RO7049389, a core protein allosteric modulator, demonstrates robust decline in HBV DNA and HBV RNA in chronic HBV infected patients

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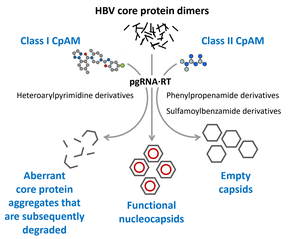
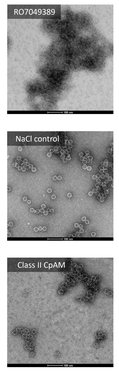
INTRODUCTION

- RO7049389 is an orally administered small molecule class I hepatitis B virus (HBV) core protein allosteric modulator (CpAM) that disrupts HBV nucleocapsids assembly and induces the depletion of functional core proteins, thereby effectively inhibiting HBV replication.
- RO7049389 demonstrated its efficacy in AAV-HBV (adeno-associated virus carrying HBV genome) infected mice by not only reducing serum HBV DNA as expected, but also reducing HBsAg and HBeAg levels [1].



Capsid assembly in vitro (electron microscopy)



Antiviral activity and cytotoxicity (HepG2.2.15 cells)

RO7049389	
EC_{50} (HBV DNA, n=3)	6.1 ± 0.9 nM
CC_{50} (n=3)	> 100 µM
Selectivity Index	> 10000

- Active against the most prevalent HBV genotypes (A-D)
- Active against nucleos(t)ide analogue resistance variants

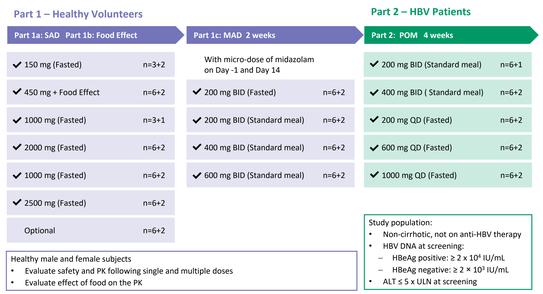
AIM

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

METHOD

The study design is shown in Figure 1.

Figure 1: Study design



QD: once per day; BID: twice daily; POM: proof of mechanism; ALT: alanine aminotransferase; ULN: upper limit of normal

RESULTS

Demography and baseline characteristics

Table 1: Demography and baseline characteristics in POM Cohorts

	200 mg BID n=6	400 mg BID n=6	200 mg QD n=6	600 mg QD n=6	1000 mg QD n=7[a]	Placebo n=6[a]
Age, median (range) y	41 (29-54)	35 (21-54)	34(27-60)	43(23-57)	47(41-58)	46(35-50)
Male, n (%)	5 (83.3%)	3 (50.0%)	5(83.3%)	4 (66.7%)	3(42.9%)	3(50.0%)
BMI, median (range)	24.7 (21.5-28.5)	21.9(18.5-26.6)	23.0(19.5-29.2)	24.0(19.9-29.8)	22.3(17.9-24.0)	27.2(20.2-30.0)
Race, n (%)						
Asian	5 (83.3%)	5 (83.3%)	5(83.3%)	5 (83.3%)	7(100%)	5(83.3%)
White	1(16.7%)	0	1(16.7%)	1(16.7%)	0	0
Native Hawaiian or other Pacific slander	0	1(16.7%)	0	0	0	1(16.7%)
HBeAg positive, n (%)	3(50.0%)	3(50.0%)	5(83.3%)	2(33.3%)	1(14.3%)	2(33.3%)
HBV DNA log_{10}IU/mL, mean (SD)	4.85(2.24)	6.83(1.89)	6.75(1.82)	5.34(2.38)	5.35(1.55)	6.35(1.58)
HBsAg log_{10}IU/mL, mean(SD)	3.61(0.72)	4.31(0.55)	3.69(1.51)	3.47(1.17)	3.16(0.98)	3.38(0.75)
HBV RNA <LLOQ[b], n (%)	4 (66.7%)	2 (33.3%)	1 (16.7%)	4 (66.7%)	4 (57.1%)	2 (33.3%)
ALT at baseline						
≤1.25 x ULN	6（100%）	4（66.7%）	5（83.3%）	6（100%）	7（100%）	4（66.7%）
1.25-10 x ULN	0	2(33.3%)	1(16.7%)	0	0	1(16.7%)
>10 x ULN	0	0	0	0	0	1(16.7%)
HBV Genotype						
A	1(16.7%)	0	0	0	0	0
B	0	2(33.3%)	2(33.3%)	4(66.7%)	6(85.7%)	3(50.0%)
C	4(66.7%)	3(50.0%)	4(66.7%)	1(16.7%)	1(14.3%)	3(50.0%)
D	0	1(16.7%)	0	0	0	0
Indeterminate	1(16.7%)	0	0	1(16.7%)	0	0

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
a. In 1000 mg QD cohort, one patient discontinued on Day 2 due to non-safety reason and was replaced.
One patient in placebo arm discontinued on Day 2 for pre-dose ALT/AST elevation>10 ULN and was replaced.
b. LLOQ (lower limit of quantification) - 4.04Log10copies/mL.

Safety and tolerability

The adverse events (AEs) during the study are shown in Table 2. All dose levels were considered safe and well tolerated, in active arms:

- The 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 (PT) or alkaline phosphatase (ALP).
  - ✓ 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.

Table 2: Adverse events and laboratory abnormalities in patients

	200 mg BID n=6	400 mg BID n=6	200 mg QD n=6	600 mg QD n=6	1000 mg QD n=7	Active Total N=31	Placebo n=6
No. of subjects with ≥ 1 AE, n (%)	4 (66.7%)	4 (66.7%)	2 (33.3%)	5 (83.3%)	4 (57.1%)	19 (61.3%)	3 (50.0%)
Total No. of AEs, n	15	8	5	14	27	69	5
Mild AEs, n	15	6	3	12	26	62	2
Moderate AEs, n	0	2	2	2	1	7	2
SAEs, n	0	0	0	0	0	0	1[a]
No. of subjects with ≥ 1 related AE, n(%)	0	0	1 (16.7%)	0	2 (28.6%)	3 (9.7%)	0
Total No. of subjects with Grade 2-4 ALT elevation, n (%)[c]	0	2 (33.3%)	2 (33.3%)	1 (16.7%)	1 (14.3%)	6 (19.4%)	1 (16.7%)[a]
Grade 2	0	0	1 (16.7%)[b]	0	1 (14.3%)	2 (6.5%)	0
Grade 3	0	2 (33.3%)[b]	0	1 (16.7%)	0	3 (9.7%)	0
Grade 4	0	0	1 (16.7%)	0	0	1 (5.3%)	1 (16.7%)[a]

a. One patient in placebo arm had pre-dose ALT/AST>10 x ULN which was reported as SAE and the patient was replaced
b. One case of ALT elevation in each group was not reported as AEs as the Investigator did not consider these to be clinically significant
c. Grade 2 ALT elevation : ALT 2.5 to <5.0 x ULN ; Grade 3 ALT elevation: ALT 5.0 to <10.0 x ULN; Grade 4 ALT elevation: ALT> 10.0 x ULN.
Upper limit of normal for ALT: for male , ALT ≤41U/L, for female, ALTs33U/L.

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 five cohorts (Figure 2 and Figure 3), with a median reduction of 2.66-3.0 Log_{10} IU/mL and 2.09-2.55 Log_{10} copies/mL, respectively (Table 3). 13/16 (81.3%) 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 HBsAg change was observed during 4 weeks treatment of RO7049389.

Figure 2: Median HBV DNA decline from baseline over time

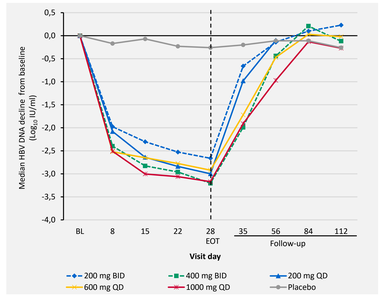
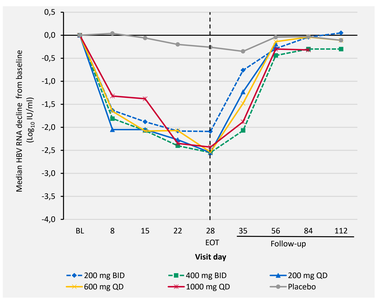


Figure 3: Median HBV RNA decline from baseline over time



EOT: end of treatment; BL: baseline

Table 3: Median HBV DNA and HBV RNA change from baseline at the end of treatment (Day 28)

	HBV DNA Log_{10}IU/mL			HBV RNA in patients with Baseline HBV RNA ≥ LLOQ [a] Log_{10}copies/mL		
Cohort	n (Baseline HBeAg+/-)	Baseline Median(range)	Change from Baseline on Day 28	n (Baseline HBeAg+/-)	Baseline Median (range)	Change from Baseline on Day 28
200 mg BID	n=6 (3/3)	4.5 (1.9-8.3)	-2.66 (-3.4, -0.6)	n=2 (2/0)	6.37 (5.7-7.1)	-2.09 (-2.5, -1.6)
400 mg BID	n=6 (3/3)	7.8 (4.0-8.5)	-3.20 (-5.3, -2.2)	n=4 (3/1)	7.01 (6.5-7.4)	-2.55 (-4.0, -2.0)
200 mg QD	n=6 (5/1)	7.14 (3.9-8.5)	-3.0 (-3.6, -2.3)	n=5(5/0)	6.9 (4.5-7.5)	-2.55 (-3.1, -0.4)
600 mg QD	n=6 (2/4)	4.43 (3.3-8.4)	-2.92 (-3.7, -2.0)	n=2(2/0)	7.02 (6.8-7.2)	-2.54 (-2.9, -2.2)
1000 mg QD	n=6 (1/5)[b]	5.1 (4.1-8.7)	-3.17 (-3.8, -2.8)	n=2 (1/1)	4.64 (4.3-7.4)	-2.43 (-3.0, -1.9)
Placebo	n=6 (2/3)[b]	5.94 (4.8-8.2)	-0.26 (-1.2, 0.2)	n=3 (2/1)	6.37 (4.7-7.3)	-0.26 (-0.5, 0.2)

a. LLOQ=4.04 Log_{10} copies/mL.
b. Only include patients who completed 28 days treatment. One patient in each group was excluded from efficacy analysis.
These two patients were discontinued early and were replaced.

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-PD 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).

Figure 4: Exposure-response (HBV DNA decline) analysis using modeling approach

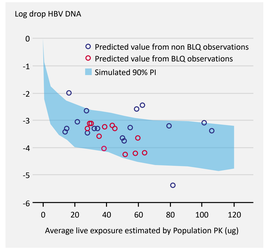
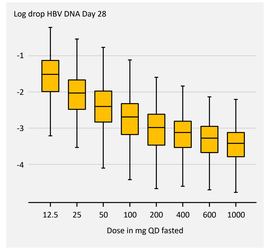


Figure 5: Dose-response (HBV DNA decline) analysis using modeling approach



BLQ: below lower limit of quantification

CONCLUSIONS

- RO7049389, an oral, small molecule, class I HBV CpAM was safe and well tolerated in patients with chronic HBV.
- 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.13/16 patients with HBeAg negative achieved HBV DNA levels <LLOQ at the end of treatment.
- RO7049389 demonstrated favorable PK profiles in patients with HBV, with a slight trend of better HBV DNA response as dose increased from 200 mg to 1000 mg.
- These preliminary data support the further development of RO7049389 as a component of novel combination HBV cure regimen.

REFERENCES

1. X. Zhou, Y. Zhou, X. Tian, et al. In vitro and in vivo antiviral characterization of RO7049389, a novel small molecule capsid assembly modulator, for the treatment of chronic hepatitis B. EASL 2018; SAT-360

ACKNOWLEDGEMENTS

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