NOVARTIS

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Pelacarsen

Trial Indication(s)

Hepatic Impairment

Protocol Number

CTQJ230A12202

Protocol Title

A single-dose, open-label, parallel-group study to assess the pharmacokinetics of pelacarsen (TQJ230) in participants with mild hepatic impairment compared to matched healthy participants

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: November 23, 2021 (Actual)
Primary Completion Date: October 19, 2022 (Actual)
Study Completion Date: October 19, 2022 (Actual)

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Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a Phase I, open-label, single-dose, parallel-group study in participants with mild Hepatic Impairment (HI) and healthy matched control participants with normal hepatic function designed to evaluate the PK of pelacarsen following a single 80 mg s.c. dose. Participants were matched by gender, age (±10 years), and body weight (±15%).

The study consisted of a Screening period of up to 28 days, followed by Baseline evaluations on Day -1.

On Day 1, participants received a single s.c. injection of 80 mg pelacarsen followed by PK sampling up to Day 60 (±3 days). Participants were domiciled for at least 4 overnight stays (Day -1 through Day 4) for PK sample collection up to 72 hours post-dose and were to return to the study site on 3 occasions (Days 8, 30 [±2 days], and 60 [±3 days]) for additional PK sample collection.

Study Completion evaluation (i.e., End of Study [EOS]) occurred with the completion of Day 60 (±3 days) assessments. The total study duration for each participant was expected to be up to a maximum of 89 (±3) days, including the Screening period.

A post study safety contact (i.e., follow-up phone call) took place on Day 112, approximately 16 weeks after dosing.

Centers

United States(1)

Objectives:

Primary objective: To assess the Pharmacokinetic properties of pelacarsen after a single s.c. injection in participants with mild hepatic impairment (Child-Pugh classification) as compared to matched healthy participants with normal hepatic function.

Secondary objective: To assess the safety and tolerability of pelacarsen after a single s.c. injection in participants with mild hepatic impairment as compared to matched healthy participants with normal hepatic function.

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

Single subcutaneous injection of 80 mg pelacarsen on Day 1.

Statistical Methods

All descriptive statistics for pelacarsen PK concentrations and PK parameters were generated using SAS® Version 9.4.

Summary statistics for plasma concentration data included geometric mean and geometric coefficient of variation (CV).

The natural logarithm (ln)-transformed PK parameters (Cmax, AUClast, and AUCinf) for pelacarsen were separately analyzed using analysis of covariance (ANCOVA) models with group and matching covariates (sex, age, and weight) as fixed effects. The difference between the mild HI group (test) and the healthy control group (reference) were calculated for each PK parameter. Back-transformed ratios and 90% confidence interval (CIs) were provided. The ANCOVA was performed using SAS® PROC MIXED.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
All participants
1. Signed informed consent must be obtained prior to participation in the study.
2. Male and non-child bearing potential female participants, 18 to 75 years of age (inclusive), at Screening.
3. Participants must weigh at least 50 kg to participate in the study, and must had a BMI within the range of 18.0 – 38.0 kg/m2, at Screening.
4. Ability to communicate well with the investigator, to understand and comply with the requirements of the study.
5. Must be a non-smoker or agree to smoke no more than 5 cigarettes (or equivalent) per day from Screening until Study Completion.

Participants with mild HI (Group 2)
6. Participants must had a prior diagnosis of liver cirrhosis and mild HI as defined by the Child Pugh classification with a score of 5-6, inclusive (Class A)
7. Participants were clinically stable and had no worsening of more than 1 point in Child Pugh score within 1 month prior to dosing of study treatment.
8. Seated vital signs must be within the following ranges at Screening and Baseline:

• Body temperature between 35.0 to 37.5°C, inclusive;
• Systolic blood pressure between 100 to 159 mmHg, inclusive;
• Diastolic blood pressure between 60 to 109 mmHg, inclusive;
• Pulse rate between 45 - 99 bpm, inclusive.
9. Participants with other stable medical disorders such as controlled diabetes, hyperlipidemia, hypothyroidism, etc., could be 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.

Healthy control participants (Group 1)
10. Each participant must match 1:1 in gender, age (± 10 years), and body weight (± 15%) to a participant with mild HI.
11. Seated vital signs must be within the following ranges at Screening and Baseline:
• Body temperature between 35.0 to 37.5°C, inclusive;
• Systolic blood pressure between 89 to 139 mmHg, inclusive;
• Diastolic blood pressure between 50 to 89 mmHg, inclusive;
• Pulse rate between 45 to 90 bpm, inclusive.
12. Participants must be in good health as determined by medical history, physical examination, ECG, and clinical laboratory tests at Screening.

Exclusion Criteria:
All participants
1. Use of other investigational drugs within 5 half-lives or 30 days prior to dosing of study treatment, whichever is longer.
2. History of hypersensitivity to the study treatment or its excipients or to drugs of similar chemical classes.
3. Treatment with any oligonucleotide (with an exception for COVID 19 vaccines) or SiRNA within 9 months prior to Screening.
4. Participants who received any COVID 19 vaccination and/or have not completed their full COVID-19 vaccination regimen within 14 days prior to Screening.
5. Women of child bearing potential, defined as all women physiologically capable of becoming pregnant. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks prior to the first dosing. In the case of oophorectomy alone, only when the reproductive status of the woman was confirmed by follow-up hormone level assessment was she considered not of child bearing potential.
6. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 16 weeks after stopping

study treatment. A condom was required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.
7. Known history of, or current clinically significant arrhythmias, history of prolonged QT interval corrected by Fridericia's formula (QTcF), QTcF > 450 msec (males), or QTcF > 460 msec (females) at Screening.
8. History of immunodeficiency diseases or have a positive HIV test result at Screening.
9. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated, within the past 5 years of Screening, regardless of whether there was evidence of local recurrence or metastases.
10. Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing of study treatment.
11. Platelet count ≤ LLN at Screening or Baseline.
12. History of unhealthy alcohol use within 12 months prior to dosing of study treatment, as defined by a recurring pattern of either binge drinking (≥ 5 drinks over 2 3 hours on ≥ 5 days/month) or heavy drinking (≥ 8 drinks/week in females or > 15 drinks/week in males). A "drink" definition includes: 12 ounces of 5% beer, 8 ounces of 7% malt liquor, 5 ounces of 12% wine or 1.5 ounces of 40% spirits.
13. Positive alcohol screen at Screening or Baseline.
14. History of drug abuse within the last 12 months or evidence of such abuse as indicated by the laboratory assay conducted during Screening or Baseline, unless the positive drug screen is due to prescription drug use that is approved by the investigator and Novartis.
15. Clinically significant illness (other than HI for participants in Group 2) within 2 weeks prior to dosing of study treatment that may jeopardize safety of the participant and/or alter the study results as judged by the investigator.
16. Significant glomerular disease (including but not limited to IgA nephropathy, diabetic nephropathy, systemic lupus erythematosus, etc.) with urinary protein-creatinine ratio > 500 mg/g (56.6 mg/mmol).
17. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs (apart from cholecystectomy), or which may jeopardize the participants in case of participation in the study. The investigator should make this determination in consideration of the participant's medical history.
18. Had tattoo(s) or scarring at or near the site of injection or any other condition which may interfere with injection site examination, in the opinion of the investigator.
19. Unwillingness or inability (e.g. physical or cognitive) to comply with study procedures, study treatment administration (i.e. injection), or schedule.

Participants with mild HI (Group 2)
20. Presence of any non controlled and clinically significant disease that could affect the study outcome or that would place the participant at undue risk.
21. Severe complications of liver disease within the preceding 3 months of Screening.

22. Have received liver transplant at any time in the past.
23. Participants requiring paracentesis more than every 30 days for the management of ascites. Participants who were receiving diuretics to manage ascites could be enrolled and would be assigned the Child Pugh score for the degree of ascites while on diuretic treatment. The diuretic dose must had been stable for at least 14 days prior to dosing of study treatment.
24. Have transjugular intrahepatic portosystemic shunt and/or have undergone portacaval shunting.
25. Have acute hepatitis B or C infection at Screening or active infection requiring therapy that will not be completed before Screening.
26. Presence of moderate to severe impaired renal function as indicated by estimated glomerular filtration rate < 45 mL/min/1.73 m2 based on MDRD calculation.
27. Hemoglobin levels below 10.0 g/dL at Screening or Baseline.
28. Have encephalopathy Grade 3 or worse within 28 days prior to dosing of study treatment.
29. Have primary biliary cholangitis or biliary obstruction.
30. History of gastrointestinal bleeding within the past 3 months prior to Screening.
31. Clinically significant abnormal findings in physical examination or clinical laboratory evaluations not consistent with known liver disease.

Healthy control participants (Group 1)
32. Any single parameter of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl-transferase (GGT), or alkaline phosphatase (ALP) exceeding 1.2 x upper limit of normal (ULN), total bilirubin ≥ 1.5 x ULN, or any elevation above ULN of more than one parameter of ALT, AST, GGT, ALP, or total bilirubin at Screening or Baseline.
33. Hemoglobin levels more than 10% below LLN at Screening or Baseline.
34. Participants known to have Gilbert's syndrome.
35. Chronic hepatitis B or hepatitis C infection. A positive HBsAg test, or if standard local practice, a positive hepatitis B virus core antigen test, was an exclusion. Participants with a positive hepatitis C virus (HCV) antibodies (Ab) test should have HCV ribonucleic acid (RNA) levels measured. Participants with positive (detectable) HCV RNA should be excluded.
36. Were taking medications prohibited with the study treatment (see Section 6.2.2 for additional details on prohibited medication) or herbal supplements, prescribed medicinal use of cannabis/marijuana, within 14 days prior to dosing of study treatment.
37. Impaired renal function as indicated by clinically significantly abnormal creatinine or blood urea nitrogen and/or urea values, or abnormal urinary constituents at screening and/or baseline.

Participant Flow Table

Overall Study

	Healthy participants	Mild hepatic impairment patients	Total
Arm/Group Description	Matched healthy participants with normal hepatic function	Participants with mild hepatic impairment	
Started	9	8	17
Completed	8	8	16
Not Completed	1	0	1
Discontinued Early after failing to show for the Day 60 visit	1	0	1

Baseline Characteristics

	Healthy participants	Mild hepatic impairment patients	Total
Arm/Group Description	Matched healthy participants with normal hepatic function	Participants with mild hepatic impairment	
Number of Participants [units: participants]	9	8	17
Baseline Analysis Population Description			
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation			
	59.0±11.82	60.1±8.25	59.5±10.00
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	4	4	8

Male	5	4	9
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Black or African American	3	1	4
White	6	7	13

Primary Outcome Result(s)

Pharmacokinetic parameters of pelacarsen: Cmax

Description	The maximum (peak) observed drug concentration in after single-dose administration (mass x volume-1). To assess the PK properties of plasma pelacarsen after a single s.c. injection in participants with mild HI (Child-Pugh classification) as compared to matched healthy participants with normal hepatic function.
Time Frame	Day 1 (0 hour (pre-dose) 0.5 hour, 1 hour, 1.5 hour, 2 hour, 3 hour, 4 hour, 6 hour, 8 hour, 12 hour), Day 2, Day 3, Day 4, Day 8, Day 30 and Day 60
Analysis Population Description	PK analysis set: all participants with at least one available valid PK concentration measurement, who received study treatment and with no protocol deviations that impact on PK data.

	Healthy participants	**Mild hepatic impairment patients**

Arm/Group Description	Matched healthy participants with normal hepatic function	Participants with mild hepatic impairment
Number of Participants Analyzed [units: participants]	9	8
Pharmacokinetic parameters of pelacarsen: Cmax (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	893 (72.5%)	943 (89.1%)

Statistical Analysis

Groups	Healthy participants, Mild hepatic impairment patients
Type of Statistical Test	Superiority
Other Geometric Mean Ratio	1.07
90 % Confidence Interval 2-Sided	0.68 to 1.69

Pharmacokinetic parameters of pelacarsen: AUClast

Description	The area under the concentration-time curve (AUC) from time zero to the last measurable concentration sampling time (mass x time x volume-1). To assess the PK properties of plasma pelacarsen after a single s.c. injection in participants with mild HI (Child-Pugh classification) as compared to matched healthy participants with normal hepatic function.
Time Frame	Day 1 (0 hour (pre-dose) 0.5 hour, 1 hour, 1.5 hour, 2 hour, 3 hour, 4 hour, 6 hour, 8 hour, 12 hour), Day 2, Day 3, Day 4, Day 8, Day 30 and Day 60
Analysis Population Description	PK analysis set: all participants with at least one available valid PK concentration measurement, who received study treatment and with no protocol deviations that impact on PK data.

	Healthy participants	**Mild hepatic impairment patients**
Arm/Group Description	Matched healthy participants with normal hepatic function	Participants with mild hepatic impairment

Number of Participants Analyzed [units: participants]	9	8
Pharmacokinetic parameters of pelacarsen: AUClast (units: ng*h/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	7690 (63.9%)	10600 (59.0%)

Statistical Analysis

Groups	Healthy participants, Mild hepatic impairment patients
Type of Statistical Test	Superiority
Other Geometric Mean Ratio	1.37
90 % Confidence Interval 2-Sided	0.96 to 1.97

Pharmacokinetic parameters of pelacarsen: AUCinf

Description	The AUC from time zero to infinity (mass x time x volume-1). To assess the PK properties of plasma pelacarsen after a single s.c. injection in participants with mild HI (Child-Pugh classification) as compared to matched healthy participants with normal hepatic function.
Time Frame	Day 1 (0 hour (pre-dose) 0.5 hour, 1 hour, 1.5 hour, 2 hour, 3 hour, 4 hour, 6 hour, 8 hour, 12 hour), Day 2, Day 3, Day 4, Day 8, Day 30 and Day 60
Analysis Population Description	PK analysis set: all participants with at least one available valid PK concentration measurement, who received study treatment and with no protocol deviations that impact on PK data.

	Healthy participants	**Mild hepatic impairment patients**
Arm/Group Description	Matched healthy participants with normal hepatic function	Participants with mild hepatic impairment
Number of Participants Analyzed [units: participants]	8	6

Pharmacokinetic parameters of pelacarsen: AUCinf (units: ng*h/mL)	**Geometric Mean** **(Geometric Coefficient of Variation)**	**Geometric Mean** **(Geometric Coefficient of Variation)**
	7860 (63.6%)	13200 (50.6%)

Statistical Analysis

Groups	Healthy participants, Mild hepatic impairment patients
Type of Statistical Test	Superiority
Other Geometric Mean Ratio	1.50
90 % Confidence Interval 2-Sided	0.98 to 2.30

Secondary Outcome Result(s)

No data identified.

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	Adverse events were reported from the single dose of study treatment until study completion, up to a maximum duration of 60 days.
Source Vocabulary for Table Default	MedDRA (24.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Healthy participants N = 9	**Mild hepatic impairment patients N = 8**
Arm/Group Description	Matched healthy participants with normal hepatic function	Participants with mild hepatic impairment
Total Number Affected	0	0
Total Number At Risk	9	8

Serious Adverse Events

Time Frame	Adverse events were reported from the single dose of study treatment until study completion, up to a maximum duration of 60 days.
Source Vocabulary for Table Default	MedDRA (24.0)

Collection Approach for Table Default	Systematic Assessment

No data identified.

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events were reported from the single dose of study treatment until study completion, up to a maximum duration of 60 days.
Source Vocabulary for Table Default	MedDRA (24.0)
Collection Approach for Table Default	Systematic Assessment

	Healthy participants N = 9	**Mild hepatic impairment patients N = 8**
Arm/Group Description	Matched healthy participants with normal hepatic function	Participants with mild hepatic impairment
Total # Affected by any Other Adverse Event	1	1
Total # at Risk by any Other Adverse Event	9	8
Infections and infestations		
Urinary tract infection	1 (11.11%)	0 (0.00%)

Nervous system disorders		
Headache	0 (0.00%)	1 (12.50%)

Other Relevant Findings

Not applicable

Conclusion:

- Pelacarsen peak (Cmax) and total (AUClast and AUCinf) exposures were greater in participants with mild HI compared to healthy matched control participants. All 90% CIs on the group (mild HI versus healthy control) GMRs included 1.00, suggesting that the effect of mild HI on pelacarsen exposure change did not have apparent power of statistical significance. Indeed, a comparison of the ranges of all PK exposure parameters, including Cmax and AUC, indicated they were similar between the mild HI and healthy matched control participants.
- Despite an observed trend towards slightly increased pelacarsen exposure with mild HI, the effect of mild HI on pelacarsen exposure change was less than the between-subject PK variability that has been reported based on the study data. For comparison with the aforementioned mild HI versus control GMRs, the geometric mean CV% of Cmax, AUClast, and AUCinf in healthy control participants were 72.5%, 63.9%, and 63.6%, respectively, while the corresponding CV% were 89.1%, 59.0%, and 50.6% in mild HI participants.
- Given the comparable PK observations and good safety findings in the study, it is not suggestive of any dose modification for pelacarsen use in patients with mild HI.
- Single subcutaneous injection of 80 mg pelacarsen, administered to participants with mild HI and healthy matched control participants, was safe and well tolerated in this study.

Date of Clinical Trial Report

18 October 2023