Pharmacokinetics, Safety, and Tolerability of the siRNA JNJ-73763989 in Healthy Chinese Adult Participants

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Introduction

- Functional cure, defined as sustained off-treatment hepatitis B surface antigen (HBsAg) loss and undetectable serum levels of hepatitis B virus (HBV) DNA, is rarely achieved by current therapies for chronic hepatitis B (CHB), which include pegylated interferon and nucleos(t)ide analogue (NA)[1-3]
- JNJ-73763989 comprises 2 short-interfering RNA (siRNA) triggers (JNJ-73763976 and JNJ-73763924) that target all HBV RNAs, resulting in their degradation via the RNA interference mechanism, thus causing a reduction in all viral proteins[4]
- Efficacy, safety, and pharmacokinetics of JNJ-73763989 were evaluated in a multicenter, double-blind, placebo-controlled, randomized study (REEF-1) over 48 weeks[5]
  - In REEF-1, JNJ-73763989 (40, 100, and 200 mg) was administered every 4 weeks (Q4W) with or without daily oral (QD) JNJ-56136379 250 mg (investigational capsid assembly modulator) in combination with QD NA in currently not treated or virally suppressed patients with hepatitis B e antigen (HBeAg)–positive or –negative CHB
  - Dose-dependent HBsAg response to JNJ-73763989 was observed with a maximum mean reduction of HBsAg of 2.6 $\log_{10}$ IU/mL from baseline with JNJ-73763989 200 mg Q4W + NA QD
- The pharmacokinetics of JNJ-73763989 have been evaluated in healthy Japanese and non-Japanese volunteers[6,7] and in participants with moderate hepatic impairment,[7] in whom it was found to be generally safe and well tolerated
- China has one of the largest populations infected with HBV, with approximately 70 million people infected, accounting for nearly 25% of the estimated cases worldwide[8,9]
- Considering that minimal ethnic differences have been observed in other clinical studies[5,6] of JNJ-73763989 and that it has a good safety profile, it is critical to investigate the potential of JNJ-73763989 as a treatment option in the Chinese population

Objective

- The pharmacokinetics, safety, and tolerability of JNJ-73763989 were investigated in healthy Chinese adult participants following single-dose administration of JNJ-73763989

Methods

- The current study (ClinicalTrials.gov Identifier: NCT04586439) was a phase 1, open-label, parallel-group, randomized study conducted at a single hospital in China
- Healthy Chinese men and women aged 18 to 55 years with a body mass index (BMI) of 18 to 27.9 kg/m^2 and body weight ≥45 kg were eligible for enrollment in the study
- Participants received a single subcutaneous dose of JNJ-73763989 100 mg (JNJ-73763976 67 mg, JNJ-73763924 33 mg) or 200 mg (JNJ-73763976 133 mg, JNJ-73763924 67 mg)
- Plasma samples for pharmacokinetic measurements of JNJ-73763989 were taken pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours post-dose
- Plasma concentrations of JNJ-73763976 and JNJ-73763924 were determined using a validated bioanalytical method (liquid chromatography–fluorescence detection) with a lower limit of quantification (LLOQ) of 2.1 and 1.0 ng/mL, respectively (Denali)
- Urine samples for pharmacokinetic measurements of JNJ-73763989 were collected over the following intervals: 0 to 6, 6 to 12, 12 to 24, 24 to 36, and 36 to 48 hours
- Urine concentrations of JNJ-73763976 and JNJ-73763924 were determined using a qualified bioanalytical method (liquid chromatography–fluorescence detection) with an LLOQ of 21.0 and 10.0 ng/mL, respectively (Denali)
- Safety and tolerability were evaluated by dose group for 28 days following JNJ-73763989 administration
- Plasma and urine pharmacokinetic analysis was performed using Phoenix™ WinNonlin® with noncompartmental analysis
- Descriptive statistics, including sample size (n), mean, standard deviation (SD), coefficient of variation, geometric mean, median, minimum, and maximum, were calculated for plasma and urine parameters at specific time points and intervals by dose (100 or 200 mg) and trigger (JNJ-73763976 and JNJ-73763924)

Results

Participants

- A total of 18 participants (9 per dose) were included, with a median age of 33 years and a median weight of 73.7 kg; 83.3% were male (**Table 1**)

Table 1. Baseline Demographics and Characteristics

Parameter*	JNJ-73763989 100 mg (n = 9)	JNJ-73763989 200 mg (n = 9)	Total (N = 18)
Age, years	33.0 (22-41)	33.0 (25-43)	33.0 (22-43)
Male, n (%)	7 (77.8)	8 (88.9)	15 (83.3)
Asian, n (%)	9 (100)	9 (100)	18 (100)
Weight, kg	70.70 (49.6-86.1)	76.00 (58.9-81.9)	73.65 (49.6-86.1)
Height, cm	166.0 (145-181)	171.0 (163-176)	168.0 (145-181)
BMI, kg/m²	25.79 (20.9-27.6)	26.31 (20.9-26.9)	26.26 (20.9-27.6)

*Median (range) unless otherwise noted.

Plasma Pharmacokinetic Parameters

- The overall mean plasma concentration-time curves for both triggers were similar between the 2 dose levels, with maximal or near-maximal plasma concentrations reached by 3 hours after administration and steady levels from 3 to 10 hours post-dose (**Figure 1**)
- The median time to reach maximum plasma concentration (t_{max}) was 10 hours for JNJ-73763976 at both doses and 8.00 and 6.02 hours with the 100 and 200 mg doses, respectively, for JNJ-73763924 (**Table 2**)
- Maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) parameters were increased in a dose-proportional manner by both triggers (**Table 2**)
- The mean apparent half-life ($t_{1/2}$) was similar for both triggers and doses, ranging between 4.5 and 4.8 hours (**Table 2**)

Urine Pharmacokinetic Parameters

- The mean cumulative amount of drug excreted in urine over time appears numerically greater for the JNJ-73763976 trigger at 200 mg than for the other trigger and doses (**Figure 2**)
- For the JNJ-73763976 trigger, the mean percentage excreted in urine up to 48 hours was 17.7% and 19.4% for the 100 and 200 mg doses, respectively (**Table 2**)
- For the JNJ-73763924 trigger, the mean percentage excreted in urine up to 48 hours was 13.2% and 13.1% for the 100 and 200 mg doses, respectively (**Table 2**)

Figure 1. Mean plasma concentration of drug over time for (A) JNJ-73763976 and (B) JNJ-73763924.

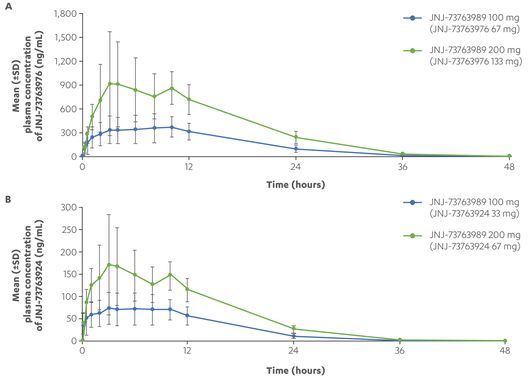
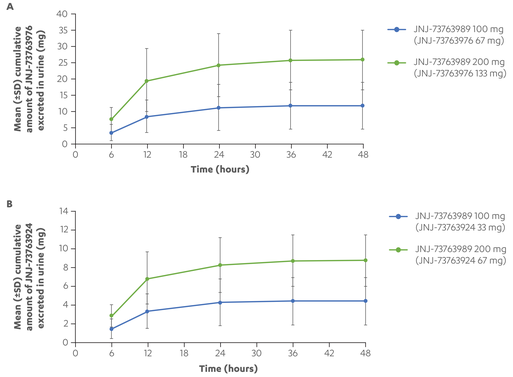


Table 2. Summary of Plasma and Urine Pharmacokinetic Parameters

Pharmacokinetic parameter*	JNJ-73763976		JNJ-73763924	
	JNJ-73763989 100 mg (n = 9)	JNJ-73763989 200 mg (n = 9)	JNJ-73763989 100 mg (n = 9)	JNJ-73763989 200 mg (n = 9)
Plasma				
C_{max}, ng/mL	410 (183)	1,060 (607)	83.5 (37.5)	195 (103)
t_{max}, h	10.00 (3.00-10.00)	10.00 (3.00-10.02)	8.00 (3.00-10.00)	6.02 (2.00-10.02)
AUC_{inf}, h·ng/mL	7,053 (2,172)	17,186 (4,029)†	1,310 (482)‡	2,641 (564)†
$t_{1/2}$, h	4.6 (0.9)	4.7 (0.4)†	4.5 (1.6)‡	4.8 (0.9)†
CL/F, L/h	10.2 (3.09)	8.21 (2.29)†	28.6 (10.4)‡	26.3 (5.96)†
V_d/F, L	69.5 (27.8)	56.5 (17.9)†	200 (149)‡	186 (70.4)†
C_{max}/dose, ng/mL/mg	6.15 (2.74)	7.98 (4.55)	2.50 (1.12)	2.92 (1.54)
AUC_{inf}/dose, h·ng/mL/mg	106 (32.6)	129 (30.2)†	39.2 (14.4)‡	39.6 (8.45)†
Urine				
Ae, % dose	17.7 (10.8)	19.4 (6.85)	13.2 (7.56)	13.1 (4.10)
CL_R, L/h	1.60 (0.479)	1.56 (0.416)	3.39 (0.804)	3.29 (0.834)

AUC_{inf}, area under the plasma concentration-time curve from time 0 to infinite time; CL/F, total clearance of drug following single-dose administration; V_d/F, apparent volume of distribution; C_{max}/dose, dose-normalized C_{max}; AUC_{inf}/dose, dose-normalized AUC_{inf}; Ae, cumulative urinary recovery represented as a percentage of dose; CL_R, renal clearance.
*All parameters are shown as mean (SD) except for t_{max}, which is shown as median (range).
†n = 8 for AUC_{inf}, $t_{1/2}$, CL/F, V_d/F, and AUC_{inf}/dose.
‡n = 7 for AUC_{inf}, $t_{1/2}$, CL/F, V_d/F, and AUC_{inf}/dose.

Figure 2. Mean cumulative amount of drug excreted in urine over time for (A) JNJ-73763976 and (B) JNJ-73763924.



Safety Evaluations

- At least 1 treatment-emergent adverse event (TEAE) was experienced by 6 (66.7%) participants who received JNJ-73763989 100 mg and by 3 (33.3%) participants who received JNJ-73763989 200 mg
- TEAEs considered to be drug related were experienced by 5 (27.8%) participants
- The most common adverse event (AE) was injection-site erythema, experienced by 5 (27.8%) participants; all other TEAEs were observed in no more than 1 participant
- All TEAEs were mild in severity and resolved by the end of the study
- There were no deaths or serious AEs (SAEs) and no TEAEs that resulted in discontinuation of study participation

Key Findings

- A single subcutaneous injection of JNJ-73763989 dose proportionally increased C_{max} and AUC in healthy Chinese adult participants
- The median t_{max} ranged from 6.02 to 10.00 hours, and mean apparent $t_{1/2}$ ranged from 4.5 to 4.8 hours for both doses of JNJ-73763989 (100 and 200 mg) and both triggers (JNJ-73763976 and JNJ-73763924)
- The mean percentage excreted in urine up to 48 hours was 17.7%, 19.4%, 13.2%, and 13.1% for the 100 and 200 mg doses of JNJ-73763976 and JNJ-73763924, respectively
- All TEAEs were of mild severity and resolved by study end, and no SAEs or TEAEs led to premature study discontinuation or death

Conclusions

- The pharmacokinetics of JNJ-73763989 in healthy Chinese participants were consistent with previous studies of different participant populations[6,7,10]
- JNJ-73763989 was generally safe and well tolerated by healthy Chinese participants
- This study supports the continued development of JNJ-73763989 as a potential treatment option for CHB in Asian patients

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Disclosures

HL has no conflict of interest with J&J to disclose. LW, YM, YJ, JJ, QC, XW, ENE, TNK, and MB are employees of Janssen Pharmaceuticals and may be Johnson & Johnson stockholders.

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