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ARTICLE

Evaluation of the safety, tolerability, and pharmacokinetics of RO7049389 in healthy Chinese volunteers

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Abstract

The objectives of this phase I study are to assess the safety, tolerability, and pharmacokinetics (PKs) of RO7049389 in healthy Chinese volunteers (HVs) and evaluate potential ethnic differences in the safety and PKs using data from this study and the first-in-human study (in which most of the HVs were non-Asian). HVs randomly received a single dose of 200–600 mg of RO7049389 or a placebo in a single ascending dose ($n = 28$) or multiple doses of 200–400 mg of RO7049389 or a placebo in multiple ascending doses ($n = 24$). Safety and tolerability were monitored throughout the study. Serial blood samples were collected for PK analysis. RO7049389 was safe and well-tolerated in the HVs. The time to maximum concentration ranged from 1.5 to 3.0 h, and terminal half-life ranged from 3.66 to 14.6 h. A single dose of 200–600 mg and multiple doses of 200–400 mg exhibited nonlinear PKs. In general, the safety profiles were comparable between non-Asian and Asian HVs, but the plasma exposure of RO7049389 in Chinese HVs was higher than that in non-Asian HVs. The data generated from this study will provide guidance for future clinical studies on RO7049389 in Chinese/Asian patients with hepatitis B virus.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

RO7049389 is a small molecule that is being developed as an orally administered solid dosage formulation for the treatment of chronic hepatitis B infection. The healthy volunteers (HVs) part of the first-in-human study of RO7049389 was completed at the time the first volunteer of this study was enrolled.

WHAT QUESTION DID THIS STUDY ADDRESS?

The objectives of this phase I study are to assess the safety, tolerability, and pharmacokinetics of RO7049389 in Chinese HVs and evaluate potential ethnic differences between Chinese and non-Asians.

Clinical trial registration: This trial was registered at www.clinicaltrials.gov under registration number NCT03570658.

Xiaojie Wu and Sheng Feng: Co-first authors.

Sheng Feng and Mingfen Zhu: Former Roche employee.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

In general, the safety profiles were comparable between non-Asian and Chinese HVs, but the plasma exposure of RO7049389 in Chinese HVs was higher than that in non-Asian HVs. The higher exposure might be due to the liver uptake of RO7049389 by OATP1B.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The data generated from this study will provide guidance for future clinical studies on RO7049389 in Chinese/Asian patients with hepatitis B virus infection.

INTRODUCTION

Hepatitis B virus (HBV) infection is a major cause of chronic liver disease and may cause cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Approximately 257 million people worldwide are living with chronic hepatitis B (CHB) infection (defined as hepatitis B surface antigen [HBsAg] positive). In 2015, HBV infection resulted in an estimated 887,000 deaths, mostly from complications, including cirrhosis and HCC.[1,2] Currently, there are two classes of drugs available for the treatment of CHB: subcutaneously administered interferon-alpha preparations and orally administered nucleos(t)ide analogs (NUCs). Although both types of treatments can effectively induce the loss of hepatitis B e antigen (HBeAg), resulting in the suppression of HBV DNA (virologic response) and normalization of liver transaminase enzymes (biochemical response), neither treatment achieves a high rate of functional cure, defined as the sustained loss of HBsAg with or without seroconversion. In addition, interferon-based therapies have many adverse effects, whereas NUCs frequently require prolonged or possibly life-long therapy, especially in those who are HBeAg negative or have cirrhosis. RO7049389 is a small molecule that is being developed as an orally administered solid dosage formulation for the treatment of CHB.[3] The healthy volunteer (HV) part of the first-in-human (FIH) study of RO7049389 was completed at the time the first volunteer of this study was enrolled.[4] RO7049389 is a substrate of human liver organic anion transporting polypeptide (OATP) 1B1 and OATP1B3. The disposition of RO7049389 is mediated mainly by liver metabolism (CYP3A4) with a minor contribution of UGT1A3. The unbound fraction of RO7049389 was 3.9%−5.2% in human plasma. This study was designed to assess the safety, tolerability, and pharmacokinetics (PKs) of single ascending doses (SADs) and multiple ascending doses (MADs) of RO7049389 in HVs. The PKs of three metabolites, RO7121986 (M5), RO7255420 (M6), and RO7255422 (M11), for which exposures in humans were found to be disproportionately higher than those in animal species in the FIH study, were also investigated after RO7049389 administration in this study. In vitro data indicated that M5 was about three times more potent than the parent drug, whereas M6 and M11 were 156-fold and 1.6-fold less potent than the parent drug, respectively. The ongoing FIH study also showed, that after a high-fat meal, the exposure of RO7049389 (450 mg) increased by ~2-fold.[4] This study leveraged data generated in the FIH study, allowing a targeted evaluation of fewer doses. The data generated from this study will help to elucidate potential ethnic differences between Chinese and non-Chinese HVs (from the FIH study) concerning safety, tolerability, and PK characteristics that will provide guidance for future clinical studies in Chinese/Asian patients with HBV.

METHODS

Ethics approval

The study was approved by the local ethics committee and the China National Medical Products Administration and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants. The trial was registered at ClinicalTrials.gov under identifier NCT03570658. The study was performed at the Phase I Clinical Research Center, Huashan Hospital, Shanghai, China.

Study design

This was a randomized, sponsor-open, investigator-blinded, subject-blinded, placebo-controlled, SAD and MAD study designed to evaluate the safety, tolerability, and PKs of RO7049389 following oral administration of SADs or MADs in Chinese HVs (Figure 1).

Three planned cohorts (cohorts 1, 2, and 3) were included in this study. In cohort 1, Chinese HVs received a single dose of 200 mg RO7049389 under fasted conditions. In cohort 2, Chinese HVs received a single dose of 400 mg

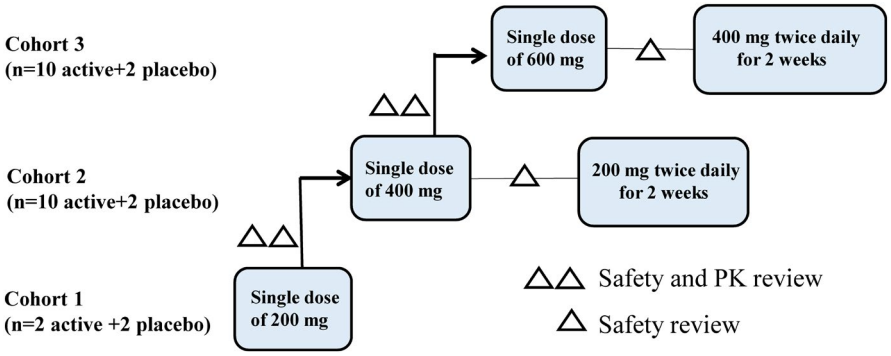

FIGURE 1 Overview of the study design. PK, pharmacokinetic.

RO7049389 under fasted conditions, followed by a washout period of ~ 1 week before entering the MAD phase of the study in which they received 200 mg RO7049389 twice daily (b.i.d.) following a standard meal for 14 days. In cohort 3, Chinese HVs received a single dose of 600 mg RO7049389 under fasted conditions, followed by a washout period and 400 mg RO7049389 twice daily following a standard meal for 14 days. In the MAD phase, on day 14, only one dose in the morning was given. Chinese HVs in the MAD cohorts were from the SAD cohorts after the washout period or from new enrollments if there were discontinuations between the SAD phase and MAD phase for reasons other than safety.

The SAD phase consisted of an up to 28-day screening period, a 4-day clinical period (days −1 to 3), an ambulatory assessment period (days 4, 5, and 8), and a safety follow-up call on day 29. The MAD phase consisted of an up to 28-day screening period, a 17-day clinical period (days −1 to 16), a safety follow-up visit on day 21, and a safety follow-up call on day 42. For subjects who participated in both the SAD phase and MAD phase of the study, no additional screening visit was needed before entering the MAD phase.

Progression to the next single-dose cohort was based primarily on the safety and available PK data at 24 h after administration of a single dose in the previous cohorts. The MAD phase started after a washout period of ~ 1 week, provided that the safety information through 24 h postdose in the SAD phase at the same cohort and available safety information in the FIH study had been reviewed.

Participants

Included in the study were healthy Chinese male and female subjects aged 18–60 years, with negative drug screening tests and an agreement to refrain from any other drugs (including vitamins, herbal supplements, over the counter, or prescription medications) for the study duration. All HVs were determined to be healthy based on their medical history, physical examination results, virology testing (hepatitis B and C, and human immunodeficiency virus) results, and routine laboratory testing (liver and kidney function and hematology) results before enrollment in the study. All male HVs agreed to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and refrain from donating sperm. HVs with prior allergic drug reactions or clinically significant concomitant diseases or conditions were excluded from the study.

Safety assessment

Vital signs, physical examination results, electrocardiograms (ECGs), safety laboratory variables, and adverse events (AEs) were monitored throughout the study. Laboratory measures included hematology, clinical chemistry, coagulation, and urinalysis.

Pharmacokinetic assessment

In the SAD cohorts, plasma PK samples were collected pre-administration and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, and 96 h after dose administration. In the MAD cohorts, plasma PK samples were collected at the following time points: (i) before administration and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after the first dose (day 1); (ii) before administration and on days 2, 3, 4, 5, and 7; and (iii) before administration and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 h after the last morning dose (day 14).

Plasma concentrations of RO7049389 and its metabolites (M5, M6, and M11) were measured using specific and validated liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-MS/MS) methods. In brief, 20 μl of plasma was combined with 20 μl of dimethyl formamide (DMF) and 20 μl of internal standard solution, placed into a 2-ml 96-well plate and vortexed for 1 min. Two hundred microliters (200 μl) of acetonitrile were added to each well, the 96-well plate was vortexed for 5 min and centrifuged for 5 min, and 50 μl of supernatant was transferred into a clean 2-ml 96-well plate. Four hundred microliters

(400 μl) of acetonitrile:water:formic acid (20:80:0.1) was added to each well, and the 96-well plate was vortexed for 5 min again. Finally, 5 μl of the mixed sample was injected into an LC-MS/MS. The LC-MS/MS analysis was carried out with a Sciex API-5500 mass spectrometer coupled with a Waters UPLC system. The autosampler tray was kept at 5°C. Chromatographic separation was achieved on a Waters ACQUITY UPLC BEH Shield RP 18, 1.7 μm, 2.1 × 50 mm ultraperformance liquid chromatography (UPLC) column with a mobile phase gradient. The mass spectrometer was operated in positive electrospray ionization (ESI) mode. The selected reaction monitoring (SRM) transitions were 599.2 → 254.2 m/z, 499.2 → 358.1 m/z, 515.2 → 154.1 m/z, and 515.2.2 → 170.1 m/z for RO7049389, M5, M6, and M11, respectively. The SRM transitions were 603.3 → 255.2 m/z, 503.2 → 362.1 m/z, 519.2 → 155.1 m/z, and 519.2 → 171.1 m/z for the internal standards and RO7049389-$^{13}C_4$, M5-$^{13}C_4$, M6-$^{13}C_4$, and M11-$^{13}C_4$. The lower limits of quantitation were 1.00 ng/ml for all four compounds, and the calibration curve ranged from 1.0 to 2000 ng/ml for all four compounds. The precision and accuracy of the assay, as determined from the analysis of quality control samples, were satisfactory throughout this portion of the study and ranged from 2.6% to 9.3% (precision) and from 96.7% to 106.0% (accuracy).

The PK parameters (e.g., area under the concentration-time curve [AUC], maximal plasma concentration [C_{max}], time to maximum observed plasma concentration [T_{max}], and terminal half-life [$t_{1/2}$]) were calculated from a noncompartmental analysis using Phoenix software (WinNonlin models version 6.4; Pharsight Corp, Cary, NC, USA). The C_{max} and T_{max} were read directly from the time-concentration data. The $t_{1/2}$ was estimated by ln(2)/λz, where λz was the terminal elimination rate constant. The AUC from time 0 to the last measurable plasma concentration time point (AUC_{last}) and AUC for a dosing interval (AUC_{τ}) were estimated by the linear up log down trapezoidal rule. The AUC extrapolated to infinity (AUC_{∞}) was determined as follows: $AUC_{last} + C_{last}/\lambda z$, where C_{last} was the last measurable plasma concentration. Data are presented as the median (range) for T_{max} and the mean (coefficient of variation [CV]) for all other parameters. The figures were drawn using R software version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Statistics

Statistical summaries were descriptive in nature. The number of study subjects was determined by practical considerations and not based on statistical power calculations. Four HVs were enrolled in SAD cohort 1 (2 received active treatment, and 2 received the placebo). Twelve HVs were enrolled in each of the other SAD and MAD cohorts. They were randomized to receive either active treatment (10 HVs per dose level) or the placebo (2 HVs per dose level).

RESULTS

Participant characteristics

The characteristics of the observed HVs, including ethnicity and demographic data, are listed in Table 1. A total of 31 healthy male HVs were enrolled in the study. In the SAD cohort, all 28 HVs received either a single dose of RO7049389 or placebo and completed the SAD phase of the study. After the washout period of 1 week, among the 24 HVs in SAD cohorts 2 and 3, 21 HVs entered the MAD phase, and three new HVs were enrolled directly into the MAD phase. Three HVs in the SAD cohort chose not to continue to the MAD phase. None of the HVs discontinued the study. The median (range) values for the demographic characteristics of HVs who were enrolled in the SAD cohorts were as follows: 30 (20–39) years old, 170.5 (161–183) cm tall, 66.5 (53.0–83.4) kg, and a body mass index (BMI) of 23.5 (19.5–25.7) kg/m^2. The characteristics of HVs who participated in the MAD cohorts were

TABLE 1 Baseline demographics

Demographics	SAD Chinese HVs *N* = 28	MAD Chinese HVs *N* = 24
Age, median (range) y	30 (20–39)	30.5 (20–39)
Male, *n* (%)	28 (100%)	24 (100%)
Height, median (range) cm	170.5 (161–183)	172 (161–183)
Body weight, median (range) kg	66.5 (53.0–83.4)	64.75 (52.6–84.2)
BMI, median (range) kg/m^2	23.5 (19.5–25.7)	22.8 (19.6–25.7)

Abbreviations: BMI, body mass index; HVs, healthy volunteers; MAD, multiple ascending dose; SAD, single ascending dose.

Twenty-one HVs from SAD cohorts 2 and 3 moved forward to MAD cohorts 1 and 2.

as follows: 30.5 (20–39) years old, 172 (161–183) cm tall, 64.75 (52.6–84.2) kg, and a BMI of 22.8 (19.6–25.7) kg/m^2. All the HVs were Chinese men.

Safety

RO7049389 was well-tolerated in all HVs. In the SAD cohorts, nine AEs were reported in five out of 28 HVs (17.9%), with eight AEs in four of 22 HVs (18.2%) in the treatment arm and one AE in one of six HVs (16.7%) in the placebo arm (Table S1). All AEs were of mild intensity, and none of these AEs were considered to be related to the study drug. In the MAD cohorts, 23 AEs were reported in 17 out of 24 HVs (70.8%), with 19 AEs in 15 of 20 HVs (75%) in the treatment arms and four AEs in two of four HVs (50%) in the placebo arm. All AEs were of mild intensity. There were 13 cases of lip dry, with two cases in the placebo arm and 11 cases in the treatment arm. This AE was considered to be related to study treatment by the investigator (Table S1). All of the AEs resolved without treatment. There were no serious adverse events (SAEs), deaths, withdrawals, or AEs that resulted in dose modification or interruption during the SAD or MAD phase of the study. There were no safety-related signals or dose-related trends in the ECG, vital sign, or laboratory safety data.

The PKs of RO7049389

The RO7049389 plasma PK profiles are shown in Figure 2, and the PK parameters are listed in Table 2. The absorption of RO7049389 occurred rapidly after single-dose administration to HVs in the SAD cohort. The peak plasma concentrations were reached within 1.0–4.0 h under fasted conditions. RO7049389 was eliminated from plasma with an arithmetic mean of apparent $t_{1/2}$ ranging from 3.66 to 14.6 h. A less than dose-proportional increase in exposure was observed.

After oral administration of 200 mg and 400 mg of RO7049389 b.i.d. with a standard meal, the time to reach T_{max} ranged from 1.5 to 3.0 h after the dose administration (Figure 3 and Table 2). The arithmetic mean elimination $t_{1/2}$ of RO7049389 at steady state on day 14 ranged from ~ 5.27–7.15 h. The AUC and C_{max} increased more than the dose proportionally. No accumulation of RO7049389 was observed after repeated dosing.

The PKs of RO7049389 metabolites

The three metabolites, RO7121986 (M5), RO7255420 (M6), and RO7255422 (M11), of RO7049389 plasma PK profiles are shown in Figures 2 and 3, and the PK parameters are listed in Tables S2 and S3. M5, M6, and M11 were present at levels similar to or exceeding parent exposure levels. Following oral administration of RO7049389 under fasted conditions or with a standard meal, M5 reached the C_{max} within 4.5–6.0 h, M6 reached the C_{max} within 4.0–8.0 h, and M11 reached the C_{max} within 4.0–8.0 h. Less than dose-proportional increases in the C_{max} and AUC were observed in both the SAD cohorts and MAD cohorts. The apparent mean arithmetic $t_{1/2}$ was 7.69–14.5 h, 11–15.5 h, and 10–17.5 h for M5, M6, and M11, respectively, indicating that the plasma exposure of metabolites could reach steady state within 14 days of b.i.d. dosing. Limited accumulation in the AUC of metabolites was observed after 200 mg and 400 mg b.i.d. dosing.

The ethnic sensitivity assessment

The data of non-Asian HV used for comparison in this manuscript comes from the HV part of the FIH study.[4] The safety profiles between non-Asian and Asian HVs were comparable. However, due to the small sample size, no robust conclusion can be drawn about any difference in the safety profile between Asian and non-Asian HVs. In general, the exposure of RO7049389 in Chinese HVs in this study was higher than that in non-Asian HVs in the FIH study (Table 3). The inconsistent numeric difference across the cohorts was believed to be attributable to high PK-related intersubject variability in response to the molecule. Considering the larger ethnic difference in the PKs, the different body weights between non-Asian HVs and Chinese may not entirely explain the much higher exposure in HVs. To precisely assess ethnic differences in PKs, a mechanistic population PK model that simultaneously models RO7049389 and its metabolite M5 was developed and will be published in a follow-up manuscript.

DISCUSSION

This phase I study evaluated the safety, tolerability, and PKs of RO7049389, an inhibitor of HBV capsid assembly, administered to HVs. This study leveraged data that had been generated in the RO7049389 FIH study, allowing the targeted evaluation of fewer doses. The results will support the further development of RO7049389 for Chinese/Asian patients with HBV.

The first SAD cohort received 200 mg (~1/4 of the total projected clinically efficacious dose). This starting dose was demonstrated to be safe and well-tolerated in the RO7049389 FIH study. Starting dose selection

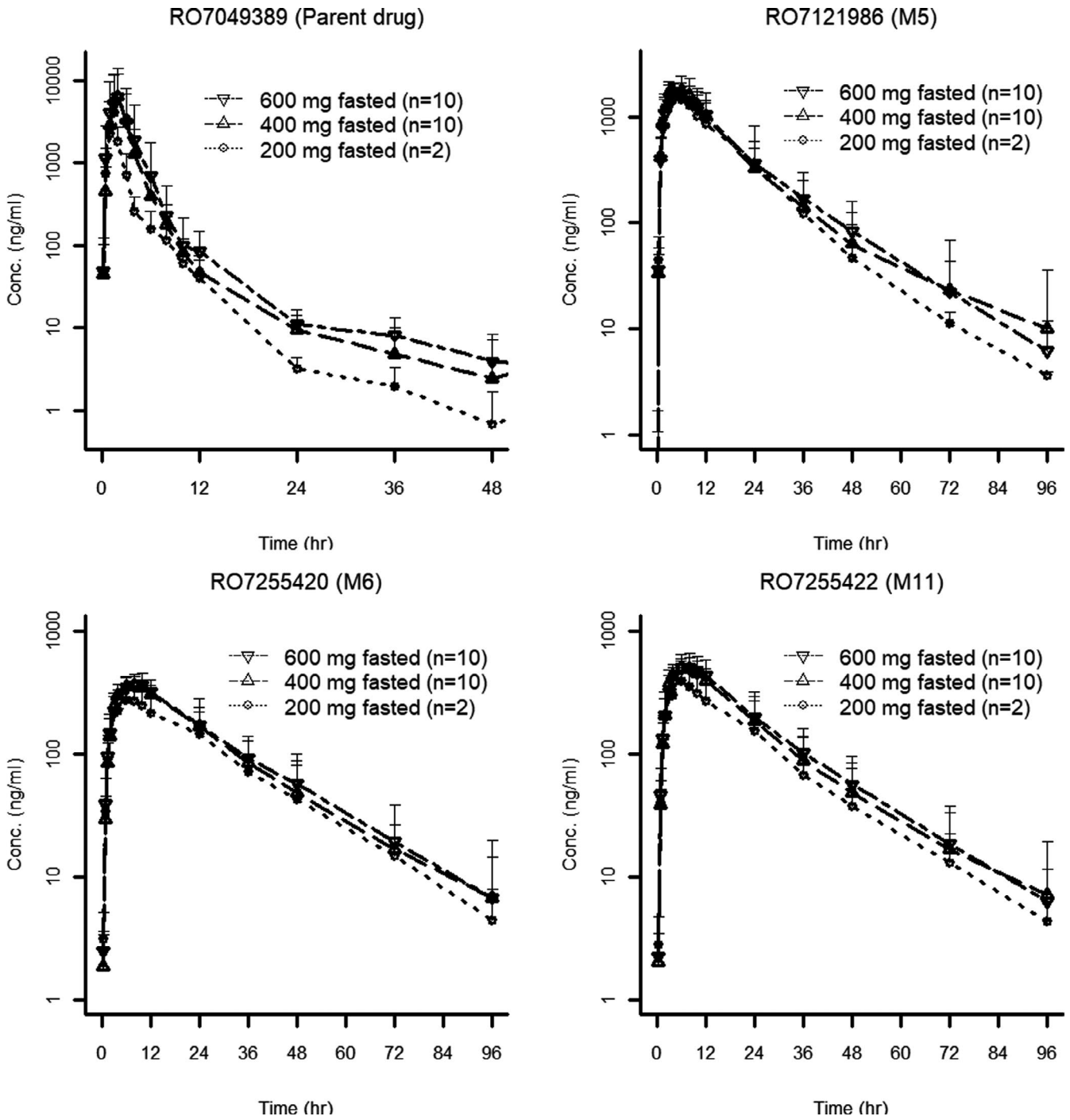

FIGURE 2 Mean (±SD) plasma concentration (Conc)-time curves of RO7049389 and its three metabolites after single doses of RO7049389 in healthy volunteers (semilog)

is pharmacology-driven and supported by nonclinical safety data. The proposed starting dose of 200 mg is predicted to provide a total plasma $C_{average}$ concentration of 73 ng/ml, which is approximately one-quarter of that expected to be efficacious in humans based on preclinical PK/pharmacodynamic studies. Furthermore, the starting dose level of 200 mg is considered to be safe based on the US Food and Drug Administration (FDA) guidance.

Subsequent dose levels may be adjusted based on the PK, tolerability, and safety results from the RO7049389 FIH study and available data from this study. In cohort 3, the planned dose for the SAD phase was 800 mg as a single dose. Based on the emerging data from completed cohorts 1 and 2 and the RO7049389 FIH study, it was found that the exposure of RO7049389 in plasma in Chinese HVs was higher than that in non-Chinese HVs in the FIH study. The projected AUC of the planned

TABLE 2 PK Parameters for RO7049389 in healthy participants

Cohorts	Doses and days		C_{max}[a] (ng/ml)	AUC[a,c] (h*ng/ml)	T_{max}[b] (h)	$t_{1/2}$[a] (h)
SAD cohorts	200 mg fasted ($N = 2$)		4010 (41.3)	9460[d]	1.5 (1.5–1.5)	3.66[d]
	400 mg fasted ($N = 10$)		7100 (84.8)	15,700 (84.6)	1.5 (1.0–3.0)	10.3 (97.8)
	600 mg fasted ($N = 10$)		7440 (116)	18,900[e] (120)	2.0 (1.0–4.0)	14.6[e] (108)
MAD cohorts	200 mg b.i.d. ($N = 10$) fed	Day 1	3620 (40.6)	5520 (38)	1.5 (1.5–2.0)	2.4 (39.4)
		Day 14	2870 (35.4)	5440 (29.7)	2.0 (1.5–2.0)	5.27 (31.6)
	400 mg b.i.d. ($N = 10$) fed	Day 1	10,500 (51.1)	23,800 (72.6)	2.0 (1.0–3.0)	1.69 (33.1)
		Day 14	9130 (60.8)	25,400 (90.7)	2.0 (1.5–3.0)	7.15 (36.4)

Abbreviations: AUC_{∞}, area under the concentration–time curve from time 0 to infinity; AUC_{τ}, area under the concentration–time curve from time 0 to 12 h; CL/F, apparent clearance; C_{max}, maximum plasma concentration; MAD, multiple ascending dose; PK, pharmacokinetic; SAD, single ascending dose; T_{max}, time to maximum concentration; $t_{1/2}$, terminal half-life.

[a]Presented as arithmetic mean (percentage of coefficient of variation).

[b]Presented as median (min–max).

[c]AUC_{∞} for SAD cohort, and AUC_{τ} for MAD cohorts.

[d]$N = 1$.

[e]$N = 9$.

800 mg single dose would be likely to be threefold higher than the AUC for cohort 2, which was 400 mg. Therefore, the dose for the SAD phase for cohort 3 was decreased to 600 mg.

The highest dose/exposure level in this study was within the dose/exposure range, which was demonstrated to be safe and well-tolerated in the RO7049389 FIH study.[4] The planned optional cohort 4 (1200 mg single dose and 600 mg b.i.d. multiple doses) analysis was canceled based on the emerging data from this study and the FIH study because the results from the first three cohorts were sufficient to assess ethnic sensitivity and support Chinese patients joining global phase II trials. Two events of eosinophil count increased in the 400 mg SAD cohort in this study were reported but none from the FIH study, but both of the two events were mild, and not related to the study treatment. Lip dry was also observed in this study but not the global FIH study. Although there is difference between the Chinese phase I study and global phase I study, the incidence of "lip dry" is comparable between the study treatment arm (55%) and the placebo arm (50%).

RO7049389 exhibited a greater than dose-proportional increase in exposure in the FIH study, which was also observed in the MAD cohorts but not in the SAD cohorts in this study. The potential reason for the difference may be high intersubject variability, especially under fasted conditions. The less than dose-proportional increase in the exposures of the three RO7048389 metabolites may be attributed to saturation of the uptake transporter OATP1B and the metabolic enzyme CYP3A4 of RO7049389.[5]

The variability of RO7049389 exposure was relatively large. However, the highest exposure in FIH study was 2500 mg for SAD cohort, and 800 mg b.i.d. under fed condition, and RO7049389 was well tolerated in all HVs.[4] These findings provided a large safety margin for RO7049389. Under this situation, although the variability of RO7049389 exposure was large, it should not affect the safety of RO7049389 even at the highest proposed dose in this study.

A faster $t_{1/2}$ was observed at 200 mg in the SAD cohort and day 1 of the MAD cohort. These apparent $t_{1/2}$ was a mix of distribution and terminal phase $t_{1/2}$ due to the lack of later timepoint data, either because the RO7049389 concentration was below the lower limit of quantification (LLOQ), or the later points were not available due to the second dose was given.

The exposure of RO7049389 in Chinese HVs was higher than that in non-Asian HVs, which cannot be explained by the difference in the body weight. Internal in vitro studies have suggested RO7049389 is a substrate of OATP1B (data not shown), and it has been reported[6] that OATP1B activity may be different between Asian and non-Asian populations. The lower OATP1B activity in Asians than in non-Asians may contribute to the observed ethnic difference in the plasma exposure of RO7049389. In the FIH study, the exposures of RO7049389 metabolites were disproportionately higher than those in animal species. The disproportionately high exposure of metabolites was not expected; therefore, the bioanalytical assay method for metabolites in plasma was not available for most HVs in the FIH study. The metabolite PK data in non-Asian patients were available for only the 600 mg b.i.d. MAD cohort. Ethnic sensitivity assessments of the PK of metabolites were not conducted.

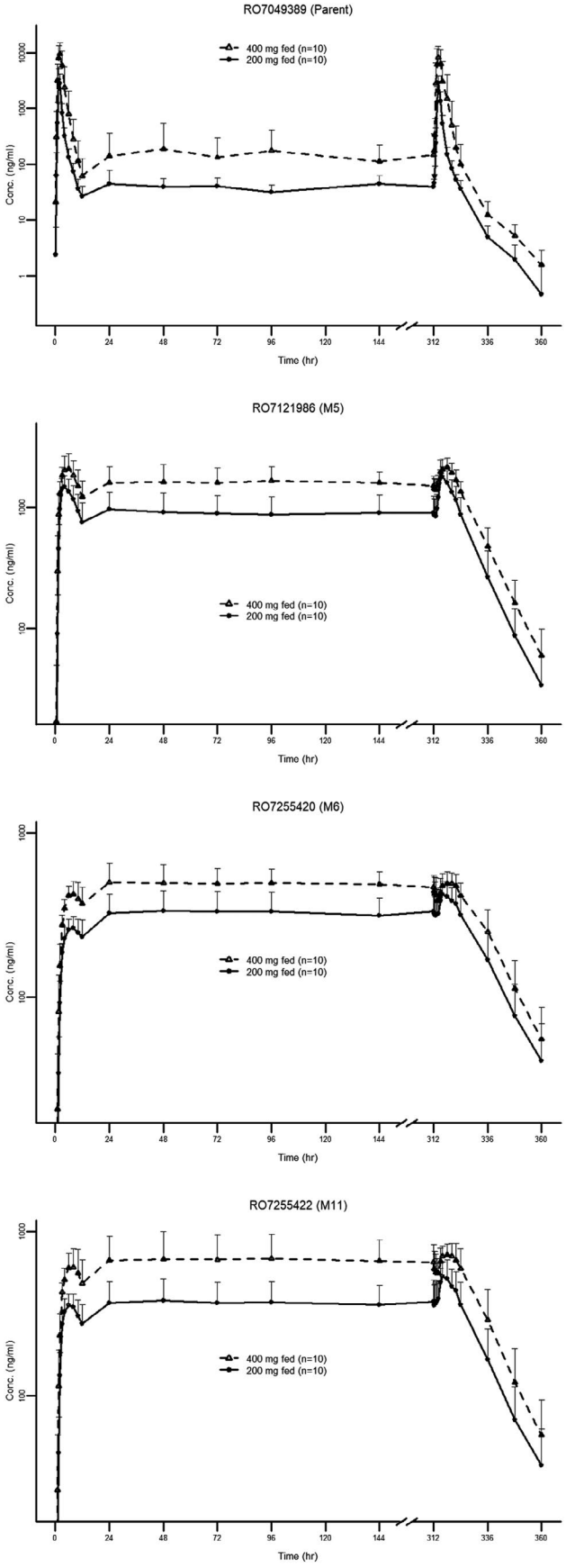

FIGURE 3 Mean (±SD) plasma concentration (Conc)-time curves of RO7049389 and its three metabolites after multiple doses of RO7049389 in healthy volunteers (semilog)

TABLE 3 Plasma AUC comparison between Non-Asian HVs and Chinese HVs

AUC_{τ}[a] (h*ng/ml) cohorts	Non-Asian HVs in FIH study	Chinese HVs in this study
200 mg b.i.d. fed	1570 ($n = 6$)	5440 ($n = 10$)
400 mg b.i.d. fed	7080 ($n = 4$)	25,400 ($n = 10$)
200 mg fasted	1750 ($n = 5$)	6620[b] ($n = 2$)
450 mg/400 mg fasted	3860[b] ($n = 5$, 450 mg)	15,700[b] ($n = 10$, 400 mg)

Abbreviations: AUC_{τ}, area under the concentration−time curve from time 0 to 12 h; FIH, first-in-human; HVs, healthy volunteers.

[a]Presented as arithmetic mean (sample size).

[b]AUC_{∞}.

Because the food effect had been assessed in the FIH study of RO7049389,[4] the different food effect between Asian and non-Asian populations was not expected. Therefore, the food effect was not assessed in the study. Under fasted conditions, the participants were not allowed to eat at least 8 h before administration and 4 h after administration. Therefore, in the MAD cohorts, from an operational and ethic perspective, it was not possible to administer RO7049389 in the fasting state considering RO7049389 was administered twice daily for 2 weeks. Therefore, in the MAD cohorts, RO7049389 was administered with a meal.

In conclusion, RO7049389 was well-tolerated at a single dose of up to 600 mg and multiple doses of up to 400 mg b.i.d. for 14 days in HVs. The absorption and elimination of RO7049389 occurred rapidly in plasma. Nonlinearity in plasma exposure was observed. In general, the safety profiles were comparable between non-Asian and Asian HVs, but the plasma exposure in Chinese HVs in this study was higher than that in non-Asian HVs in the FIH study. These results provide guidance for future clinical studies in Chinese/Asian patients with HBV.

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CONFLICTS OF INTEREST

X.W., J.Z., and W.Z. are full-time employees of Huashan Hospital. Y.Z., M.T., N.Z., Q.B., and Y.J. are full-time employees of F. Hoffmann-La Roche. S.F. and M.Z. were previously a full-time employee of F. Hoffmann-La Roche during this work.

AUTHOR CONTRIBUTIONS

S.F. and Y.C.Z. wrote the manuscript. X.J.W., S.F., J.Z., W.H.Z., M.F.Z., M.T., N.Z., QY.B., and Y.Y.J. designed and performed the research. S.F., M.F.Z., M.T., N.Z., Q.Y.B., and Y.Y.J. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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