Sponsor

Novartis

Generic Drug Name

JDQ443

Trial Indication(s)

Hepatic impairment

Protocol Number

CJDQ443B12103

Protocol Title

A Phase 1, open-label, single-dose, multi-center, parallel group study to evaluate the pharmacokinetics of JDQ443 in participants with mild, moderate or severe hepatic impairment compared to matched healthy control participants

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

- Study initiation date: 03-May-2022 (first participant first visit)
- Early termination date: 11-Jul-2024
- Study completion date: 07-Apr-2024 (last participant last visit)

Reason for Termination

The study was terminated early after the Sponsor decided to discontinue the development of opnurasib (JDQ443) based on business reasons.

Study Design/Methodology

This was a Phase 1, open-label, single-dose, multi-center, parallel group study to evaluate the PK of oral JDQ443 in participants with mild, moderate, and severe HI compared to matched healthy control participants.

The study was comprised of 28-day Screening period (Days −28 to −2), a baseline evaluation period (Day −1), a single dose administration of 200 mg of JDQ443 (Day 1), and a follow-up period of 4 days (Days 2 to 4) for PK sample collection. All participants had a post-study safety follow up contact conducted approximately 30 days after last administration of study treatment.

The study was considered complete once all the participants had finished the required assessments, had dropped out or were lost to follow-up. A total of up to 48 participants were planned to be enrolled in this study. Approximately 8 participants were planned to be enrolled in each HI group, mild (Child-Pugh A; Group 2), moderate (Child-Pugh B; Group 3), and severe (Child Pugh C; Group 4) HI groups (to have at least 6 evaluable participants in each group). Each participant in the healthy control group (Group 1) were matched to 1 or more evaluable participants with HI with respect to age, body weight and sex. Up to 24 participants were planned to be enrolled in the healthy control group to ensure proper matching to each of the 3 HI groups All participants were planned to receive a single 200 mg JDQ443 dose.

Upon completion of the mild and moderate impairment groups and as the matching control participants, an interim analysis (IA) was conducted to compare the PK exposure of the 2 HI groups (Groups 2 and 3) to that of the control participants. The IA was performed to mitigate the potential safety risks in participants with severe HI. If the IA results did not show a clinically relevant

increase in exposure of JDQ443 geometric mean ratios (GMR) for AUC (AUCinf and AUClast) and Cmax (test: reference) < 2 and was well tolerated from a safety perspective (none of the stopping rules met), then severe HI participants were enrolled. Participants with severe HI were enrolled only after the completion of the IA.

Approximately 8 participants were planned to be enrolled in the severe HI group in order to have at least 6 evaluable participants. However, only 5 participants were enrolled because the study was terminated early after the Sponsor decided to discontinue the development of opnurasib (JDQ443) based on business reasons. Due to the study being terminated with < 6 participants in the severe impairment group, only summary statistics were provided for the severe impairment group.

Centers

USA (2)

Objectives:

Primary objectives and related endpoints

Objectives	Endpoints
To assess the systemic pharmacokinetic (PK) properties of JDQ443 after a single oral dose of 200 mg in participants with mild, moderate, or severe HI (Child-Pugh classification) as compared to matched healthy participants with normal hepatic function.	• Primary systemic PK parameters of JDQ443 in plasma including: AUClast, AUCinf, AUC0-t (as needed), Cmax, Tmax. • Secondary PK parameters in plasma including: Tlag, Tlast, T1/2, CL/F, Vz/F.

Secondary objectives and related endpoints

Objectives	Endpoints
• To assess the safety and tolerability of JDQ443 after a single oral dose of 200 mg of JDQ443 in healthy participants and participants with mild, moderate, or severe HI. • To assess JDQ443 plasma protein binding in participants with mild, moderate, or severe HI as compared to matched healthy participants with normal hepatic function.	• All safety endpoints including, vital signs, electrocardiogram (ECG), safety laboratory evaluation and adverse events (AEs). • Unbound fraction (fu) and plasma PK parameters: unbound Cmax (Cmax,u), unbound AUClast (AUClast,u), unbound AUCinf (AUCinf,u), unbound AUC0-t (AUC0-t,u; as needed) and unbound CL/F (CL/F,u).

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational drug JDQ443 100 mg was provided by Novartis Global Clinical Supply and supplied to the Investigator as open-label bulk supplies/medication to the site pharmacist. The site pharmacist or authorized designee was required to dispense the study drug.

Drug was administered at the clinical sites by the study personnel in accordance with the specified study procedures.

Statistical Methods

A linear model, incorporating normal, mild, moderate and severe HI groups, were used to fit the log transformed PK parameters (AUClast, AUCinf, Cmax) of the groups and other baseline covariates of sex, age, and weight, to assess the effect of HI on the PK of a single oral dose of 200 mg JDQ443.

Log transformed PK parameters (AUClast, AUCinf, Cmax) were analyzed using group as fixed effect and sex, age and weight as covariates to compare each of HI group (mild, moderate or severe) to its matching control group (normal hepatic).

For analysis, mild, moderate, or severe are the test group and matching control (normal) was the reference group.

Least squares mean for each group as well as the difference between each hepatically impaired group and its matching control group along with the corresponding 90% confidence interval (CI) on the log-scale were calculated for each PK parameter.

Point estimates of differences between the groups and the corresponding 90% CIs were calculated and anti-logged to obtain the point estimates and 90% CIs for the GMR of the test versus reference on the original scale.

The study was terminated with < 6 participants in the severe HI group; hence the linear model was not run to include all four groups, however the summary statistics were provided for all groups, including severe HI group (Group 4). The healthy matched control participants of the severe HI group were included in the statistical analysis of the mild and moderate healthy controls as those participants were same as matched control with either mild or moderate HI.

The secondary PK as well as safety and tolerability outcome measures, including AEs, serious AEs, cardiovascular safety parameters (12-lead ECG and vital signs), and general safety parameters (blood laboratory parameters) were analyzed descriptively using summary statistics by group (healthy participants, mild, moderate, and severe HI).

For the Interim Analysis (IA): A linear model, incorporating normal, mild and moderate HI groups, were used to fit the log transformed PK parameters (AUClast, AUCinf or Cmax) of the groups and other baseline covariates of sex, age, and weight, to assess the effect of HI on the PK of a single oral dose of 200 mg JDQ443.

Log transformed PK parameters (AUClast, AUCinf or Cmax) were analyzed using group as fixed effect and sex, age, and weight as covariates to compare each of HI group (mild and moderate) to its matching control group (normal hepatic).

For the analysis, mild and moderate were the test group and matching control (normal) was the reference group.

Least squares mean for each group as well as the difference between each hepatically impaired group and its matching control group along with the corresponding 90% CI on the log-scale were calculated for each PK parameter.

Point estimates of differences between the groups and the corresponding 90% CIs were calculated and anti-logged to obtain the point estimates and 90% CIs for the GMR of the test versus reference on the original scale.

If the IA results (results of statistical analysis) did not show a clinically relevant increase in exposure for mild and moderate impairment group [GMR for AUC (AUCinf and AUClast and Cmax (test: reference) < 2] and JDQ443 was well tolerated from a safety perspective (none of the stopping rules met), then participants with severe HI were enrolled (Group 4) plus additional healthy matched controls as needed in the study.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion criteria

Participants eligible for inclusion in this study must have met all of the following key criteria:

- Signed informed consent must have been obtained before any assessment was performed.
- Male or female participants of non-childbearing potential 18 to 75 years of age (inclusive).
- Participants weight must have been at least 50.0 kg to participate in the study and must have had a body mass index within the range of 18 to 40 kg/m^2.
- Must have had the ability to communicate well with the Investigator, to understand and comply with the requirements of the study.
- Participant must have remained in the clinical research unit as required by the protocol.

Participants with mild, moderate, or severe HI (Groups 2, 3, and 4) must have met the following criteria:

- Seated vital signs within the following ranges at screening:
  - Body temperature, 35.0 to 37.5°C, inclusive.
  - Systolic blood pressure, 89 to 160 mmHg, inclusive.
  - Diastolic blood pressure, 50 to 100 mmHg, inclusive.
  - Pulse rate, 50 to 100 bpm, inclusive.
- Participants with HI as defined by the Child-Pugh classification for severity of liver disease and have the same Child-Pugh score in line with HI of one of the following groups at screening and baseline:
  - Group 2; mild; Child-Pugh score 5-6, inclusive; Class A.
  - Group 3; moderate; Child-Pugh score 7-9, inclusive; Class B.
  - Group 4; severe; Child-Pugh score 10-15, inclusive; Class C.
- Stable Child-Pugh score (+/- 2 scores), and liver status with no significant alteration as determined by the Investigator within 28 days prior to dosing of study treatment.
- Participants with HI with other stable medical disorders such as controlled diabetes, hyperlipidemia, hypothyroidism, etc., were eligible as long as they were considered appropriate for enrollment as determined by the Investigator by medical history, physical examination, ECG, and clinical laboratory tests at screening and baseline.

Key Exclusion criteria

Participants who met any of the following criteria were not eligible for inclusion in this study:

- Use of other investigational drugs within the last 30 days or 5 half-lives prior to dosing, whichever was longer.
- Use of drugs (prescription, non-prescription and herbal remedies such as St John's wort) known to affect cytochrome p 3A, including both strong and moderate inhibitors and inducers, within 2 weeks prior to dosing until completion of the End-of-study (EOS) visit.
- Contradiction or hypersensitivity to the investigational compound/compound class or its excipients being used in this study.

- Pregnant or nursing (lactating) women. Pregnancy is defined as the state of a female after conception and until termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test.

Known history of, or current clinically significant arrhythmias, history of prolonged QT correction formula (QTcF) interval or QTcF > 480 msec.

Participant Flow Table:

Disposition at Screening (All Screened participants)

Disposition Reason	Overall (N=58) n (%)
Screened	
Completed screening phase and treated	33 (56.9)
Completed screening, not treated	1 (1.7)
Did not Complete screening	24 (41.4)
Primary reason for study discontinuation	
Participant withdraws consent	1 (1.7)
Screen Failure	23 (39.7)
Other	1 (1.7)

N = Number of participants for overall screened; n = Number of participants in that category; % = (n/N)*100.
Source: [Table 14.1-1.1]

Participant disposition (Safety analysis set)

Disposition Reason	Normal Hepatic function (N=12) n (%)	Mild HI (N=8) n (%)	Moderate HI (N=8) n (%)	Severe HI (N=5) n (%)	Overall (N=33) n (%)
Participant					
Completed	12 (100)	8 (100)	8 (100)	5 (100)	33 (100)

HI = Hepatic impairment; N = Number of participants in the safety analysis set in respective group or overall; n = Number of participants in that category in safety analysis set in respective group or overall; % = (n/N)*100.
Source: [Table 14.1-1.2]

Baseline Characteristics

Characteristic	Statistics	Normal Hepatic Function (N=12)	Mild HI (N=8)	Moderate HI (N=8)	Severe HI (N=5)	Overall (N=33)
Age (years)	n	12	8	8	5	33
	Mean (SD)	60.5 (9.62)	61.1 (7.24)	62.0 (7.19)	53.8 (5.72)	60.0 (8.13)
	Median	65.0	65.0	61.0	54.0	61.0
	Min, Max	40, 70	50, 69	49, 72	46, 61	40, 72
Sex - n(%)	Male	6 (50.0)	3 (37.5)	4 (50.0)	2 (40.0)	15 (45.5)
	Female	6 (50.0)	5 (62.5)	4 (50.0)	3 (60.0)	18 (54.5)
Race - n(%)	Asian	0	1 (12.5)	0	0	1 (3.0)
	Black or African American	1 (8.3)	2 (25.0)	0	0	3 (9.1)
	White	11 (91.7)	5 (62.5)	8 (100)	5 (100)	29 (87.9)
Ethnicity - n(%)	Hispanic or Latino	5 (41.7)	4 (50.0)	4 (50.0)	3 (60.0)	16 (48.5)
	Not Hispanic or Latino	6 (50.0)	4 (50.0)	4 (50.0)	2 (40.0)	16 (48.5)
	Unknown	1 (8.3)	0	0	0	1 (3.0)
Weight (kg)	n	12	8	8	5	33
	Mean (SD)	80.89 (14.566)	87.33 (18.419)	89.64 (10.956)	89.26 (9.743)	85.84 (14.157)
	Median	86.40	85.45	90.90	86.40	87.10
	Min, Max	54.5, 99.2	64.5, 116.1	67.4, 104.5	77.2, 99.9	54.5, 116.1
Height (cm)	n	12	8	8	5	33
	Mean (SD)	171.33 (9.540)	166.38 (10.084)	167.10 (8.269)	167.30 (7.887)	168.49 (9.007)
	Median	169.00	161.50	165.50	168.00	167.50
	Min, Max	158.0, 188.0	157.0, 179.0	157.0, 180.5	155.0, 177.0	155.0, 188.0
Body Mass Index (kg/m^2)	n	12	8	8	5	33
	Mean (SD)	27.53 (4.693)	31.30 (4.133)	32.15 (3.712)	31.84 (2.104)	30.22 (4.385)
	Median	27.25	31.80	31.80	31.90	30.60

Characteristic	Statistics	Normal Hepatic Function (N=12)	Mild HI (N=8)	Moderate HI (N=8)	Severe HI (N=5)	Overall (N=33)
	Min, Max	21.5,37.8	24.3,36.6	25.7,37.8	29.5,35.1	21.5,37.8
Child-Pugh Total Score	n		8	8	5	21
	Mean (SD)		5.1 (0.35)	7.4 (0.52)	11.0 (1.00)	7.4 (2.38)
	Median		5.0	7.0	11.0	7.0
	Min, Max		5, 6	7, 8	10, 12	5, 12

BMI = body mass index; N = Number of participants in the safety analysis set in respective group or overall; n = Number of participants in specific category in safety analysis set in respective group or overall.

Height, Weight, BMI, and Child-Pugh total score at Screening visit are considered for calculation of summary statistics.

Child-Pugh total score is considered only for HI groups.

Source: [Table 14.1-3.1]

Outcome Result(s)

Plasma concentrations and single-dose PK parameters of total JDQ443 and unbound JDA443 were determined. Pharmacokinetic parameters of JDQ443 (Cmax, Tmax, Tlag, AUClast, AUCinf, T1/2, CL/F, and Vz/F) were determined using non compartmental data analysis of plasma concentration-time data (Phoenix WinNonlin Version 8.3).

- Primary PK parameters: Tmax, Cmax, AUClast, AUCinf
- Secondary PK parameters: T1/2, CL/F, Vz/F, Tlag, Tlast
- Unbound Cmax (Cmax,u), unbound AUClast (AUClast,u), unbound AUCinf (AUCinf,u), and unbound CL/F (CL/F,u).

Summary statistics of PK parameters for plasma total JDQ443 by group (Pharmacokinetic analysis set)

Compound: JDQ443, Matrix: Plasma, Analyte: JDQ443

Group	Statistics	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)	Tlag (h)	Tlast (h)	T1/2 (h)	CL/F (L/h)	Vz/F (L)	Lambda_z (1/h)
Mild HI (N=8)	n	8	8	8	8	8	8	8	8	8	8
	Mean (SD)	2470 (776)	22200 (7650)	22400 (7650)				6.68 (3.17)	10.0 (3.76)	98.8 (60.7)	0.119 (0.0376)
	CV% mean	31.4	34.4	34.2				47.5	37.5	61.5	31.6
	Geo-mean	2360	21000	21200				6.18	9.45	84.2	0.112
	CV% geo-mean	33.2	37.9	37.6				41.0	37.6	65.5	41.0
	Median	2580	22600	22800	3.50	0.00	42.00	5.19	8.89	72.5	0.133
	Min; Max	1430; 3840	11900; 32900	12000; 32900	2.00; 6.00	0.00; 0.50	36.00; 72.08	4.34; 13.4	6.07; 16.7	42.6; 192	0.0516; 0.160
Moderate HI (N=8)	n	8	8	8	8	8	8	8	8	8	8
	Mean (SD)	1720 (643)	16100 (7440)	16300 (7460)				4.74 (0.841)	15.1 (7.43)	101 (46.9)	0.150 (0.0251)
	CV% mean	37.4	46.1	45.9				17.7	49.2	46.5	16.8
	Geo-mean	1590	14600	14700				4.68	13.6	91.8	0.148
	CV% geo-mean	46.3	52.5	52.1				17.3	52.1	49.0	17.3
	Median	1970	17000	17100	6.00	0.00	36.00	4.55	11.8	80.9	0.152
	Min; Max	782; 2440	7410; 28900	7450; 29100	2.00; 6.00	0.00; 1.00	24.00; 48.00	3.64; 6.30	6.87; 26.9	48.8; 167	0.110; 0.190
Severe HI (N=4)	n	4	4	3	4	4	4	3	3	3	3
	Mean (SD)	1430 (929)	16600 (14500)	19000 (17000)				6.12 (1.28)	26.6 (31.3)	250 (319)	0.117 (0.0279)

Group	Statistics	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)	Tlag (h)	Tlast (h)	T1/2 (h)	CL/F (L/h)	Vz/F (L)	Lambda_z (1/h)
	CV% mean	64.9	87.3	89.3				20.9	117.7	127.4	23.8
	Geo-mean	1160	11600	12600				6.02	15.9	138	0.115
	CV% geo-mean	96.7	144.4	194.4				22.8	194.4	215.1	22.8
	Median	1460	13500	16900	5.00	0.00	30.00	6.85	11.8	79.2	0.101
	Min; Max	408; 2400	2920; 36700	3200; 37000	4.00; 8.03	0.00; 0.00	24.00; 48.00	4.64; 6.86	5.40; 62.5	53.5; 618	0.101; 0.149
Normal Hepatic function (N=12)	n	12	12	12	12	12	12	12	12	12	12
	Mean (SD)	2430 (811)	22800 (11900)	23100 (12100)				6.35 (1.77)	10.3 (4.38)	91.1 (36.2)	0.117 (0.0317)
	CV% mean	33.4	52.3	52.5				27.8	42.5	39.7	27.1
	Geo-mean	2310	20800	21000				6.14	9.51	84.1	0.113
	CV% geo-mean	33.2	45.3	45.2				27.8	45.2	45.1	27.8
	Median	2320	20400	20500	4.00	0.00	48.00	6.10	9.79	82.0	0.114
	Min; Max	1230; 4370	8960; 57400	9190; 58300	1.50; 6.00	0.00; 0.50	24.00; 48.00	3.88; 10.3	3.43; 21.8	36.3; 151	0.0676; 0.179

N: number of participants in pharmacokinetic analysis set in respective group; n = number of observations used for analysis.
CV% = sd/mean*100; CV% Geo-mean = sqrt (exp(variance for log transformed data)-1) * 100; Geo = Geometric.
For Tmax, Tlag and Tlast only n, median, min and max are displayed.
This table is presented based on Child-Pugh criteria.
Source: [Table 14.2-2.1]

Statistical analysis of plasma total JDQ443 primary PK parameters (Pharmacokinetic analysis set)

Compound: JDQ443, Matrix: Plasma, Analyte: JDQ443

				Group Comparison		
PK Parameter (unit)	Group	n	Adjusted geo-mean (90% CI)	Comparison	Geo-mean ratio (Test/Reference)	(90% CI)
Cmax (ng/mL)	Normal Hepatic function (Reference)	12	2320 (1980, 2730)			
	Mild HI (Test)	8	2150 (1760, 2610)	Test vs Reference	0.923	(0.715, 1.19)
	Moderate HI (Test)	8	1610 (1320, 1950)	Test vs Reference	0.691	(0.532, 0.896)

				Group Comparison		
PK Parameter (unit)	**Group**	**n**	**Adjusted geo-mean (90% CI)**	**Comparison**	**Geo-mean ratio (Test/Reference)**	**(90% CI)**
AUClast (h*ng/mL)	Normal Hepatic function (Reference)	12	20900 (17100, 25700)			
	Mild HI (Test)	8	19000 (14800, 24500)	Test vs Reference	0.908	(0.656, 1.26)
	Moderate HI (Test)	8	14700 (11500, 18900)	Test vs Reference	0.702	(0.504, 0.977)
AUCinf (h*ng/mL)	Normal Hepatic function (Reference)	12	21200 (17300, 25900)			
	Mild HI (Test)	8	19200 (14900, 24600)	Test vs Reference	0.905	(0.656, 1.25)
	Moderate HI (Test)	8	14800 (11600, 19000)	Test vs Reference	0.701	(0.504, 0.973)

n = number of observations used for analysis.

Model is a linear model of the log-transformed PK parameters of plasma total JDQ443, the model included age group (< 65 years, >= 65 years), sex, weight, and group as fixed factors.

Results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI. This table is presented based on Child-Pugh criteria.

Source: [Table 14.2-3.1]

Non-parametric analysis: Hodges-Lehmann Test for Tmax to assess plasma total JDQ443 effect of group (Pharmacokinetic analysis set)

Compound: JDQ443, Matrix: Plasma, Analyte: JDQ443

				Group Comparison		
PK Parameter (unit)	**Group**	**n**	**Median (Q1, Q3)**	**Comparison**	**Median Difference**	**(90% CI)**
Tmax (h)	Normal Hepatic function (Reference)	12	4.00 (4.00, 4.00)			
	Mild HI (Test)	8	3.50 (2.50, 4.00)	Test vs Reference	-0.50	(-2.00, 0.00)
	Moderate HI (Test)	8	6.00 (3.00, 6.00)	Test vs Reference	2.00	(-1.00, 2.00)

n = number of observations used for analysis. Q1= first quartile; Q3= third quartile.

The median difference and 90% CI of the median difference are from Hodges-Lehmann method.

Source: [Table 14.2-3.4]

Summary statistics of PK parameters for plasma unbound JDQ443 by group (Pharmacokinetic analysis set)

Compound: JDQ443, Matrix: Plasma, Analyte: JDQ443

Group	Statistics	FU (Ratio)	Cmax,u (ng/mL)	AUClast,u (h*ng/mL)	AUCinf,u (h*ng/mL)	CL/F,u (L/h)	Vz/F,u (L)
Mild HI (N=8)	n	8	8	8	8	8	8
	Mean (SD)	0.00375 (0.00150)	8.46 (2.01)	76.7 (23.0)	77.3 (23.0)	2840 (1020)	30900 (28400)
	CV% mean	40.1	23.8	30.0	29.8	36.0	91.7
	Geo-mean	0.00349	8.25	73.3	73.9	2700	24100
	CV% geo-mean	42.2	24.3	33.9	33.7	33.7	77.2
	Median	0.00380	8.23	76.0	76.3	2620	18400
	Min; Max	0.00199; 0.00645	5.71; 11.8	39.9; 106	40.2; 107	1870; 4980	11700; 96600
Moderate HI (N=8)	n	8	8	8	8	8	8
	Mean (SD)	0.00328 (0.000907)	5.20 (1.35)	48.5 (16.2)	48.9 (16.3)	4500 (1460)	30100 (8600)
	CV% mean	27.7	26.0	33.3	33.2	32.4	28.6
	Geo-mean	0.00317	5.05	46.2	46.6	4290	29000
	CV% geo-mean	29.1	26.7	34.6	34.4	34.4	30.4
	Median	0.00341	5.12	44.1	44.3	4560	30900
	Min; Max	0.00226; 0.00458	3.33; 7.25	30.2; 71.7	31.0; 72.8	2750; 6450	19500; 41900
Severe HI (N=4)	n	4	4	4	3	3	3
	Mean (SD)	0.00261 (0.000934)	3.30 (1.82)	36.9 (28.4)	43.1 (31.8)	7750 (6960)	71300 (72500)
	CV% mean	35.7	55.0	76.8	73.8	89.8	101.6
	Geo-mean	0.00251	2.90	29.1	34.0	5880	51100
	CV% geo-mean	32.7	65.9	96.6	112.8	112.8	124.7
	Median	0.00223	3.32	30.3	40.4	4950	33100
	Min; Max	0.00201; 0.00399	1.63; 4.94	11.7; 75.5	12.8; 76.2	2620; 15700	26000; 155000
Normal Hepatic function (N=12)	n	12	12	12	12	12	12
	Mean (SD)	0.00230 (0.000417)	5.45 (1.64)	50.0 (18.8)	50.6 (19.0)	4450 (1620)	39600 (14800)
	CV% mean	18.1	30.2	37.5	37.5	36.4	37.3
	Geo-mean	0.00227	5.24	47.1	47.7	4200	37100
	CV% geo-mean	19.1	29.5	37.2	37.0	37.0	39.1

Group	Statistics	FU (Ratio)	Cmax,u (ng/mL)	AUClast,u (h*ng/mL)	AUCinf,u (h*ng/mL)	CL/F,u (L/h)	Vz/F,u (L)
	Median	0.00238	5.30	47.5	48.5	4120	36300
	Min; Max	0.00167; 0.00279	3.20; 9.21	23.3; 95.9	23.9; 97.3	2060; 8370	21800; 61400

N: number of participants in pharmacokinetic analysis set in respective group; n = number of observations used for analysis.

CV% = sd/mean*100; CV% Geo-mean = sqrt (exp(variance for log transformed data)-1) * 100; Geo = Geometric. FU = The unbound concentrations were calculated by multiplying the respective JDQ443 concentrations by the plasma protein unbound fraction at 4h (i.e., unbound concentration= total concentration*plasma protein unbound fraction).

This table is presented based on Child-Pugh criteria.

Source: [Table 14.2-2.2]

Statistical analysis of plasma unbound JDQ443 primary PK parameters (Pharmacokinetic analysis set)

Compound: JDQ443, Matrix: Plasma, Analyte: JDQ443

				Group Comparison		
PK Parameter (unit)	**Group**	**n**	**Adjusted geo-mean (90% CI)**	**Comparison**	**Geo-mean ratio (Test/Reference)**	**(90% CI)**
Cmax,u (ng/mL)	Normal Hepatic function (Reference)	12	5.20 (4.50, 6.02)			
	Mild HI (Test)	8	8.21 (6.86, 9.82)	Test vs Reference	1.58	(1.25, 1.99)
	Moderate HI (Test)	8	5.10 (4.27, 6.09)	Test vs Reference	0.980	(0.774, 1.24)
AUClast,u (h*ng/mL)	Normal Hepatic function (Reference)	12	46.9 (38.9, 56.4)			
	Mild HI (Test)	8	72.8 (57.9, 91.5)	Test vs Reference	1.55	(1.16, 2.09)
	Moderate HI (Test)	8	46.6 (37.2, 58.5)	Test vs Reference	0.995	(0.737, 1.34)
AUCinf,u (h*ng/mL)	Normal Hepatic function (Reference)	12	47.4 (39.4, 57.0)			
	Mild HI (Test)	8	73.3 (58.4, 92.1)	Test vs Reference	1.55	(1.15, 2.08)
	Moderate HI (Test)	8	47.1 (37.6, 59.0)	Test vs Reference	0.994	(0.737, 1.34)

n = number of observations used for analysis.

Model is a linear model of the log-transformed PK parameters of plasma JDQ443, the model included age group (< 65 years, >= 65 years), sex, weight, and group as fixed factors.

Results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI. This table is presented based on Child-Pugh criteria.

Source: [Table 14.2-3.2]

Safety Results

Overall incidence of AEs – number of events and number of participants (Safety analysis set)

	Normal Hepatic function (N=12) nE, nS (%)	Mild HI (N=8) nE, nS (%)	Moderate HI (N=8) nE, nS (%)	Severe HI (N=5) nE, nS (%)	Overall (N=33) nE, nS (%)
Participants with at least 1 AE	0	0	2, 2 (25.0)	0	2, 2 (6.1)
AEs of grade 1	0	0	1, 1 (12.5)	0	1, 1 (3.0)
AEs of grade 2	0	0	1, 1 (12.5)	0	1, 1 (3.0)
AEs of grade 3	0	0	0	0	0
AEs of grade 4	0	0	0	0	0
AEs of grade 5	0	0	0	0	0
AEs related to study drug	0	0	1, 1 (12.5)	0	1, 1 (3.0)
Serious AEs	0	0	0	0	0
AEs leading to discontinuation of study drug	0	0	0	0	0
Study-drug related AEs leading to discontinuation of study drug	0	0	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = Number of participants in safety analysis set in respective group or overall. nE = Number of AEs in the category; nS = Number of participants with at least 1 AE in the category. % = (nS/N)*100

CTCAE Grade: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life threatening; Grade 5 = Death.

CTCAE version 5.0 is used.

Only on-treatment period AEs are presented in this table.

Source: [Table 14.3.1-1.1.8]

Participants with adverse events by primary system organ class and group (Safety analysis set)

Primary system organ class	Normal Hepatic function (N=12) nE, nS (%)	Mild HI (N=8) nE, nS (%)	Moderate HI (N=8) nE, nS (%)	Severe HI (N=5) nE, nS (%)	Overall (N=33) nE, nS (%)
Number of participants with at least 1 AE	0	0	2 (25.0)	0	2 (6.1)
Nervous system disorders	0	0	2 (25.0)	0	2 (6.1)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of participants in safety analysis set in respective group or overall; n = Number of participants with at least 1 AE in the category; % = n/N*100.

A participant with multiple AEs is counted only once in the “at least 1 AE” row. A participant with multiple AEs within a primary system organ class is counted only once for that primary system organ class and HI impairment group.

MedDRA version 27.0 coding dictionary applied. Only on-treatment period AEs are presented in this table.

Source: [Table 14.3.1-1.1.1]

Conclusion:

This was an open-label, single-dose, multi-center, parallel group study to evaluate the PK of oral KRAS G12C inhibitor JDQ443 in participants with mild, moderate and severe HI compared to matched healthy control participants.

A total of 33 participants were enrolled in the study. All 33 participants received study drug and were included in the safety analysis set. However, one participant received 100 mg of study treatment instead of 200 mg on Day 1 and therefore was excluded from the PK analysis set.

Overall, the peak and total exposure of plasma total JDQ443 decreased with an increased degree of HI, while the peak and total exposure of plasma unbound JDQ443 increased in the mild HI group but was similar in the moderate HI group compared to the normal hepatic function group.

The disposition of unbound JDQ443 was compared in participants with HI and participants with normal hepatic function. The total body clearance of unbound JDQ443 (CL/F,u) was reduced by about 35.7% in participants with mild HI and was increased by 2.14% and 40.0% in participants with moderate and severe HIs, respectively. Half-life of total JDQ443 (T1/2) was not changed in participants with mild, moderate, or severe HI. Protein binding of JDQ443 (FU) showed no trend with increased degree of hepatic function. Metabolite ratio of the peak and total exposure for plasma HZC320 increased with increasing degree of HI.

Overall, JDQ443 was well tolerated after a single 200 mg oral dose in healthy participants and participants with mild, moderate, or severe HI.

Date of Clinical Study Report

30-Jan-2025