NOVARTIS

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Icenticaftor

Trial Indication(s)

hepatic impairment

Protocol Number

CQBW251A2104

Protocol Title

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

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1

Study Start/End Dates

Study Start Date: October 30, 2020 (Actual)
Primary Completion Date: September 15, 2022 (Actual)
Study Completion Date: September 15, 2022 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a Phase 1, open-label, single-dose, parallel group study to evaluate the systemic PK of icenticaftor in participants with mild, moderate, or severe hepatic impairment (HI) compared to matched healthy control participants.

The healthy control participants in Group 1 were matched 1:1 to a participant with HI, with respect to gender, age (± 10 years), body weight (± 15%), and smoking status (smoker or non-smoker). Each participant in the healthy control group (Group 1) may have been matched to 1 or more evaluable participant with HI, but could not be matched to more than 1 participant from the same HI group.

Participants who met the eligibility criteria at Screening were admitted to the study site for Baseline evaluations. Baseline safety assessments were performed on Day -1. Each participant received a single oral dose of 300 mg icenticaftor on Day 1 under fasting conditions.

PK samples were collected prior to dosing (0 hours) and at the specified postdose time points on Day 1 (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours), Day 2 (24 and 36 hours), Day 3 (48 hours), Day 4 (72 hours), Day 5 (96 hours), Day 6 (120 hours), Day 7 (144 hours), and Day 8 (168 hours) as indicated in the protocol. The free fraction in plasma fraction unbound (fu) of icenticaftor was evaluated at 3 hours postdose using equilibrium dialysis method.

The planned total duration of this study was approximately 8 days from the first Baseline visit to the EOS visit. End of Study (EOS) procedures were completed 7 days after dosing of study treatment and a post-study safety contact (e.g., follow-up telephone call, e-mail) took place approximately 30 days after dosing of study treatment.

Centers

United States(2)

Objectives:

Primary:

• To assess the systemic pharmacokinetic (PK) properties of icenticaftor after a single oral dose of 300 mg in participants with mild, moderate, or severe hepatic impairment (HI) (Child-Pugh classification) as compared to matched healthy control participants with normal hepatic function.

Secondary:

• To assess the safety and tolerability of icenticaftor after a single oral dose of 300 mg in participants with mild, moderate, or severe HI (Child-Pugh classification) as compared to matched healthy control participants with normal hepatic function.

• To assess the relationship between Baseline hepatic function parameters and icenticaftor PK parameters.

• To assess the plasma protein binding free fraction of icenticaftor (fu) in participants with mild, moderate, or severe HI (Child-Pugh classification) as compared to matched healthy control participants, and its effect on PK parameters.

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

Single oral dose of Icenticaftor (QBW251) 300 mg was administered.

Statistical Methods

The natural log (ln)-transformed PK parameters (Cmax, AUClast, and AUCinf) for icenticaftor were separately analyzed using analysis of covariance (ANCOVA) models with group and matching covariates (sex, age, weight and smoking status) as fixed effects. Least-squares means (LSMs) for each group as well as the difference between each HI group and the matched healthy participants (reference group) and the difference between each HI group and matching healthy control participants along with the corresponding 90% confidence interval (CI) on the log-scale were calculated for each PK parameter and back-transformed ratios and 90% CIs were provided. The secondary analysis consisted of comparing each HI group to the pooled healthy participants. There were no adjustments for multiple comparisons.

NOVARTIS

Study Population: Key Inclusion/Exclusion Criteria

All Participants:
Inclusion Criteria:
• Male and non-child bearing potential female participants, 18 to 75 years of age (inclusive) at Screening.
• Participants must weigh at least 50.0 kg and must have a body mass index (BMI) within the range of 18.0 to 38.0 kg/m2, inclusive, at Screening.
• Must be a non-smoker or agree to smoke no more than 5 cigarettes (or equivalent) per day from Screening until the End of Study. Participants must maintain the same smoking status throughout the study (i.e. smoker or non smoker).
Exclusion Criteria:
• Use of other investigational drugs within 5 half-lives prior to dosing of study treatment, or within 30 days, whichever is longer; or longer if required by local regulations.
• Are taking medications prohibited to be taken with the study treatment
• Known history of, or current clinically significant arrhythmias. Have clinically significant ECG abnormality or history of long-QT syndrome or whose QT interval corrected by Fridericia's formula (QTcF) is prolonged (> 480 msec) at Screening. Participants having myocardial infarction ≥ 5 years ago are eligible to participate.
• Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.

Healthy Participants:
• Each participant must match in age (± 10 years), gender, weight (± 15%), and smoking status to participants in Group 2, 3, or 4.
• Seated vital signs must be within the following ranges at Screening and Baseline:
• Body temperature, 35.0 to 37.5°C, inclusive.
• Systolic blood pressure, 89 to 149 mmHg, inclusive.
• Diastolic blood pressure, 50 to 89 mmHg, inclusive.
• Pulse rate, 40 to 90 bpm, inclusive.
• Participants must be in good health as determined by medical history, physical examination, ECG, and clinical laboratory tests at Screening.
Exclusion Criteria:
• Liver disease or liver injury as indicated by abnormal liver function tests.
• Chronic infection with HBV or HCV.
• History or presence of impaired renal function.

Hepatic Impairment Participants:
Inclusion Criteria:
• Seated vital signs must be within the following ranges at Screening and Baseline:

• Body temperature, 35.0 to 37.5°C, inclusive.
• Systolic blood pressure, 89 to 159 mmHg, inclusive.
• Diastolic blood pressure, 50 to 99 mmHg, inclusive.
• Pulse rate, 50 to 99 bpm, inclusive.
• Hepatic impairment as defined by the Child-Pugh classification for severity of liver disease
Exclusion Criteria:
• Have severe complications of liver disease within the preceding 3 months of Screening.
• Emergency room visit or hospitalization due to liver disease within the preceding 3 months of Screening.
• Have received liver transplant at any time in the past.
• Have encephalopathy Grade 3 or worse within 28 days prior to dosing of study treatment.
• Have acute hepatitis B (HBV) or hepatitis C (HCV) infection.
• Clinically significant abnormal findings in physical examination or clinical laboratory evaluations not consistent with known liver disease.
Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

	QBW251 300mg in Healthy participants	QBW251 300mg with mild hepatic impairment	QBW251 300mg with moderate hepatic impairment	QBW251 300mg with severe hepatic impairment	Total
Arm/Group Description	QBW251 300 mg single oral dose. Healthy participants with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.	
Started	18	8	8	6	40
Completed	17	8	8	6	39
Not Completed	1	0	0	0	1
Withdrawal by Subject	1	0	0	0	1

NOVARTIS

Baseline Characteristics

	QBW251 300mg in Healthy participants	QBW251 300mg with mild hepatic impairment	QBW251 300mg with moderate hepatic impairment	QBW251 300mg with severe hepatic impairment	Total
Arm/Group Description	QBW251 300 mg single oral dose. Healthy participants with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.	
Number of Participants [units: participants]	18	8	8	6	40
Baseline Analysis Population Description					
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation					
	59.6±6.25	59.3±6.32	61.9±4.32	59.3±7.28	59.9±5.95
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants					
Female	7	2	6	2	17
Male	11	6	2	4	23
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants					
Asian	0	1	0	0	1
Black or African American	2	2	2	0	6
White	16	5	6	6	33

NOVARTIS

Primary Outcome Result(s)

Maximum observed icenticaftor plasma concentration (Cmax)

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Cmax is the maximum (peak) observed plasma concentration of icenticaftor after single oral dose.
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI

	QBW251 300mg in Healthy Matched Control (Mild HI)	**QBW251 300mg in Healthy Matched Control (Moderate HI)**	**QBW251 300mg in Healthy Matched Control (Severe HI)**	**QBW251 300mg with mild hepatic impairment**	**QBW251 300mg with moderate hepatic impairment**	**QBW251 300mg with severe hepatic impairment**
Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Maximum observed icenticaftor plasma concentration (Cmax) (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	1040 (60.8%)	1220 (44.2%)	1150 (48.3%)	1310 (53.4%)	785 (51.7%)	1440 (48.5%)

NOVARTIS

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Mild HI), QBW251 300mg with mild hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	1.33	Geometric Mean Ratio (GMR) = Test/Reference. Mild HI (Test) vs Healthy Matched Control (Mild HI) (Reference)
90 % Confidence Interval 2-Sided	0.74 to 2.39	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Moderate HI), QBW251 300mg with moderate hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	0.66	Geometric Mean Ratio (GMR) = Test/Reference. Moderate HI (Test) vs Healthy Matched Control (Moderate HI) (Reference)
90 % Confidence Interval 2-Sided	0.45 to 0.97	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Severe HI), QBW251 300mg with severe hepatic impairment

Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	1.23	Geometric Mean Ratio (GMR) = Test/Reference. Severe HI (Test) vs Healthy Matched Control (severe HI) (Reference)
90 % Confidence Interval 2-Sided	0.85 to 1.77	

Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of icenticaftor

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. AUClast is the area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration (tlast) of icenticaftor
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

	QBW251 300mg in Healthy Matched Control (Mild HI)	QBW251 300mg in Healthy Matched Control (Moderate HI)	QBW251 300mg in Healthy Matched Control (Severe HI)	QBW251 300mg with mild hepatic impairment	QBW251 300mg with moderate hepatic impairment	QBW251 300mg with severe hepatic impairment
Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.

Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of icenticaftor (units: ng*h/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	4880 (35.3%)	5220 (30.8%)	4720 (29.4%)	3850 (44.2%)	5000 (41.9%)	11500 (13.0%)

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Mild HI), QBW251 300mg with mild hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA Geometric Mean Ration	
Other Geometric Mean Ration	0.79	Geometric Mean Ratio (GMR) = Test/Reference. Mild HI (Test) vs Healthy Matched Control (Mild HI) (Reference)
90 % Confidence Interval 2-Sided	0.52 to 1.19	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Moderate HI), QBW251 300mg with moderate hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	

Other Geometric Mean Ratio	0.97	Geometric Mean Ratio (GMR) = Test/Reference. Moderate HI (Test) vs Healthy Matched Control (Moderate HI) (Reference)
90 % Confidence Interval 2-Sided	0.72 to 1.31	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Severe HI), QBW251 300mg with severe hepatic impairment
Type of Statistical Test	Other
Method	ANCOVA

Other Geometric Mean Ratio	2.48	Geometric Mean Ratio (GMR) = Test/Reference. Severe HI (Test) vs Healthy Matched Control (severe HI) (Reference)
90 % Confidence Interval 2-Sided	1.97 to 3.13	

Area under plasma concentration-time curve from time zero to infinity (AUCinf) of icenticaftor

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. The AUC from time zero to infinity.
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

QBW251 300mg in Healthy Matched Control (Mild HI)	QBW251 300mg in Healthy Matched Control (Moderate HI)	QBW251 300mg in Healthy Matched Control (Severe HI)	QBW251 300mg with mild hepatic impairment	QBW251 300mg with moderate hepatic impairment	QBW251 300mg with severe hepatic impairment

Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Area under plasma concentration-time curve from time zero to infinity (AUCinf) of icenticaftor (units: ng*h/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	4920 (35.0%)	5270 (30.5%)	4770 (29.1%)	3900 (43.3%)	5070 (41.5%)	11700 (12.9%)

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Mild HI), QBW251 300mg with mild hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	0.79	Geometric Mean Ratio (GMR) = Test/Reference. Mild HI (Test) vs Healthy Matched Control (Mild HI) (Reference)
90 % Confidence Interval 2-Sided	0.53 to 1.19	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Moderate HI), QBW251 300mg with moderate hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	0.97	Geometric Mean Ratio (GMR) = Test/Reference. Moderate HI (Test) vs Healthy Matched Control (Moderate HI) (Reference)
90 % Confidence Interval 2-Sided	0.72 to 1.31	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Severe HI), QBW251 300mg with severe hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	2.49	Geometric Mean Ratio (GMR) = Test/Reference. Severe HI (Test) vs Healthy Matched Control (severe HI) (Reference)
90 % Confidence Interval 2-Sided	1.98 to 3.15	

Time to reach maximum icenticaftor plasma concentration (Tmax)

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Tmax is the time to reach maximum (peak) drug concentration after single-dose administration.
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose

Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

	QBW251 300mg in Healthy Matched Control (Mild HI)	QBW251 300mg in Healthy Matched Control (Moderate HI)	QBW251 300mg in Healthy Matched Control (Severe HI)	QBW251 300mg with mild hepatic impairment	QBW251 300mg with moderate hepatic impairment	QBW251 300mg with severe hepatic impairment
Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Time to reach maximum icenticaftor plasma concentration (Tmax) (units: hours)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**
	2.00 (0.50 to 6.00)	1.50 (0.50 to 3.00)	1.00 (1.00 to 2.00)	1.00 (0.50 to 2.00)	3.00 (0.50 to 4.00)	1.00 (0.50 to 2.00)

Apparent plasma clearance (CL/F) of icenticaftor

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. CL/F is the apparent total body clearance of icenticaftor from plasma following extravascular administration.
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

	QBW251 300mg in Healthy Matched Control (Mild HI)	QBW251 300mg in Healthy Matched Control (Moderate HI)	QBW251 300mg in Healthy Matched Control (Severe HI)	QBW251 300mg with mild hepatic impairment	QBW251 300mg with moderate hepatic impairment	QBW251 300mg with severe hepatic impairment
Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Apparent plasma clearance (CL/F) of icenticaftor (units: L/h)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	64.3 ± 23.2	59.4 ± 21.0	65.0 ± 17.8	83.9 ± 43.2	63.3 ± 24.7	25.9 ± 3.27

Apparent volume of distribution during terminal phase (Vz/F) of icenticaftor

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Vz/F is the apparent volume of distribution during terminal elimination phase following extravascular administration.
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

	QBW251 300mg in Healthy Matched Control (Mild HI)	QBW251 300mg in Healthy Matched Control (Moderate HI)	QBW251 300mg in Healthy Matched Control (Severe HI)	QBW251 300mg with mild hepatic impairment	QBW251 300mg with moderate hepatic impairment	QBW251 300mg with severe hepatic impairment

Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Apparent volume of distribution during terminal phase (Vz/F) of icenticaftor (units: Liter)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	1960 ± 968	1990 ± 827	2410 ± 903	2360 ± 1820	2330 ± 1150	1080 ± 250

Elimination half-life (T1/2) of icenticaftor

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. T1/2 is the elimination half-life associated with the terminal slope.
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

	QBW251 300mg in Healthy Matched Control (Mild HI)	**QBW251 300mg in Healthy Matched Control (Moderate HI)**	**QBW251 300mg in Healthy Matched Control (Severe HI)**	**QBW251 300mg with mild hepatic impairment**	**QBW251 300mg with moderate hepatic impairment**	**QBW251 300mg with severe hepatic impairment**
Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild	QBW251 300mg single oral dose. Healthy matched control participants	QBW251 300mg single oral dose. Healthy matched control participants	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.

	hepatic impairment) with normal hepatic function	(Moderate hepatic impairment) with normal hepatic function	(Severe hepatic impairment) with normal hepatic function			
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Elimination half-life (T1/2) of icenticaftor (units: hours)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	21.1 ± 5.19	23.1 ± 3.89	25.4 ± 5.77	17.9 ± 6.29	26.5 ± 8.45	28.7 ± 4.89

Secondary Outcome Result(s)

Maximum observed icenticaftor plasma concentration of unbound icenticaftor (Cmax,u)

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Cmax,u is the maximum (peak) observed plasma concentration of unbound icenticaftor after single oral dose.
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

	QBW251 300mg in Healthy Matched Control (Mild HI)	**QBW251 300mg in Healthy Matched Control (Moderate HI)**	**QBW251 300mg in Healthy Matched Control (Severe HI)**	**QBW251 300mg with mild hepatic impairment**	**QBW251 300mg with moderate hepatic impairment**	**QBW251 300mg with severe hepatic impairment**
Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.

	normal hepatic function	normal hepatic function	normal hepatic function			
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Maximum observed icenticaftor plasma concentration of unbound icenticaftor (Cmax,u) (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	93.4 (61.2%)	104 (49.3%)	102 (52.3%)	121 (54.7%)	67.7 (63.6%)	123 (57.2%)

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Mild HI), QBW251 300mg with mild hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	1.38	Geometric Mean Ratio (GMR) = Test/Reference. Mild HI (Test) vs Healthy Matched Control (Mild HI) (Reference)
90 % Confidence Interval 2-Sided	0.78 to 2.43	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Moderate HI), QBW251 300mg with moderate hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	

Other Geometric Mean Ratio (GMR)	0.67	Geometric Mean Ratio (GMR) = Test/Reference. Moderate HI (Test) vs Healthy Matched Control (Moderate HI) (Reference)
90 % Confidence Interval 2-Sided	0.42 to 1.05	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Severe HI), QBW251 300mg with severe hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio (GMR)	1.19	Geometric Mean Ratio (GMR) = Test/Reference. Severe HI (Test) vs Healthy Matched Control (severe HI) (Reference)
90 % Confidence Interval 2-Sided	0.76 to 1.85	

Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time of unbound icenticaftor (AUClast,u)

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. AUClast is the area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration (tlast) of unbound icenticaftor. Icenticaftor AUClast,u was calculated as AUClast*fu.
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

	QBW251 300mg in Healthy Matched Control (Mild HI)	QBW251 300mg in Healthy Matched Control (Moderate HI)	QBW251 300mg in Healthy Matched Control (Severe HI)	QBW251 300mg with mild hepatic impairment	QBW251 300mg with moderate hepatic impairment	QBW251 300mg with severe hepatic impairment
Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time of unbound icenticaftor (AUClast,u) (units: ng*h/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	440 (32.8%)	444 (29.3%)	417 (33.7%)	354 (43.7%)	431 (49.8%)	987 (16.2%)

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Mild HI), QBW251 300mg with mild hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	0.81	Geometric Mean Ratio (GMR) = Test/Reference. Mild HI (Test) vs Healthy Matched Control (Mild HI) (Reference)

90 % Confidence Interval 2-Sided	0.55 to 1.20	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Moderate HI), QBW251 300mg with moderate hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	0.98	Geometric Mean Ratio (GMR) = Test/Reference. Moderate HI (Test) vs Healthy Matched Control (Moderate HI) (Reference)
90 % Confidence Interval 2-Sided	0.68 to 1.41	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Severe HI), QBW251 300mg with severe hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	2.40	Geometric Mean Ratio (GMR) = Test/Reference. Moderate HI (Test) vs Healthy Matched Control (Moderate HI) (Reference)
90 % Confidence Interval 2-Sided	1.80 to 3.19	

NOVARTIS

Area under plasma concentration-time curve from time zero to infinity (AUCinf,u) of unbound icenticaftor

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. The AUC from time zero to infinity (mass x time x volume-1). Icenticaftor AUCinf,u will be calculated as AUCinf*fu.
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

	QBW251 300mg in Healthy Matched Control (Mild HI)	**QBW251 300mg in Healthy Matched Control (Moderate HI)**	**QBW251 300mg in Healthy Matched Control (Severe HI)**	**QBW251 300mg with mild hepatic impairment**	**QBW251 300mg with moderate hepatic impairment**	**QBW251 300mg with severe hepatic impairment**
Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Area under plasma concentration-time curve from time zero to infinity (AUCinf,u) of unbound icenticaftor (units: ng*h/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	444 (32.5%)	449 (29.0%)	421 (33.4%)	359 (42.8%)	437 (49.3%)	1000 (16.1%)

NOVARTIS

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Mild HI), QBW251 300mg with mild hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	0.82	Geometric Mean Ratio (GMR) = Test/Reference. Mild HI (Test) vs Healthy Matched Control (Mild HI) (Reference)
90 % Confidence Interval 2-Sided	0.56 to 1.20	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Moderate HI), QBW251 300mg with moderate hepatic impairment	
Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	0.98	Geometric Mean Ratio (GMR) = Test/Reference. Moderate HI (Test) vs Healthy Matched Control (Moderate HI) (Reference)
90 % Confidence Interval 2-Sided	0.68 to 1.42	

Statistical Analysis

Groups	QBW251 300mg in Healthy Matched Control (Severe HI), QBW251 300mg with severe hepatic impairment

Type of Statistical Test	Other	
Method	ANCOVA	
Other Geometric Mean Ratio	2.41	Geometric Mean Ratio (GMR) = Test/Reference. Severe HI (Test) vs Healthy Matched Control (severe HI) (Reference)
90 % Confidence Interval 2-Sided	1.80 to 3.21	

Apparent plasma clearance of unbound icenticaftor (CL/F,u)

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. CL/F,u is the apparent total body clearance of unbound icenticaftor from plasma following extravascular administration.
Time Frame	pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

	QBW251 300mg in Healthy Matched Control (Mild HI)	**QBW251 300mg in Healthy Matched Control (Moderate HI)**	**QBW251 300mg in Healthy Matched Control (Severe HI)**	**QBW251 300mg with mild hepatic impairment**	**QBW251 300mg with moderate hepatic impairment**	**QBW251 300mg with severe hepatic impairment**
Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6

Apparent plasma clearance of unbound icenticaftor (CL/F,u) (units: L/h)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	705 ± 218	691 ± 190	743 ± 224	904 ± 405	761 ± 403	303 ± 47.5

Plasma protein binding free fraction (unbound fraction [fu]) of icenticaftor

Description	Pharmacokinetic (PK) parameters were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. The fraction unbound, fu, is the fraction of the icenticaftor that was not bounded to proteins. The free fraction in plasma of icenticaftor was evaluated using equilibrium dialysis method.
Time Frame	3 hours post-dose
Analysis Population Description	The PK set included all participants with at least one available valid PK concentration measurement, who received study treatment and experienced no protocol deviations with relevant impact on PK data. Participants enrolled in the Healthy Matched Control Cohort may have been matched to 1 or more evaluable participants with HI.

	QBW251 300mg in Healthy Matched Control (Mild HI)	**QBW251 300mg in Healthy Matched Control (Moderate HI)**	**QBW251 300mg in Healthy Matched Control (Severe HI)**	**QBW251 300mg with mild hepatic impairment**	**QBW251 300mg with moderate hepatic impairment**	**QBW251 300mg with severe hepatic impairment**
Arm/Group Description	QBW251 300mg single oral dose. Healthy matched control participants (Mild hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Healthy matched control participants (Severe hepatic impairment) with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Number of Participants Analyzed [units: participants]	8	8	6	8	8	6
Plasma protein binding free fraction (unbound fraction [fu]) of icenticaftor (units: no units)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**

0.0903 (9.6%)	0.0852 (18.0%)	0.0882 (5.9%)	0.0921 (19.7%)	0.0862 (19.0%)	0.0857 (11.0%)

Safety Results

Time Frame	Adverse events were reported from the day of study drug administration (Day 1) approximately 30 days post dose.
Source Vocabulary for Table Default	MedDRA (23.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	QBW251 300mg in Healthy participants N = 18	**QBW251 300mg with mild hepatic impairment N = 8**	**QBW251 300mg with moderate hepatic impairment N = 8**	**QBW251 300mg with severe hepatic impairment N = 6**
Arm/Group Description	QBW251 300 mg single oral dose. Healthy participants with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Total Number Affected	0	0	0	0
Total Number At Risk	18	8	8	6

NOVARTIS

Serious Adverse Events

No data identified.

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold	5%

	QBW251 300mg in Healthy participants N = 18	QBW251 300mg with mild hepatic impairment N = 8	QBW251 300mg with moderate hepatic impairment N = 8	QBW251 300mg with severe hepatic impairment N = 6
Arm/Group Description	QBW251 300 mg single oral dose. Healthy participants with normal hepatic function	QBW251 300mg single oral dose. Participants with mild hepatic impairment	QBW251 300mg single oral dose. Participants with moderate hepatic impairment.	QBW251 300mg single oral dose. Participants with severe hepatic impairment.
Total # Affected by any Other Adverse Event	3	0	2	1
Total # at Risk by any Other Adverse Event	18	8	8	6
Gastrointestinal disorders				
Nausea	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Nervous system disorders				
Headache	3 (16.67%)	0 (0.00%)	1 (12.50%)	1 (16.67%)
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)

Conclusion:

No apparent trend in icenticaftor Cmax was observed with increasing severity of HI. Icenticaftor AUClast and AUCinf increased about 2-fold in participants with severe HI. A similar trend was observed for icenticaftor when comparing each of the HI groups to pooled healthy matched control subjects and for unbound icenticaftor Cmax, AUClast, and AUCinf.

Single oral doses of 300 mg icenticaftor were well tolerated when administered to participants with mild, moderate, or severe HI and to healthy matched control participants in this study.

Date of Clinical Trial Report

15-Jun-2023