Adv Ther (2019) 36:2450–2462
https://doi.org/10.1007/s12325-019-01017-1

ORIGINAL RESEARCH

Pharmacokinetics, Safety and Tolerability of JNJ-56136379, a Novel Hepatitis B Virus Capsid Assembly Modulator, in Healthy Subjects

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Received: April 15, 2019 / Published online: July 2, 2019

ABSTRACT

Introduction: Hepatitis B viral capsid assembly is an attractive target for new antiviral treatments. JNJ-56136379 (JNJ-6379) is a potent capsid assembly modulator in vitro with a dual mode of action. In Part 1 of this first-in-human study in healthy adults, the pharmacokinetics (PK), safety and tolerability of JNJ-6379 were evaluated following single ascending and multiple oral doses.

Methods: This was a double-blind, randomized, placebo-controlled study in 30 healthy adults. Eighteen subjects were randomized to receive single doses of JNJ-6379 (25 to 600 mg) or placebo. Twelve subjects were randomized to receive 150 mg JNJ-6379 or placebo twice daily for 2 days, followed by 100 mg JNJ-6379 or placebo daily for 10 days.

Results: The maximum observed plasma concentration and the area under the curve increased dose proportionally from 25 to 300 mg JNJ-6379. Following multiple dosing, steady-state conditions were achieved on day 8. Steady-state clearance was similar following single and multiple dosing, suggesting time-linear PK. All adverse events (AEs) reported were mild to moderate in severity. There were no serious AEs or dose-limiting toxicities and no apparent relationship to dose for any AE.

Conclusion: JNJ-6379 was well tolerated in this study. Based on the safety profile and plasma exposures of JNJ-6379 in healthy subjects, a dosing regimen was selected for Part 2 of this study in patients with chronic hepatitis B. This is anticipated to achieve trough plasma exposures of JNJ-6379 at steady state of more than three times the 90% effective concentration of viral replication determined in vitro.

Trial registration: Clinicaltrials.gov identifier, NCT02662712.

Funding: Janssen Pharmaceutica.

Enhanced Digital Features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.8256479.

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Keywords: Antiviral activity; Capsid assembly; Hepatitis B virus; Infectious diseases; Phase 1

INTRODUCTION

More than 290 million individuals are estimated to be chronically infected with hepatitis B virus (HBV) worldwide [1], with serologic

evidence of past or present HBV infection in approximately one-third of the world's population [2]. HBV is a hepatotropic virus associated with a wide range of liver damage. Indeed, HBV infection leads to high morbidity and mortality, with nearly 1 million deaths each year, often resulting from associated liver disease, e.g., hepatocellular carcinoma [3]. Previous attempts to eradicate HBV have been unsuccessful; the prevalence of HBV was reduced by 32% from 1990 to 2017 following the development of a safe and effective vaccine; however, the incidence of new HBV infections remains high [4].

Currently available treatments for HBV, predominantly nucleos(t)ide analogs (NAs) and pegylated-interferon-alpha-2a (PEG-IFN-α), both prevent HBV replication and the progression of liver disease, but rarely induce HBV surface antigen seroconversion indicative of a successful immunologic response to HBV and a functional cure. Additionally, NAs are associated with a long treatment duration and PEG-IFN-α with significant morbidity [5, 6]. Development of novel drugs for the treatment of chronic HBV infection (Fig. 1) that are safe to use and can achieve a functional cure would improve the current standard of care and, in conjunction with an effective vaccine, could help advance progress toward the eradication of HBV infection [7].

A critical stage in the replication cycle of HBV is the assembly of viral capsids within infected hepatocytes, making this process an attractive target for the development of novel antiviral therapies. Capsid assembly modulators (CAMs) prevent HBV replication by accelerating the kinetics of HBV capsid assembly and blocking the encapsidation of the polymerase-pregenomic RNA (Pol-pgRNA) complex, thereby preventing reverse transcription of pgRNA (Fig. 1) [8]. While NAs are only capable of suppressing HBV DNA replication, CAMs can inhibit pgRNA encapsidation and the production of HBV virion and RNA particles with equal efficiency [5]. Several CAMs are currently under investigation for treatment of CHB, including JNJ-56136379 (JNJ-6379) currently in phase 2a and JNJ-64530440 currently in phase 1 development in healthy volunteers (Fig. 1) [9].

JNJ-6379 is a potent CAM with a dual mode of action, interfering with both de novo covalently closed circular DNA (cccDNA) formation

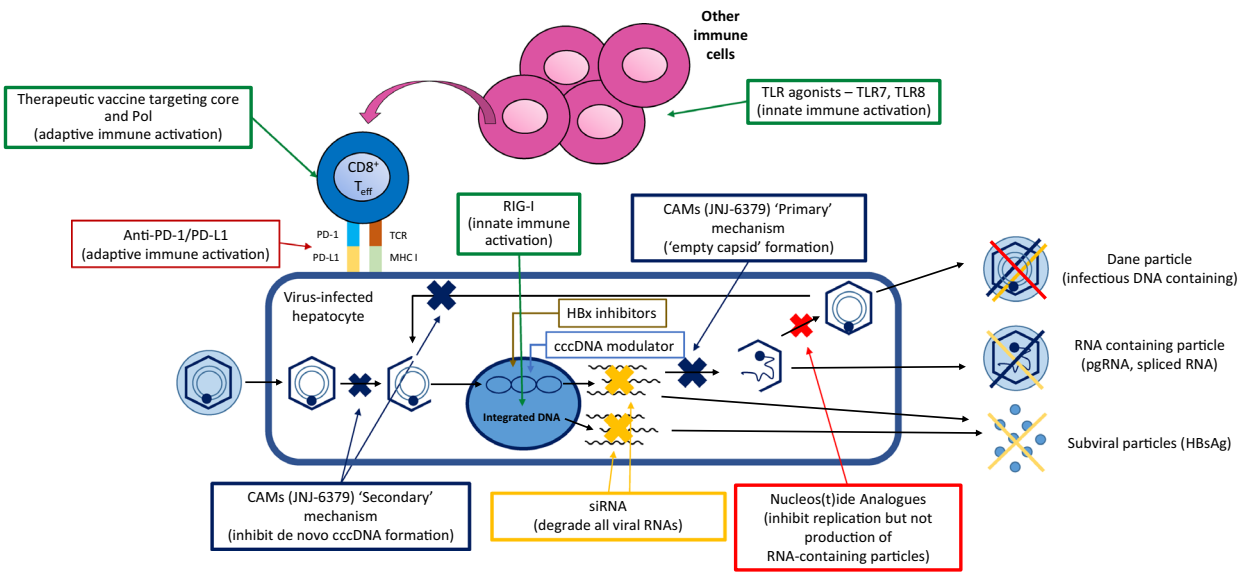

Fig. 1 Drug targets for HBV, highlighting the site of the CAM JNJ-6379 study drug. TLR, Toll-like receptor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand-1; TCR, T-cell receptor; MHC I, major histocompatibility complex class I; RIG-I, retinoic acid inducible gene I; CAM, capsid assembly modulator; cccDNA, covalently closed circular DNA; HBx, HBV X protein; siRNA, small interfering ribonucleic acid; pgRNA, pregenomic RNA; HBsAg, hepatitis B surface antigen

and capsid assembly (Fig. 1) [10]. In a stable HBV replicating HepG2.117 cell line, JNJ-6379 inhibited HBV replication with a median 50% effective concentration (EC_{50}) and 90% effective concentration (EC_{90}) values of 54 nM and 226 nM, respectively, with a selectivity index of > 463 [10]. Addition of 40% human serum protein reduced the antiviral activity by 3.8-fold. Consistent with the anti-HBV activity observed in the HepG2.117 cells, JNJ-6379 reduced HBV DNA levels in the cell culture supernatant of HBV-infected primary human hepatocytes with a median EC_{50} and EC_{90} value of 118 nM and 347 nM, respectively [10].

In preclinical studies in rats and dogs, JNJ-6379 appeared well tolerated and demonstrated significant tissue distribution (volume of distribution 5.4 l kg^{-1} and 2.4 l kg^{-1}, respectively), low intrinsic clearance and an apparent elimination half-life of 7 and 34 h in these species, respectively. Liver:plasma ratios ranged from 6 to 18.3 in mouse, rat and dog. A starting dose of 25 mg JNJ-6379 was chosen for this study based on the no observed adverse effect level (NOAEL) obtained in dog and considering an additional safety margin. Subsequent doses were based on the results of the previous dose, but anticipated mean exposure could not exceed the maximum observed plasma concentration (C_{max}) attained in the cardiovascular safety study in dog (7930 ng/ml) and the area under the plasma concentration-time curve from 0 to 24 h ($AUC_{0–24h}$) from 1-month repeat dosing in rat after combined oral and subcutaneous administration (201,000 ng h/ml). The dose could not exceed the limit of 2000 mg (20 tablets) for feasibility reasons.

Part 1 of this phase 1 study (NCT02662712) in healthy adult volunteers, reported here, was conducted to evaluate the pharmacokinetics (PK), safety and tolerability of: (1) single ascending oral doses of JNJ-6379; (2) multiple oral doses given over 12 days. The effect of food on the PK of a single-dose level of JNJ-6379 was also evaluated. Based on the plasma exposures observed in healthy subjects, a starting dose was to be selected for Part 2 of this study, which will be conducted in chronic HBV patients.

METHODS

Study Drug

JNJ-6379 used in this study was provided as oral 5 mg, 25 mg and 100 mg tablets.

Compliance with Ethics Guidelines

This study was approved by the Ethics Committee, UZA, Wilrijkstraat 10, 2650 Edegem, Belgium (ethisch.comite@uza.be).

It was performed in accordance with the Helsinki Declaration of 1964 and its later amendments and in compliance with Good Clinical Practice and applicable regulatory requirements. All volunteers provided written informed consent to participate in the study.

Study Design and Subjects

This was a double-blind, randomized, placebo-controlled study in 30 healthy subjects aged 18–55 years. Subjects were excluded from the study if they had: hepatitis A, B, C or E; human immunodeficiency virus type 1 (HIV-1) or HIV-2 infection; a history of cardiac arrhythmias; or one or more laboratory abnormalities at screening as defined by the World Health Organization (WHO) Toxicity Grading Scale.

Single-Dose Phase

Eighteen subjects were divided equally between two panels (panels 1 and 2). Once-daily (QD) doses of JNJ-6379 were escalated over five levels, alternating between the two panels and starting at 25 mg (Table 1). Sessions were conducted sequentially. There was a washout period of at least 14 days between subsequent doses for each subject; if no dose-limiting toxicity was observed, then the dose was escalated as planned. In each session, six subjects were to receive JNJ-6379 and three were to receive placebo (2:1 randomization). Subjects in panels 1 and 2 were administered study medication in a fasted state, except for session 5 where they were dosed after a standardized breakfast.

Table 1 Overview of planned study dosing

Session	Panel	Number of subjects		JNJ-6379 dose	Fasted/fed
		JNJ-6379	Placebo		
1	1[a]	6	3	25 mg QD	Fasted
2	2[b]	6	3	50 mg QD	Fasted
3	1[a]	6	3	150 mg QD	Fasted
4	2[b]	6	3	300 mg QD	Fasted
5	1[a]	6	3	150 mg QD	Fed
6	2[b]	6	3	600 mg QD	Fasted
7	3	9	3	150 mg BID for 2 days, 100 mg QD for 10 days	Fed

BID, twice daily; QD, once daily

[a] The nine subjects in panel 1 were scheduled to partake in sessions 1, 3 and 5, with a minimum 14-day washout period between sessions

[b] The nine subjects in panel 2 were scheduled to partake in sessions 2, 4 and 6, with a minimum 14-day washout period between sessions

Multiple-Dose Phase

In panel 3, 12 subjects (in a fed state) were randomized to receive 150 mg JNJ-6379 or placebo (3:1 ratio) twice daily (BID) for 2 days, followed by 100 mg JNJ-6379 or placebo QD for a further 10 days (session 7; Table 1). There was the option to extend dosing for a further 7 days if needed following analysis of PK data up to day 7.

End Points and Assessments

The two primary end points of this study were as follows: (1) PK parameters of JNJ-6379 in plasma following single and repeated dose administration; (2) safety data, such as adverse events (AEs) and clinical laboratory results.

All PK samples (plasma and urine) from subjects who received study drug were analyzed for JNJ-6379 concentrations. Plasma samples were analyzed using a regulated, validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method. Urine samples were analyzed using a validated (scientific validation) LC-MS/MS method.

Statistical Analysis and Calculations

All subjects who received JNJ-6379 (n = 21) were included in the PK analyses, and all subjects enrolled on to the study (n = 30) were included in the safety analyses. Descriptive statistics [sample size (n), mean, standard deviation (SD), median and range] were calculated for continuous variables where appropriate.

Human PK Predictions

Human PK predictions were made based on extensive mechanistic in vitro work. The parameters obtained for absorption, distribution and elimination were built into a physiologically based pharmacokinetic (PBPK) model using Simcyp v14.1 (Simcyp Ltd, UK) software.

Absorption

Data from relative bioavailability studies in dogs were used to model human absorption. The fraction of JNJ-6379 absorbed in humans was estimated to be < 15%, based on 300 mg JNJ-6379 in simulated fed-state conditions.

Distribution

The apparent volume of distribution was calculated based on measured tissue distribution values in the rat complemented with tissue concentrations predicted by the Berezhkovskiy method for the tissues without observed rat tissue distribution data [11].

Clearance

The human JNJ-6379 renal clearance was predicted based on empirical allometric scaling [12] of the observed renal clearance in preclinical species. Human JNJ-6379 metabolic clearance was predicted based on extrapolation of the in vitro metabolic intrinsic clearance obtained in the human hepatocyte relay model as published by Di et al. [13], with minor modifications to in vivo.

RESULTS

Subject Demographics

The demographics of all 30 healthy adult subjects enrolled in the study are provided in Table 2. Subjects were predominantly male and white and were comparable in terms of age, weight and body mass index across the three panels.

PK

Single-Dose Phase

After single-dose administration of 25 to 300 mg JNJ-6379, the area under the plasma concentration time curve (AUC_{inf}) and the C_{max} increased in proportion with the dose (Fig. 2 and Table 3). At a dose of 600 mg, C_{max} and AUC_{inf} increased less than dose proportionally. Median time to reach C_{max} (T_{max}) ranged from 1.26 to 4.00 h, with individual values ranging between 1.00 and 4.12 h (Table 3).

From 25 to 150 mg, mean apparent clearance (CL/F) and volume of distribution (Vd/F) were comparable. Clearance of the study drug appeared to decrease at higher dose levels, with mean values of 1.15 l/h and 0.915 l/h for the 300 mg and 600 mg doses, respectively. Mean values of Vd/F were generally comparable for all dose groups, averaging between 151 and 194 l. In the 25 to 300 mg dose sessions, mean terminal elimination times ($t_{1/2term}$) were comparable, averaging from 93.3 to 110.5 h. The mean for the 600 mg dose group was 141.3 h (5.9 days), while the overall mean half-life across doses was 109.5 h (4.6 days).

The mean renal clearance of JNJ-6379 was 0.168 ± 0.073 l/h (Session 3: 150 mg QD); 5.44% of the administered dose was recovered as unchanged drug in urine.

Table 2 Baseline subject demographics

	Panel 1 (*n* = 9)	**Panel 2 (*n* = 9)**	**Panel 3 (*n* = 12)**
Age, years: median (range)	34.0 (26–51)	43.0 (32–51)	42.5 (23–55)
Male, *n* (%)	8 (89)	8 (89)	11 (92)
BMI (kg/m^2), median (range)	23.8 (21.8–26.0)	24.5 (21.5–29.0)	26.4 (19.1–29.8)
Weight at baseline (kg), median (range)	74.0 (58.0–84.6)	76.0 (58.8–94.1)	79.5 (62.3–91.1)
Race, *n* (%)			
Native American or Alaskan	1 (11)	0	0
Asian	0	1 (11)	0
Black or African American	0	0	3 (25)
White	8 (89)	8 (89)	9 (75)

BMI, body mass index

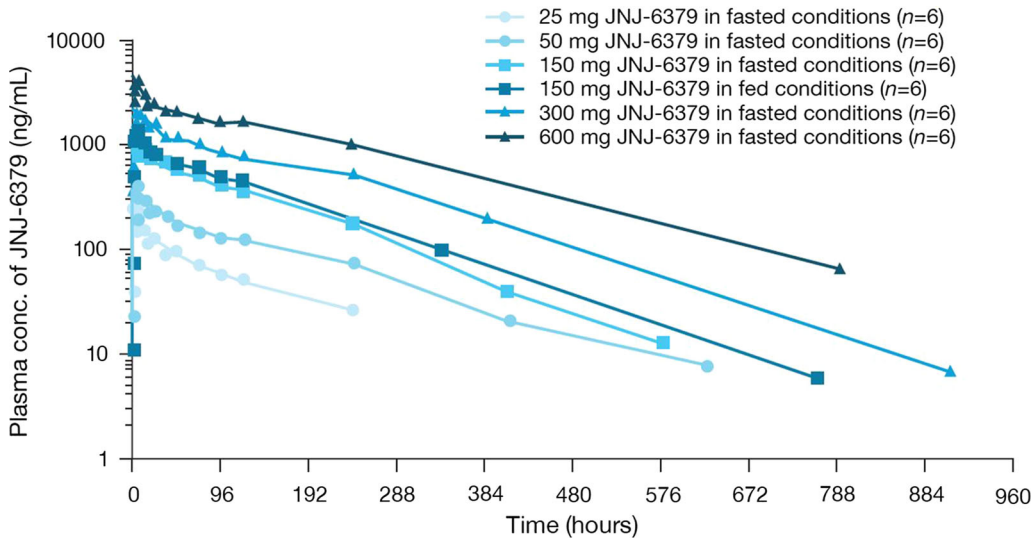

Fig. 2 Mean plasma concentration-time curves for JNJ-6379 after administration of escalating single oral doses (25 to 600 mg) under fasted or fed conditions

When a single dose of 150 mg JNJ-6379 (QD) was administered under fed conditions, C_{max}, AUC_{last} and AUC_{inf} were 25%, 27% and 27% higher, respectively, compared with fasting conditions in the same subjects. Median t_{max} was reached 2.5 h later compared with fasted conditions.

Multiple-Dose Phase

Steady-state conditions were achieved on day 8 following a loading dose of 150 mg BID JNJ-6379 for 2 days, and 100 mg QD for 6 days, prior to dense PK sampling on day 12. Steady-state CL/F following multiple dosing was similar to single-dose administration, suggesting time-linear PK (Fig. 3). C_{max} averaged at 4653 ng/ml, whilst AUC_{24h} averaged at 88,101 ng h/ml. C_{max}, C_{12h} and AUC_{12h} were approximately 3.97-, 4.83- and 4.68-fold higher on day 12 than day 1 relative to a 1.5 times higher dose that was administered on day 1. This accumulation was in line with the theoretical accumulation ratio of approximately 6 for a QD regimen, based upon the terminal elimination rate after single-dose treatment. A relatively flat PK profile was observed during dosing intervals; fluctuations in plasma were moderate to low, averaging 43.0%. Mean renal clearance was 0.177 ± 0.069 l/h. At steady state during the dosing interval approximately 15% of the dose was excreted as unchanged drug in urine.

Verification of Predicted JNJ-6379 Human PK

Simulated JNJ-6379 PK profiles for the 25 mg starting dose were similar to those observed, as shown in Fig. 4. All human PK parameters [C_{max}, AUC, Vd/F and total plasma clearance (CLp)] were predicted within twofold of the observed parameters, although observed values were slightly higher than predicted values in all parameters except CLp (Table 4).

Safety

Single-Dose Phase

Overall, AEs were reported in 14/18 (78%) subjects receiving JNJ-6379 and 8/14 (57%) receiving placebo (Table 5). Five subjects receiving study drug (28%) experienced at least one AE of grade 2 severity with no subjects reporting an AE of greater severity.

Two subjects were discontinued from further dose escalation of JNJ-6379 in subsequent sessions: one subject after receiving a single 50-mg dose of JNJ-6379 because of laboratory abnormalities and the other after receiving a single

Table 3 Summary of PK parameters of JNJ-6379 after administration of escalating single oral doses (25 to 600 mg) under fasted or fed conditions

	JNJ-6379					
	25 mg (fasted) (*n* = 6)	**50 mg (fasted) (*n* = 6)[a]**	**150 mg (fasted) (*n* = 6)[a]**	**300 mg (fasted) (*n* = 6)**	**600 mg (fasted) (*n* = 5)**	**150 mg (fed) (*n* = 5)**
C_{max} (ng/ml), mean (SD)	299 (66.4)	484 (154)	1328 (175)	2632 (703)	4224 (1684)	1688 (427)
t_{max} (h), median (range)	1.26 (1.00–4.12)	1.77 (1.50–3.01)	1.50 (1.00–3.00)	2.50 (1.50–4.00)	4.00 (2.00–4.05)	4.01 (1.49–4.04)
AUC_{inf} (ng h/ml), mean (SD)	18,722 (4223)	44,049 (19,544)	121,508 (25,843)	312,149 (120,258)	700,444 (225,307)	156,760 (25,609)
AUC_{last} (ng h/ml), mean (SD)	16,824 (4305)	43,185 (21,598)	124,148 (27,867)	305,923 (120,764)	686,508 (225,307)	155,801 (25,201)
$t_{1/2term}$ (h), mean (SD)	93.3 (19.3)	110.5 46.7)	95.6 (31.2)	106.8 (36.4)	141.3 (24.1)	97.1 (19.2)
CL/F (l/h), mean (SD)	1.41 (0.397)	1.36 (0.693)	1.28 (0.255)	1.15 (0.624)	0.915 (0.233)	0.977 (0.158)
Vd/F (l), mean (SD)	177 (21.0)	194 (75.3)	180 (86.1)	151 (35.7)	191 (73.3)	136 (29.5)

AUC, area under the plasma concentration-time curve; C_{max}, maximum observed plasma concentration; CL/F, total apparent oral clearance; PK, pharmacokinetic; SD, standard deviation; $t_{1/2term}$, half-life; t_{max}, time to reach the maximum observed plasma concentration; Vd/F, apparent volume of distribution

[a] $N = 5$ for AUC_{last}

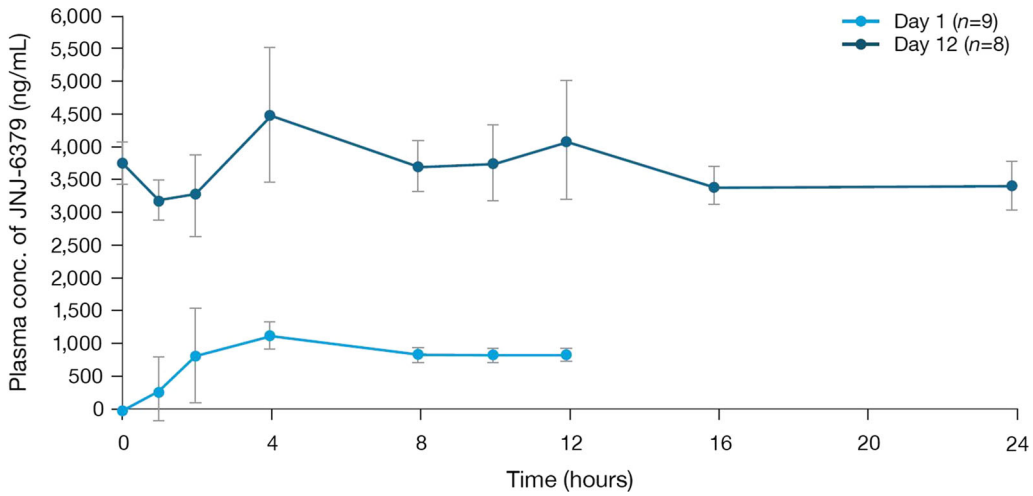

Fig. 3 Mean (± SD) plasma-concentration–time curves of JNJ-6379 after 150 mg BID JNJ-6379 for 2 days followed by 100 mg QD until day 12

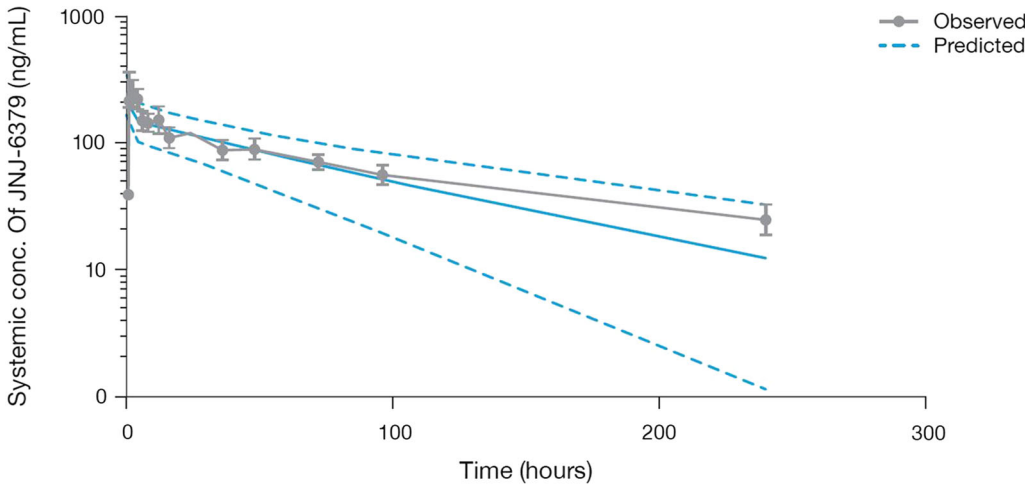

Fig. 4 Mean (± SD) observed human PK profile and predicted human PK profile of JNJ-6379 following a starting dose of 25 mg in male Caucasian healthy volunteers

Table 4 Geometric mean observed (n = 6) and simulated human PK parameters of JNJ-6379 at a single dose of 25 mg in male Caucasian healthy volunteers

	C_{max} (ng/ml), mean (SD)	T_{max} (h), median (range)	AUC_{inf} (ng h/ml), mean (SD)	CLp (l/h), mean (SD)	Vd/F (l), mean (SD)
Simulated	148 ± 53	–	11,600 ± 5390	2.1 ± 0.83	126 ± 7.56
Observed	299 ± 66.4	1.26 (1.00–4.12)	18,722 ± 4223	1.34 ± 0.397	177 ± 21

AUC, area under the plasma concentration-time curve; C_{max}, maximum observed plasma concentration; Clp, total plasma clearance; t_{max}, time to reach the maximum observed plasma concentration; Vd/F, apparent volume of distribution

150-mg dose of JNJ-6379 because of an AE. The first experienced grade 3 pancreatic lipase elevation and grade 2 amylase elevation not associated with clinical symptoms or signs. These laboratory abnormalities were considered mild in severity, very likely related to the study drug, and lasted from the day of dosing until the following day when the subject had returned to pre-dosing levels. The second subject experienced vertigo positional (MedDRA-derived term) of moderate severity, beginning 18 days post-dosing with 150 mg JNJ-6379 and lasting for 13 days. This was considered by the investigator to be possibly related to the study drug.

AEs occurring in two or more subjects receiving JNJ-6379 and considered to be at least possibly related to the study drug were headache, epistaxis and lipase increase. The only AE that was experienced by > 20% of subjects was headache, reported in 9/18 (50%) receiving study drug and 3/14 (21%) receiving placebo. There appeared to be no relationship between the dose of JNJ-6379 administered and the frequency or severity of AEs reported.

Multiple-Dose Phase

In the multiple-dose phase, 8/9 (89%) subjects receiving JNJ-6379 experienced AEs compared with 2/3 (67%) receiving placebo (Table 6). AEs occurring in two or more subjects receiving JNJ-6379 and considered to be at least possibly related to the study drug were abdominal pain and lipase increase, which were experienced by separate subjects. One subject experienced AEs that led to treatment discontinuation: lower abdominal pain and dizziness postural, which started on day 11 of treatment and resolved 3 days after discontinuation of study

Table 5 Summary of treatment-emergent AEs in the single-dose escalation phase

	JNJ-6379							Placebo (*n* = 14)
	25 mg (fasted) (*n* = 6)	50 mg (fasted) (*n* = 6)	150 mg (fasted) (*n* = 6)	150 mg (fed) (*n* = 5)	300 mg (fasted) (*n* = 6)	600 mg (fasted) (*n* = 5)	All (*n* = 18)	
Any AE, *n* (%)	1 (17)	6 (100)	4 (67)	4 (80)	3 (50)	5 (100)	14 (78)	8 (57)
AE leading to discontinuation, *n* (%)	0	1 (17)[a]	0	1 (20)[b]	0	0	2 (11)	0
Most common AEs, *n* (%)[c]								
Headache	1 (17)	4 (67)	2 (33)	2 (40)	1 (17)	3 (60)	9 (50)	3 (21)
Rhinitis	1 (17)	0	0	0	1 (17)	1 (20)	3 (17)	2 (14)
Cough	1 (17)	0	0	2 (40)	0	0	3 (17)	0
Diarrhea	0	0	0	0	0	2 (40)	2 (11)	1 (7)
Epistaxis	0	0	0	2 (40)	0	0	2 (11)	1 (7)
Constipation	0	0	0	0	1 (17)	1 (20)	2 (11)	0
Lipase increased	0	1 (17)	1 (17)	0	0	0	2 (11)	0
Back pain	0	1 (17)	1 (17)	0	0	0	2 (11)	0
Oropharyngeal pain	1 (17)	0	0	0	0	1 (20)	2 (11)	0

AE, adverse event
[a] Lipase increased, amylase increased
[b] Vertigo positional
[c] Two or more subjects in the overall JNJ-6379 treatment group (all doses)

medication. Both AEs were considered possibly related to the study drug, were mild in severity and were not associated with elevations in liver or pancreatic enzymes.

Laboratory Abnormalities

The only laboratory abnormality greater than grade 2 in severity was lipase elevation (grade 3) that led to treatment discontinuation for one subject in the single-dose escalation phase. This subject's lipase measurement returned to pre-dose levels within 24 h.

Table 7 shows laboratory abnormalities reported in ≥ 3 subjects in the single-dose escalation phase in all dose groups receiving JNJ-6379. Only one laboratory abnormality was reported in ≥ 3 subjects in the multiple-dose phase, which was a grade 1 cholesterol elevation (Table 8).

DISCUSSION

JNJ-6379 administered orally at single doses of up to 600 mg and at multiple doses of 150 mg BID for 2 days followed by 100 mg QD for 10 days was well tolerated and demonstrated dose-proportional PK up to 300 mg in healthy subjects.

Exposure was higher at steady-state conditions than after single-dose administration and in line with the theoretical accumulation ratio:

Table 6 Summary of treatment-emergent AEs in the multiple-dose phase

	JNJ-6379 150 mg BID (days 1–2) and 100 mg QD (days 3–12) (*n* = 9)	Placebo All (*n* = 3)
Any AE, *n* (%)	8 (89)	2 (67)
AE leading to permanent discontinuation, *n* (%)	1 (11)[a]	0
Most common AEs, *n* (%)[b]		
Abdominal pain[c]	2 (22)	0
Lipase increased[c]	2 (22)	0
Headache	2 (22)	0

AE, adverse event; BID, twice daily; QD, once daily
[a] Abdominal pain lower and dizziness postural (derived terms)
[b] Two or more subjects
[c] Different subjects experienced lipase elevations and abdominal pain

Table 8 Incidence of treatment-emergent laboratory abnormalities in the multiple-dose phase

	JNJ-6379 mg BID (days 1–2) and 100 mg QD (days 3–12) (*n* = 9)	Placebo (*n* = 3)
Chemistry		
Cholesterol, *n* (%)		
Grade 1	3 (33)	1 (33)
LDL-C, *n* (%)		
Grade 1	2 (22)	0
Lipase, pancreatic, *n* (%)		
Grade 2	2 (22)	0
Hematology		
Activated partial thromboplastin time, *n* (%)		
Grade 1	1 (11)	0

BID, twice daily; LDL-C, low-density lipoprotein cholesterol; QD, once daily

Table 7 Incidence of treatment-emergent laboratory abnormalities in the single-dose escalation phase[a]

	JNJ-6379							Placebo (*n* = 14)
	25 mg (*n* = 6)	50 mg (*n* = 6)	150 mg (*n* = 6)	150 mg (fed) (*n* = 5)	300 mg (*n* = 6)	600 mg (*n* = 5)	All (*n* = 18)	
ALT, *n* (%)								
Grade 1	0	2 (33)	1 (17)	0	2 (33)	0	3 (17)	1 (7)
Cholesterol, *n* (%)								
Grade 1	2 (33)	0	1 (17)	2 (40)	0	2 (40)	5 (28)	1 (7)
Grade 2	0	0	0	0	0	0	0	1 (7)
LDL-C, *n* (%)								
Grade 1	1 (17)	0	0	2 (40)	1 (17)	1 (20)	5 (28)	2 (14)
Grade 2	0	0	0	0	0	0	0	1 (7)
Triglycerides, *n* (%)								
Grade 1	1 (17)	0	1 (17)	2 (40)	2 (33)	1 (20)	5 (28)	4 (29)
Grade 2	0	0	0	0	0	0	0	1 (7)

ALT, alanine aminotransferase; LDL-C, low-density lipoprotein cholesterol
[a] Three or more 3 subjects in the JNJ-6379 treatment group (all doses)

average C_{max} following multiple-dose administration was 4653 ng/ml compared with 1328 ng ml when JNJ-6379 was administered as a single dose of 150 mg. Renal clearance was low (0.177 l/h in the multiple-dose phase and 0.168 l/h at 150 mg in the single-dose phase). JNJ-6379 had an elimination half-life of over 100 h, which exceeds the predictions based on in vitro studies. This long elimination time should allow the drug to persist in the liver and at the target for longer, with the potential for sustained efficacy between doses and decreased concern in the case of a missed dose. In addition, given the safe daily-dosing profile of JNJ-6379 observed in this study, and the long half-life, this regimen should prove convenient for a longer term treatment. In subjects administered 150 mg JNJ-6379 under fed conditions, C_{max}, AUC_{last} and AUC_{∞} were 25–27% higher than in those administered JNJ-6379 under fasted conditions, supporting administration under fed conditions to patients with chronic HBV in Part 2 of this study.

All assumptions made through modeling for PK parameters were within twofold of the observed PK parameters. The predicted PK profile showed slight under-prediction of the terminal phase of the observed PK profile, which was most likely the result of an over-prediction of the clearance phase as renal clearance was scaled from rat renal clearance (predicted to be 0.36 l/h, but observed renal clearance was 0.2 l/h). This successful verification of the PBPK modeling suggests the appropriateness of the modeling assumptions with respect to clearance and disposition and supports future model-based simulations.

Any treatment for chronic HBV has to be well tolerated to increase compliance. PEG-IFN-α is associated with a wide range of frequent side effects, ranging from headache and fatigue to alopecia and psychiatric disorders [14]. NAs are associated with milder and less persistent side effects [14]. In this study, 14 (78%) healthy volunteers given JNJ-6379 experienced any AE compared with 8 (57%) of the volunteers given placebo. Two volunteers discontinued JNJ-6379 during the SAD phase, one as a result of pancreatic lipase elevation and amylase elevation, which lasted until the volunteer returned to pre-dosing levels, and the other as a result of moderate vertigo positional which lasted for 13 days. One discontinued in the MAD phase because of the mild AEs lower abdominal pain and dizziness postural starting on day 11 of study treatment and lasting for 3 days. No serious AEs or deaths occurred. All AEs associated with JNJ-6379 were considered mild to moderate in severity, and no serious AEs or dose-limiting toxicities were identified. These results support the administration of JNJ-6379 to patients with chronic HBV in Part 2 of this study.

Based on the plasma exposures of JNJ-6379 observed in healthy subjects in Part 1 of this study, the following starting dosing regimen was selected for Part 2 to be conducted in treatment-naïve, non-cirrhotic patients with chronic HBV: a loading dose of 100 mg JNJ-6379 on the 1st day, followed by 25 mg JNJ-6379 QD for a further 27 days. This regimen is anticipated to quickly achieve plasma exposures of JNJ-6379 of three times the EC_{90} of viral replication determined in HepG2.117 cells in vitro (226 nM) and to achieve steady-state concentrations more rapidly. This is predicted to shorten the time to detect antiviral activity, e.g., declines in circulating HBV DNA and HBV RNA. Patients will receive daily doses in a fed state to further increase exposure, as suggested by the food effect observed in Part 1 of this study.

As there may be numerous physiologic differences between healthy volunteers, any PK predictions would need to be confirmed in patients with CHB. Additionally, as the multiple ascending dose phase only evaluated one dose for 12 days, there are limited data to support sustained dosing. These limitations will be addressed in Part 2 of the study, in which periodical safety, PK and antiviral activity assessments will take place.

CONCLUSIONS

In the first part of this first-in-human study, we have determined that JNJ-6379 was well tolerated by healthy volunteers, with dose-proportional PK up to 300 mg. Based on these results, a

dose range of JNJ-6379 was chosen for Part 2 of the study. The aims of this study will be to determine the PK, safety and antiviral activity of JNJ-6379 in patients with chronic HBV.

ACKNOWLEDGEMENTS

The authors would like to thank the participants of the study and acknowledge Hans Stieltjes and Freya Rasschaert (Janssen Pharmaceutica NV) whose contributions enabled the conduct and analysis of the study.

The investigator for this study, Dr. Maarten van den Boer, had direct clinical responsibility for subjects in this Phase 1 study and, as an author, has reviewed and approved this manuscript.

Funding. This study and the article processing charges were funded by Janssen Pharmaceutica. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Medical Writing and Editorial Assistance. Editorial support was provided by Andy Shaw, Lydia Travis and Ian Woolveridge of Zoetic Science, an Ashfield company, part of UDG Healthcare plc, and was funded by Janssen Pharmaceutica.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Joris Vandenbossche is a Janssen employee and a Johnson & Johnson stockholder. Wolfgang Jessner was part of Janssen Pharmaceutica at the time of this study and is now employed by Roche Pharma Research & Early Development, Basel, Switzerland and a Johnson & Johnson and Roche stockholder. Maarten van den Boer is a Janssen employee and a Johnson & Johnson stockholder. Jeike Biewenga is a Janssen employee. Jan Martin Berke is a Janssen employee and a Johnson & Johnson stockholder. Willem Talloen is a Janssen employee and a Johnson & Johnson stockholder. Loeckie De Zwart is a Janssen employee and a Johnson & Johnson stockholder. Jan Snoeys is a Janssen employee and a Johnson & Johnson stockholder. Jeysen Z. Yogaratnam was a Janssen employee at the time of the study and has a patent application pending.

Compliance with Ethics Guidelines. This study was approved by the Ethics Committee, UZA, Wilrijkstraat 10, 2650 Edegem, Belgium (ethisch.comite@uza.be). It was performed in accordance with the Helsinki Declaration of 1964, its later amendments and in compliance with Good Clinical Practice and applicable regulatory requirements. All volunteers provided written informed consent to participate in the study.

Data Availability. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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