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Pharmacokinetics and Safety of JNJ-73763989, an RNA Interference Therapy for Hepatitis B Virus, in Moderately Hepatically-impaired Participants

Thomas N. Kakuda[1], Atef Halabi[2], Carine Guinard-Azadian[3], Katja Nedoschinsky[3], Julius Nangosyah[3], Emmanuel Njumbe Ediage[3], Peter Verboven[3], Michael Biermer[3]

[1]Janssen BioPharma Inc., South San Francisco, CA, USA; [2]Clinical Research Services Kiel GmbH, Kiel, Germany; [3]Janssen Pharmaceutica NV, Beerse, Belgium

Introduction

- Current therapies for chronic hepatitis B (CHB) with a nucleos(t)ide analogue (NA) or pegylated interferon (pegIFN)[1,2] have functional cure rates of approximately 10% for pegIFN and 3% on an NA for the subset eligible to attempt to stop treatment.[1–3] Functional cure is defined as hepatitis B surface antigen (HBsAg) loss and undetectable hepatitis B virus (HBV) DNA in serum sustained for ≥6 months off-treatment, with or without anti-HBs seroconversion.[1–3]
- A promising mode of action to include in CHB treatment regimens is RNA interference (RNAi). JNJ-73763989 comprises the hepatitis B virus (HBV)-specific, liver-targeted N-galactosamine-conjugated short interfering RNA (siRNA) triggers, JNJ-73763976 and JNJ-73763924, which silence HBV RNA transcripts from host-integrated HBV DNA and episomal cccDNA.[4–6]
- JNJ-73763989 administered subcutaneously (SC) as three monthly 100–400 mg doses with an NA daily, demonstrated an HBsAg decline ≥1 $\log_{10}$ IU/mL in CHB patients, which was sustained in 39% of patients for up to 48 weeks off treatment.[7]
- As JNJ-73763989 is being developed for inclusion in treatment regimens for CHB, the potential impact of hepatic impairment on pharmacokinetics (PK) therefore needs to be understood.

Study Aims and Objectives

- This study aimed to assess the plasma PK, safety and tolerability of JNJ-73763989 in participants with moderate hepatic impairment (Child-Pugh B) for reasons other than HBV infection, and to compare the data with those obtained from healthy participants with normal liver function.

Methods

- Study 73763989HPB1002 (NCT04208386) was a Phase 1 single-dose, open-label, parallel group study conducted at a single site in Germany.
- The study was performed in accordance with current International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and the study protocol was approved by the local independent ethics committee/institutional review board. Written informed consent was obtained from all study participants.
- Participants aged 18–75 years with body mass index 18.0–38.0 kg/m² and with moderate hepatic impairment (Child-Pugh B, score 7–9) and healthy participants matching them for sex, age (±10 years) and body weight (±10 kg) were eligible for enrollment.
- JNJ-73763989 was administered to study participants as a single 200 mg SC injection in the abdomen on Day 1 of the study following an overnight fast of ≥10 hours.
- Plasma samples were collected pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72 hours post-dose and urine samples at 0–6, 6–12, 12–24, 24–36, 36–48 and 48–72 hours post-dose for analysis of JNJ-73763976 and JNJ-73763924 concentrations using liquid chromatography coupled to a fluorescence detector.
- PK parameters were estimated using non-compartmental analysis (WinNonlin; Certara, Princeton, NJ).
- The plasma protein binding of JNJ-73763976 and JNJ-73763924 was determined with ultrafiltration in pre-dosed plasma samples spiked with 5000 ng/ml JNJ-73763989 and in plasma samples collected 6 hours after dosing of 200 mg JNJ-73763989.
- The safety and tolerability of study treatment were assessed throughout the study.

Results

- The baseline demographics and other selected clinical characteristics of the enrolled eight Child-Pugh B participants and eight healthy participants are shown in **Table 1**.

Table 1. Baseline Demographics and Clinical Characteristics in Hepatically-impaired (Child-Pugh B) and Healthy Participants.

Parameter*	Child-Pugh B	Healthy participants
N	8	8
Age, years; median (range)	64.5 (53–72)	57 (46–69)
Female, n (%)	3 (37.5)	3 (37.5)
White, n (%)	8 (100)	8 (100)
Not Hispanic or Latino, n (%)	8 (100)	8 (100)
BMI, kg/m²; median (range)	25.8 (21.3–30.7)	26.0 (24.4–31.2)
eGFR, mL/min/1.73m²; median (range)	89.7 (51.2–99.6)	90.9 (73.0–122.0)
Child-Pugh Score; median (range)	8 (7–9)	N/A
Serum bilirubin, mg/dL		
<2	7 (87.5)	N/A
2–3	0	
>3	1 (12.5)	
Serum albumin, g/dL		
>3.5	4 (50)	N/A
3.5–2.8	4 (50)	
<2.8	0	
INR		
<1.7	6 (75)	N/A
1.7–2.3	2 (25)	
>2.3	0	
Ascities		
Absent	1 (12.5)	N/A
Mild	6 (75)	
Moderate	1 (12.5)	
Encephalopathy		
Absent	1 (12.5)	N/A
Mild (I–II)	7 (87.5)	
Severe (III–IV)	0	

*All values are n (%) unless otherwise stated; BMI: body mass index; eGFR: estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation; INR: international normalized ratio; N/A: not applicable.

Pharmacokinetics of JNJ-73763976 and JNJ-73763924 Following a Single SC Dose of JNJ-73763989

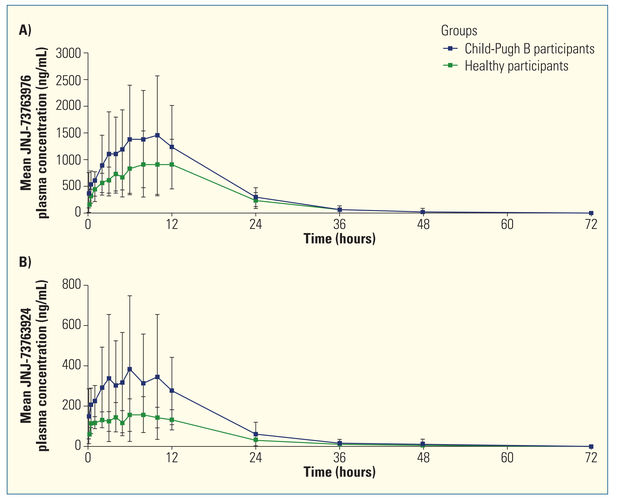
- PK parameters for JNJ-73763976 and JNJ-73763924 following a single SC dose of JNJ-73763989 are summarised in **Table 2**.
- For JNJ-73763976, the geometric mean ratios for C_{max} and AUC_{last} were 1.4- and 1.3-fold higher, respectively, in Child-Pugh B participants than in healthy participants.
- For JNJ-73763924, the geometric mean ratios for C_{max} and AUC_{last} were 2.2- and 2.0-fold higher, respectively, in Child-Pugh B participants than in healthy participants.
- In addition, the half-life and amount of drug renally excreted (Ae) were slightly higher for both analytes in Child-Pugh B participants than in those with normal liver function.
- **Figure 1** shows the mean plasma concentrations of the two analytes were higher at each timepoint up to 24 hours in Child-Pugh B participants than in healthy participants following a single SC dose of JNJ-73763989.

Table 2. PK Parameters for JNJ-73763976 and JNJ-73763924 Following a Single SC Dose of JNJ-73763989.

Liver status	JNJ-73763976		JNJ-73763924	
	Child-Pugh B	Healthy participants	Child-Pugh B	Healthy participants
N	8	8	8	8
C_{max} (ng/mL)	1,640 (1,087)	1,068 (565)	444 (355)	190 (75)
t_{max} (h)	7.00 (0.25–12.00)	9.00 (4.00–12.00)	6.00 (0.25–12.00)	8.00 (0.50–12.00)
AUC_{last} (ng.h/mL)	26,569 (13,132)	18,237 (6,192)	6,410 (3,605)	2,862 (694)
AUC_{∞} (ng.h/mL)	26,711 (13,085)	18,273 (6,194)	6,335 (4,172), [n=6]	3,023 (634), [n=7]
$t_{½}$ (h)	6.93 (3.76)	5.39 (1.75)	7.11 (5.74), [n=6]	4.34 (1.55), [n=7]
CL/F (L/h)	6.31 (3.25)	8.05 (2.76)	14.7 (8.16) [n=6]	22.9 (4.53) [n=7]
V_d/F (L)	64.0 (45.1)	64.9 (37.3)	159 (132) [n=6]	142 (51.0) [n=7]
Ae (% dose)	34.4 (14.1)	26.6 (7.47)	29.1 (13.6)	21.2 (5.83)
Geometric mean ratio (90% CI) Child-Pugh B vs healthy participants				
C_{max}	139.4% (89.4–217.2)	–	218% (135.7–350.2)	–
AUC_{last}	131.2% (100.6–171.2)	–	201.6% (140.6–289.1)	–
AUC_{∞}	131.7% (100.9–172.1)	–	180.1% (121.1–267.8)	–

C_{max}: maximum plasma concentration; t_{max}: time to reach C_{max}; AUC: area under the plasma concentration-time curve from time 0 to the time of the last measured concentration (AUC_{last}) or extrapolated to infinity (AUC_{∞}); $t_{½}$: half-life; CL/F: apparent clearance; V_d/F: apparent volume of distribution; Ae: amount of drug excreted; CI: confidence interval.
All data in top part of table expressed as mean (standard deviation) except for t_{max}, median (range).

Figure 1. Mean Plasma Concentration vs Time Profiles for A) JNJ-73763976 and B) JNJ-73763924 in Child-Pugh B and Healthy Participants Following a Single SC Dose of JNJ-73763989.



Plasma Protein Binding of JNJ-73763976 and JNJ-73763924 Following a Single SC Dose of JNJ-73763989

- In spiked pre-dose samples of healthy participants, the mean (SD) unbound fraction in plasma was 0.086 (0.024) and 0.115 (0.025) for JNJ-73763976 and JNJ-73763924, respectively, and in plasma samples 6 hours after dosing, it was 0.090 (0.061) and 0.142 (0.070), respectively.
- In pre-dose samples of Child-Pugh B participants, the mean (SD) unbound fraction in plasma was 0.110 (0.039) and 0.126 (0.036) for JNJ-73763976 and JNJ-73763924, respectively, and in 6 hours postdose plasma samples it was 0.091 (0.037) and 0.132 (0.041), respectively.

Safety and Tolerability

- There were no deaths, serious adverse events (AEs) or discontinuations.
- Two participants, one in each group, reported ≥1 treatment-emergent AE (TEAE)
  - One Child-Pugh B participant experienced a Grade 2 TEAE of gastrointestinal infection on Day 27, which resolved on Day 30 without any treatment, and Grade 1 worsening hypokalaemia on Day 32, which resolved on Day 37 after treatment with potassium bicarbonate/potassium citrate
  - One healthy participant experienced a Grade 1 TEAE of back pain on Day 3, which resolved on Day 4 after treatment with ibuprofen.
- All TEAEs were not considered to be related to JNJ-73763989 by the study investigator.
- All treatment-emergent graded laboratory abnormalities were of mild/moderate severity except for transient platelet reductions (from Grade 2 at screening to Grade 3) in two Child-Pugh B participants.
- No clinically relevant findings were reported from physical examination, ECG or vital signs.

Conclusions

- JNJ-73763976 and JNJ-73763924 plasma exposures were 1.3- and 2.0-fold higher, respectively, in participants with moderate hepatic impairment. This increase in exposures was not considered to be clinically relevant
  - AUC_{last} of the analytes in participants with moderate hepatic impairment were 1.3–1.8 lower than in healthy volunteers receiving 300–400 mg JNJ-73763989 in study AROHBV1001, in which all AEs were mild/moderate.[8]
- The fraction of JNJ-737639276 and JNJ-73763924 unbound in plasma was not significantly different between healthy participants and Child-Pugh B participants.
- A single 200 mg SC dose of JNJ-73763989 was in general safe and well-tolerated in participants with and without moderate hepatic impairment.
- JNJ-73763989 is currently being evaluated in patients with CHB and HDV co-infection, including patients with compensated liver cirrhosis (Child-Pugh A) (REEF-D, NCT04535544).

References

1. Terrault NA, et al. Hepatology 2018;67:1560–1599; 2. EASL HBV Clinical Practice Guidelines. J Hepatol 2017;67:370–398; 3. Lok AS, et al. Hepatology 2017;66:1296–1313; 4. Butler EK, et al. J Viral Hepat 2018;25(suppl 2):190–210; 5. Wooddell CI, et al. Sci Transl Med 2017;27:409; 6. Yuen MF, et al. J Hepatol 2018;68(suppl 1):S526; 7. Gane EJ, et al. J Hepatol 2020;73(suppl 1):S20; 8. Kakuda TN, et al. International Workshop on Clinical Pharmacology on HIV, Hepatitis and Other Antiviral Drugs 2020. Abstract #16.

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Disclosures

TNK, CG-A, KN, JN, ENE, PV and MB are employees of Janssen Pharmaceuticals and may be Johnson & Johnson stockholders. AH is an employee of Clinical Research Services Kiel GmbH, Kiel, Germany, and the site Principle Investigator.

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