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

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Introduction

• Chronic treatments for hepatitis B (CHB) with a nucleoside analogues (NA) or pegylated interferon (PEG-IFN) have functional cure rates of approximately 10% for pegyIFN and 3% on an NA for the sustaiined response to stop treatment: 2,3 Functional cure is defined as hepatitis B surface antigen (HBsAg) loss and undetectable hepatitis B virus (HBV) DNA in serum sustained for ≥12 months off treatment, with or without anti-HBs immunization: 4,5
• A promising mode of action to include in CHB treatment regimen is RNA interference (RNAi). JNJ-73763989 comprises the hepatitis B virus (HBV) specific, liver-targeted GalNAc-oligoconjugated short interfering RNA (siRNA) trigger JNJ-73763976 and JNJ-73763924, which silence HBV RNA transcripts from host-integrated HBV DNA and episomal cccDNA: 6,7 JNJ-73763989 was administered subcutaneously (SC) to three month >400 mg doses with an NA daily, demonstrated an HBsAg decline of log10 K/ml in CHB patients, which was sustained in 30% of patients for up to 6-months off treatment: 8
• 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 (NCT04123063) 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) scores 7–16 and healthy participants matching them for sex, age (>65 years and body weight (>54 kg) were eligible for enrollment.
• JNJ-73763989 was administrated to study participants as a single 200 mg SC injection on Day 1 of the study.
• Plasma samples were collected pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 hours post dose and urine samples at any time ≥12 hours post dose for analysis of JNJ-73763976 and JNJ-73763924 concentrations using liquid chromatography tandem mass spectrometry coupled to a fluorescence detector.
• PK parameters were estimated using non-compartmental analysis (WinNonlin;NONMEM, Berkeley, CA, USA).
• The plasma protein binding of JNJ-73763976 and JNJ-73763924 was determined with ultrafiltration in preequilibrated plasma samples spiked with 1000 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.

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.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Child-Pugh B</th>
<th>Healthy participants</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Vd/F (L)</td>
<td>6.31 (3.25)</td>
<td>8.05 (2.76)</td>
<td>14.7 (8.16) [n=6]</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>22.9 (4.53)</td>
<td>33.5 (11.7)</td>
<td>66.6 (24.3)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>5.6 (4.8)</td>
<td>3.5 (2.2)</td>
<td>7.0 (5.2)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1,640 (1,087)</td>
<td>1,068 (565)</td>
<td>444 (355)</td>
</tr>
<tr>
<td>AUC∞ (ng.h/mL)</td>
<td>26,569 (13,132)</td>
<td>18,237 (6,192)</td>
<td>6,410 (3,605)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>7.00 (0.25–12.00)</td>
<td>9.00 (4.00–12.00)</td>
<td>6.00 (0.25–12.00)</td>
</tr>
</tbody>
</table>

Safety and Tolerability

• There were no deaths, serious adverse events (SAEs) or discontinuations.
• Two participants, in each group, reported ≥1 treatment-emergent AE (TEAE).
• One Child-Pugh B participant experienced a Grade 1 TEAE of gastrointestinal infection on Day 27, which resolved on Day 30 without any treatment, and Grade 1 worsening hyperbilirubinemia on Day 30, which resolved on Day 37 after treatment with potassium bicarbonate/paracetamol.
• One healthy participant experienced a Grade 1 TEAE of back pain on Day 3, which resolved on Day 4 after treatment with ibuprofen.

Conclusions

• JNJ-73763976 and JNJ-73763924 plasma exposures were 1.3- to 2.0-fold higher, respectively, in participants with moderate hepatic impairment. This increase in exposures was not considered to be clinically relevant.

References


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

• In spiked pro-dose studies of healthy participants, the mean (SD) unbound fraction in plasma was 0.08 (0.03) and 0.07 (0.02) for JNJ-73763976 and JNJ-73763924, respectively, and in plasma samples 8 hours after dosing, it was 0.08 (0.03) and 0.12 (0.07), respectively.
• In pro-dose studies of Child-Pugh B participants, the mean (SD) unbound fraction in plasma was 0.11 (0.03) and 0.12 (0.03) for JNJ-73763976 and JNJ-73763924, respectively, and in 6 hours postdose plasma samples it was 0.09 (0.03) and 0.12 (0.04), respectively.

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