Safety and Pharmacokinetics of PPI-461, a Potent New HCV NS5A Inhibitor with Pan-Genotype Activity

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Abstract

Pharmacokinetics (PK) of PPI-461 after each single dose

Demographics & Baseline Clinical Features

Safety Profile: All Adverse Events

Multiple-Dose PK Results (200 mg × 5)

Phase 1a Trial (Volunteers) Summary

Introduction

HCV-related severe morbidity and mortality projected to increase by 3 to 4-fold

Potential treatment advances offered by current HCV PK focused on HCV genotype-1 infection, comprising less than half of all HCV infections.

PPI-461 is a highly potent & selective NS5A inhibitor with pan-genotypic HCV activity in replication assays (EC50 of 0.2 nM, 6.01 ± 3.8 nM, 4.1 ± 3.8 nM, 24 ± 12 nM, 7.6 ± 9.2 nM, respectively).

Combination studies in HCV replicon cell assays showed additive to synergistic activity with other classes of HCV inhibitors.

No cross-resistance between PPI-461 and other classes of HCV inhibitors.

PPI-461 was well-tolerated in a battery of preclinical toxicology studies.

Objectives

Safety and tolerability of four single doses (20, 50, 100, and 200 mg) of PPI-461 taken after an overnight fast.

Pharmacokinetics (PK) of PPI-461 after each single dose

Preliminary food effect sub-study: Compare PK profile for fed vs. fasted doses

Safety, tolerability, and PK for highest well-tolerated dose administered once daily for 5 days.

Intake of a high-fat meal (250 mg of PPI-461 15 min after a high-fat meal) is not expected to influence the PK profile.

Assessments

Safety-related observations included viral loads, physiologic, clinical adverse events (AEs), serum ECGs, and safety-related laboratory assessments: complete blood counts with leukocyte differentials, full clinical chemistry panels, coagulation and other standard laboratory tests.

Intravenous plasma sampling for PK after each single-dose exposure (cohort A-D).

Intensive plasma sampling for PK after each multi-dose test (96-dose) study, for identification of possible PK trough.

Study conducted with applicable approvals from the U.K. MRA and the local Ethics Committee.

Study Design and Population

Single-Dose PK Results

PK Parameters for Cohorts A-E

Phase 1a Trial (Volunteers) Summary

Subjects were healthy volunteers ages 18-65 with a BMI of 18-30 kg/m² and able to provide informed consent.

Both males and females were eligible (female of non-child-bearing capacity only).

Five sequential study cohorts (B subjects/cohort, total study subjects = 46).

Cohort A received single and doses of PPI-461 (20, 50, 100 mg or placebo), and cohort E received placebo and 5 days of consecutive dosing at the highest tested dose (200 mg) after an overnight fast.

Eight subjects/cohort were randomized to active PPI-461 or placebo (6:2 ratio).


Study advancement to each higher dosing level contingent on satisfactory safety and pharmacokinetics (PK) results.

There were no serious adverse events (SAEs) and no treatment-related SAEs.

No evidence of accumulation after third dose.

Consistent oral bioavailability and substantial 24 h systemic exposure observed.

Plasma levels at 24 h (C24 h) post-dosing substantially exceeded replicon EC50 levels (all genotypes) in all subjects, and exceeded the EC50s of all HCV genotypes by orders of magnitude.

Results support ongoing evaluation of PPI-461 in HCV patients.

PPI-461 was well tolerated, clinical and laboratory safety monitoring did not indicate any pattern of clinical adverse events or abnormalities in the tested dosing range of 20-200 mg, with a treatment duration of up to five days.

Substantial dose-related systemic exposures were consistently obtained in subjects dosed with PPI-461.

Cmax plasma levels achieved quickly in all subjects (1-4 h), and a consistently long half-life of >100 h (ca. 8-10 h) resulted in EC50c levels exceeding replicon EC50 levels (all genotypes) in all subjects dosed with 250 mg.

 steadystate concentrations reached within 2 days in 5 day repeat-dose cohort (200 mg QD).

Dosing with a high-fat meal resulted in a 43% reduction in AUC0-24 h levels in subjects treated with 50 mg PPI-461. Cmax levels were minimally changed.

Results support ongoing evaluation of PPI-461 in HCV patients with QD dosing.

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