04508179

Ethics Approval Ethics approval for this study was obtained from the Frontage Clinical Services utilized IRB. All study participants gave written informed consent prior to taking part in any study procedures.