**INTRODUCTION**

- RO7049389 is an orally administered small molecule class I hepatitis B virus (HBV) core protein allosteric modulator (CPAM) that disrupts HBV nucleocapsid assembly and induces the depletion of functional core proteins, thereby effectively inhibiting HBV replication.
- RO7049389 demonstrated its efficacy in an ADV-HBV (adenovirus-associated virus carrying HBV genome) infected mice by not only reducing serum HBV DNA as expected, but also reducing HBcAg and HBsAg levels.

**AIM**

Objectives of this Phase I study are to investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of RO7049389 in healthy volunteers (HV) and patients chronically infected with HBV.

**METHOD**

The study design is shown in Figure 1.

**RESULTS**

- **Demography and baseline characteristics**
  - Table 1: Demography and baseline characteristics in POM Cohorts

**Antiviral activity and cytotoxicity [propG2.3.35 cells]**

- **Safety and tolerability**
  - The adverse events (AEs) during the study were shown in Table 2. All dose levels were considered safe and well tolerated, in active arms:
    - Most common AEs in active arms were headache (16.1%) and ALT elevation (16.1%). The majority of these AEs were of mild intensity and resolved without study drug dose change or interruption.
    - No serious AEs or AEs leading to drug discontinuation were reported.
    - No clinically significant changes were noted in vital signs, ECG parameters, or laboratory results (except for six cases of ALT elevation).
    - Six out of 31 patients experienced Grade 2–4 ALT elevation in active arms:
      - Not accompanied by changes in total bilirubin, international normalized ratio (INR), prothrombin time, or alkaline phosphatase (AP).
      - All patients completed the 28-day treatment without dose change or interruption.
      - All ALT elevations resolved or were resolving during follow up without any treatment.
      - There was no evidence for an association between ALT elevation and dose or drug exposure.

**Antiviral activity of RO7049389 in CHB patients**

- After 4 weeks of treatment with RO7049389, a robust HBV DNA and HBV RNA decline was observed across all cohorts (Figure 2 and Figure 3), with a median reduction of 2.65-5.20 Log10 IU/mL and 2.09-2.35 Log10 copies/mL, respectively (Table 5). 5/16 (31.3%) patients who were HBeAg negative at baseline achieved HBV DNA levels lower than LLOQ (<20 IU/mL).
- Viral breakthrough was not observed during treatment. HBV DNA and HBV RNA returned to baseline levels post treatment.
- No HBVAg change was observed during 4 weeks treatment of RO7049389.

**Pharmacokinetics and dose-response analysis in patients**

- RO7049389 was rapidly absorbed into and eliminated from plasma.
- There was no accumulation after 28 days dosing.
- A trend of greater than dose proportional increases in exposure was noted.
- The exposure was similar between healthy volunteers and HBV patients.
- It is difficult to draw conclusion on PK-PO relationship due to small sample size in each dose level and heterogeneity in patient baseline characteristics.

An advanced mechanistic population PK model and disease model were developed to infer the dose-response relationship (Figure 4 and 5). The modeling results showed that there was a slight trend of HBV DNA decline with the dose increasing (200 mg - 1000 mg QD).

**CONCLUSIONS**

- RO7049389 is an oral, small molecule, class I HBV CPAM that is safe and well tolerated in patients with chronic hepatitis B.
- RO7049389 at different dose regimens (200mg BID, 400mg BID, or 200 mg QD, 600mg QD, 1000mg QD) for 28 days demonstrated robust HBV DNA and HBV RNA declines in both HBeAg positive and negative patients. 12/16 patients with HBeAg negative achieved HBV DNA levels <LLOQ at the end of treatment.
- RO7049389 demonstrated favorable PK profile in patients with HBV, with a slight trend of better HBV DNA response as dose increased from 200 mg to 1000 mg.

**REFERENCES**


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