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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Siremadlin (HDM201)

Trial Indication(s)

Hepatic impairment

Protocol Number

CHDM201X2105

Protocol Title

A Phase 1, open-label, multi-center, single-dose, parallel group study to evaluate the pharmacokinetics of siremadlin (HDM201) in participants with mild, moderate and severe hepatic impairment compared to matched healthy control participants

Clinical Trial Phase

Phase 1

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Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: December 02, 2022 (Actual)
Primary Completion Date: September 18, 2023 (Actual)
Study Completion Date: September 18, 2023 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a Phase 1, open-label, multi-center, single oral dose, parallel-group study to assess the plasma pharmacokinetics (PK) of oral siremadlin in participants with mild, moderate, and severe HI compared to matched healthy control participants with normal hepatic function.

The study population was comprised of at least 32 and up to 48 male and non-childbearing potential female participants. Eight (8) participants were planned to be enrolled in each of the mild (Child-Pugh A; Group 2), moderate (Child-Pugh B; Group 3), and severe (Child-Pugh C; Group 4) Hepatic impairment (HI) groups to have at least 6 participants who completed the study in each group. Recruitment was not aimed to balance the groups with regard to sex. Up to a total of 24 matched healthy control participants (Group 1) may have been enrolled. Each participant in the matched healthy control group (Group 1) may have been matched to 1 or more participants in any HI group (Groups 2, 3, and 4).

Additional participants, beyond the planned number of participants for each group (e.g., > 8 participants for each HI group [Groups 2-4] and > 24 participants in the healthy control group [Group 1]) may have been enrolled if a participant discontinued from the study for reasons other than safety before completion of the PK assessment to ensure there were at least 6 participants who completed the study in each HI group.

The study planned to enroll the 4 groups in parallel. Therefore, enrollment in Group 1 remained open until enrollment in the mild, moderate, and severe HI groups was complete and each HI participant had a matched healthy control (Group 1) participant. Healthy control participants (Group 1) commenced enrollment after at least 3 participants from each of Groups 2 and 3 had completed all scheduled assessments.

The study consisted of a screening period of up to 28 days (Days -29 to -2), a baseline evaluation on Day -1, a single dose administration of siremadlin on Day 1 followed by PK sampling up to 144 hours postdose (Day 7). All baseline safety evaluation results were available and reviewed prior to the dosing. All eligible participants were domiciled from Day -1 until Day 7.

Safety assessments included physical examinations, electrocardiogram (ECGs), vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis, coagulation), adverse event (AE), and serious adverse event (SAE) monitoring.

All participants had a post-study safety follow-up contact conducted approximately 30 days after administration of study treatment. The study was considered complete once all the participants had finished the required assessments, dropped out, or been lost to follow-up before completing the required assessments.

The total study duration for each participant was expected to be up to a maximum of 59 days, including the screening period and the 30-day post-study safety contact follow-up period.

Centers

United States(3)

Objectives:

The primary objective was to assess the PK of siremadlin after a single oral dose of 10 mg in participants with mild, moderate and severe HI (Child-Pugh classification) as compared to matched healthy control participants with normal hepatic function.

The secondary objective was to assess the safety and tolerability of siremadlin after a single oral dose of 10 mg in participants with mild, moderate, and severe HI and in matched healthy control participants with normal hepatic function.

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

Siremadlin (HDM201) single dose of 10 mg, which was administered orally.

Statistical Methods

A formal statistical analysis was performed for the primary PK parameters (Maximum observed plasma concentration following a single dose administration (Cmax), Area under the concentration-time curve from time zero to the last measurable plasma concentration sampling time (AUClast), and Area under the concentration-time curve from time zero to infinity (AUCinf)) from plasma siremadlin concentrations. PK parameters from participants with mild, moderate, and severe HI were compared to the PK parameters from healthy control participants, to assess the effect of HI on siremadlin

PK. For all the analysis, the healthy matched control group refers to the pooled sample of the healthy participants irrespective of matching criteria.

A linear fixed effect model, analysis of covariance (ANCOVA), was fitted to the log-transformed primary PK parameters Cmax, AUClast, and AUCinf separately to assess the effect of HI on the PK of a single oral dose of 10 mg siremadlin. The model included HI group, sex, age group (< 65 years, ≥ 65 years),and weight (at Baseline [Day -1]) as fixed factors. Sex and age group were categorical covariates and weight was a continuous covariate. There was one model for each primary PK parameter with pooled data from all HI and matched healthy control groups. Each HI group was compared to the pooled healthy control participants for each primary PK parameter.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

All participants:

- Male and non-child-bearing potential females between 18 and 75 years of age, inclusive, at Screening.
- Participant must have been a non-smoker or moderate smoker (up to 10 cigarettes or equivalent nicotine containing products per day) at Screening. Participant must have agreed to maintain the same smoking status (i.e., smoker or non-smoker) from Screening until after Study Completion evaluations.

Additional key inclusion criteria for healthy participants (Group 1):

- Participants must have weighed at least 50.0 kg and must have had a BMI within the range of 18.0 to 38.0 kg/m2, inclusive at Screening.
- Participants with no clinically significant abnormalities as determined by past medical history, physical examination, ECG and clinical laboratory test at Screening.

Additional inclusion criteria for mild, moderate and severe HI participants (Groups 2-4):

- Participants must have weighed at least 50.0 kg and must have had a BMI within the range of 18.0 to 38.0 kg/m2, inclusive at Screening. For participants without overt ascites, the BMI must have been within the range of 18.0 to 40.0 kg/m2, inclusive. For participants with overt ascites, the BMI must have been within the range of 18.0 to 45.0 kg/m2, inclusive.
- Participant must have satisfied the criteria for HI as evidenced by a Child-Pugh class of A, B, or C at Screening and Baseline (see Table 8-2 Child-Pugh classification criteria):

• Group 2: Class A; Mild; Child-Pugh score 5-6, inclusive
• Group 3: Class B; Moderate; Child-Pugh score 7-9, inclusive
• Group 4: Class C; Severe; Child-Pugh score 10-15, inclusive.

If the results of the assessments at Screening and Baseline indicated different Child-Pugh class, a third assessment must have been conducted. If the results of the 2 most recent assessments (the second and third) were in agreement with regard to the participant's Child-Pugh class, the participant may have been enrolled at the Child-Pugh class determined by the most recent assessment. If the second and third measurements differ, the participant would not be eligible for the study on the basis that their liver function was not stable.

- Participants with impaired hepatic function and other stable medical disorders such as diabetes, hypertension, hyperlipidemia, hypothyroidism etc., may have been eligible, as long as they were considered appropriate for enrollment, as determined by past medical history, physical examination, vital signs, ECG, and clinical laboratory tests at Screening.

Key Exclusion Criteria:

All participants (Groups 1-4):

- Contraindication or hypersensitivity to the investigational compound/compound class or excipients being used in this study.
- History or presence of clinically significant ECG abnormalities or a family history or presence of prolonged QT-interval syndrome.
- History of malignancy of any organ system, treated or untreated, within 3 years prior to Screening, regardless of whether there were

recurrence or metastases. Those with localized basal cell carcinoma of the skin, in-situ cervical cancer, or hepatocellular cancer treated with local ablative therapy more than 6 months prior to Screening may have been enrolled.
- Use of investigational drugs, other than siremadlin (i.e., participation in any clinical investigation) within 4 weeks prior to dosing or longer if required by local regulation, or within 5 half-lives of the investigational agent taken prior to dosing (whichever was longer).
- Clinically significant illness within 2 weeks prior to dosing that may have jeopardized safety of the study participant and/or alter the study results as judged by the Investigator.

Additional key exclusion criteria for healthy participants (Group 1):
- Any single parameter of ALT, AST, GGT, or ALP that exceeded 1.2 x ULN or ≥ 1.5 x ULN TBL or any elevation above ULN of more than one parameter of ALT, AST, GGT, ALP, or serum TBL at Screening.
- Participants known to have Gilbert's syndrome.
- Participants with abnormal laboratory values for the following parameters at Screening:
• Hemoglobin levels < 12.0 g/dL (males) or < 11.0 g/dL (females).
• WBC count outside the range of 3.5 x 109-10.7 x 109 /L (unless deemed not clinically significant by the Investigator).
• Platelet count < 100 x 109 /L (unless deemed not clinically significant by the Investigator).
- Presence of impaired renal function as indicated by serum creatinine > ULN or abnormal urinary constituents at Screening.

Additional key exclusion criteria for mild and moderate HI participants (Groups 2-3):
- Participants with abnormal laboratory values for the following parameters at Screening:
• Hemoglobin < 9 g/dL.
• Platelet count < 30 x 109/L.
• WBC count < 2.5 x 109/L.
• TBL > 8 mg/dL.

• Serum amylase > 5 x ULN with no abdominal symptoms (> 2 x ULN with abdominal symptoms)

• INR > 2.5.

• Corrected serum calcium < 8.6 or > 10.2 mg/dL.

- Presence of moderate to severe impaired renal function as indicated by creatinine clearance < 50 mL/min as calculated using the Cockcroft-Gault formula.

- Severe complications of liver disease within the preceding 3 months prior to dosing..

- Trans-jugular intrahepatic portosystemic shunt and/or have undergone portacaval shunting.

Additional key exclusion criteria for severe HI participants (Group 4):

- Participants with abnormal laboratory values for the following parameters at Screening:

• Hemoglobin < 8.5 g/dL.

• Platelet count < 30 x 109/L.

• WBC count < 2.5 x 109/L.

• TBL > 8 mg/dL.

• Serum amylase > 5 x ULN with no abdominal symptoms (> 2 x ULN with abdominal symptoms).

• INR > 2.5.

- Presence of moderate to severe impaired renal function as indicated by creatinine clearance < 50 mL/min as calculated using the Cockcroft-Gault formula.

- Severe complications of liver disease within the preceding 3 months prior to dosing.

- Trans-jugular intrahepatic portosystemic shunt and/or have undergone portacaval shunting.

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Participant Flow Table

Overall Study

	Group 1: Healthy Control	Group 2: Mild; Child-Pugh A	Group 3: Moderate; Child-Pugh B	Group 4: Severe; Child-Pugh C	Total
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201	
Started	15	8	8	7	38
Completed	15	8	8	7	38
Not Completed	0	0	0	0	0

Baseline Characteristics

	Group 1: Healthy Control	Group 2: Mild; Child-Pugh A	Group 3: Moderate; Child-Pugh B	Group 4: Severe; Child-Pugh C	Total
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201	
Number of Participants [units: participants]	15	8	8	7	38
Baseline Analysis Population Description					
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
Female	5	3	2	3	13

Male	10	5	6	4	25
Race (NIH/OMB) (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
American Indian or Alaska Native	1	0	0	0	1
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	0	0	0	2
White	12	8	8	6	34
More than one race	0	0	0	0	0
Unknown or Not Reported	0	0	0	1	1
Ethnicity (NIH/OMB) (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
Hispanic or Latino	9	4	5	6	24
Not Hispanic or Latino	6	3	3	1	13
Unknown or Not Reported	0	1	0	0	1
Age Continuous (units: Years) Analysis Population Type: Participants Mean ± Standard Deviation					
	57.6±10.74	56.6±13.07	55.9±9.39	57.7±13.24	57.1±11.03

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Primary Outcome Result(s)

Pharmacokinetics (PK): Cmax

Description	Maximum Observed Blood Concentrations (Cmax) for siremadlin plasma - mean value reported from the below collection times.
Time Frame	pre-dose, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, and 144 hours
Analysis Population Description	Pharmacokinetic Analysis Results (PAS) - all treated patients with a valid measurement

	Group 1: Healthy Control	Group 2: Mild; Child-Pugh A	Group 3: Moderate; Child-Pugh B	Group 4: Severe; Child-Pugh C
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201
Number of Participants Analyzed [units: participants]	15	8	8	7
Pharmacokinetics (PK): Cmax (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	84.2 ± 17.6	91.1 ± 22.9	73.0 ± 16.8	79.1 ± 21.3

Pharmacokinetics (PK): Tmax

Description	Time to Reach Maximum Blood Concentrations (Tmax) for siremadlin plasma - median value reported from the below collection times.
Time Frame	pre-dose, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, and 144 hours
Analysis Population Description	Pharmacokinetic Analysis Results (PAS) - all treated patients with a valid measurement

	Group 1: Healthy Control	Group 2: Mild; Child-Pugh A	Group 3: Moderate; Child-Pugh B	Group 4: Severe; Child-Pugh C
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201
Number of Participants Analyzed [units: participants]	15	8	8	7
Pharmacokinetics (PK): Tmax (units: h)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**
	2.00 (1.00 to 4.00)	2.50 (1.00 to 4.00)	3.50 (2.00 to 4.00)	2.00 (1.00 to 3.00)

Pharmacokinetics (PK): Tlast

Description	Last measurable plasma concentration (Tlast) for siremadlin plasma - median value reported from the below collection times.
Time Frame	pre-dose, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, and 144 hours
Analysis Population Description	Pharmacokinetic Analysis Results (PAS) - all treated patients with a valid measurement

	Group 1: Healthy Control	Group 2: Mild; Child-Pugh A	Group 3: Moderate; Child-Pugh B	Group 4: Severe; Child-Pugh C
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201
Number of Participants Analyzed [units: participants]	15	8	8	7
Pharmacokinetics (PK): Tlast (units: h)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**

71.17 (36.00 to 120.00)	72.00 (36.00 to 120.00)	108.00 (72.00 to 144.00)	120.00 (72.00 to 144.00)

Pharmacokinetics (PK): AUC0-24h

Description	Area Under Plasma Concentration from time zero to 24-hour post-dose sampling time (AUC0-24h) for siremadlin plasma - mean value reported from the below collection times.
Time Frame	pre-dose, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, and 144 hours
Analysis Population Description	Pharmacokinetic Analysis Results (PAS) - all treated patients with a valid measurement

	Group 1: Healthy Control	**Group 2: Mild; Child-Pugh A**	**Group 3: Moderate; Child-Pugh B**	**Group 4: Severe; Child-Pugh C**
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201
Number of Participants Analyzed [units: participants]	15	8	8	7
Pharmacokinetics (PK): AUC0-24h (units: ng•h/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	943 ± 263	1020 ± 307	996 ± 196	1030 ± 265

Pharmacokinetics (PK): AUClast

Description	Area Under Plasma Concentration-time Curve from time zero to the last measurable concentration sampling time (AUClast) for siremadlin plasma - mean value reported from the below collection times.
Time Frame	pre-dose, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, and 144 hours

Analysis Population Description	Pharmacokinetic Analysis Results (PAS) - all treated patients with a valid measurement

	Group 1: Healthy Control	Group 2: Mild; Child-Pugh A	Group 3: Moderate; Child-Pugh B	Group 4: Severe; Child-Pugh C
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201
Number of Participants Analyzed [units: participants]	15	8	8	7
Pharmacokinetics (PK): AUClast (units: ng•h/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	1310 ± 540	1460 ± 608	1810 ± 566	1960 ± 812

Pharmacokinetics (PK): AUCinf

Description	Area Under Plasma Concentration from time zero to infinity (AUCinf) for siremadlin plasma - mean value reported from the below collection times.
Time Frame	pre-dose, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, and 144 hours
Analysis Population Description	Pharmacokinetic Analysis Results (PAS) - all treated patients with a valid measurement

	Group 1: Healthy Control	Group 2: Mild; Child-Pugh A	Group 3: Moderate; Child-Pugh B	Group 4: Severe; Child-Pugh C
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201

Number of Participants Analyzed [units: participants]	15	8	8	7
Pharmacokinetics (PK): AUCinf (units: ng•h/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	1350 ± 549	1500 ± 608	1860 ± 583	2030 ± 828

Pharmacokinetics (PK): T1/2

Description: Terminal Elimination Half-life (T1/2) for siremadlin plasma - mean value reported from the below collection times.

Time Frame: pre-dose, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, and 144 hours

Analysis Population Description: Pharmacokinetic Analysis Results (PAS) - all treated patients with a valid measurement

	Group 1: Healthy Control	**Group 2: Mild; Child-Pugh A**	**Group 3: Moderate; Child-Pugh B**	**Group 4: Severe; Child-Pugh C**
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201
Number of Participants Analyzed [units: participants]	15	8	8	7
Pharmacokinetics (PK): T1/2 (units: h)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	13.4 ± 4.72	14.0 ± 3.82	20.6 ± 4.29	22.7 ± 4.57

Pharmacokinetics (PK): CL/F

Description: Apparent total body clearance of siremadlin from plasma (CL/F) - mean value reported from the below collection times.

Time Frame	pre-dose, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, and 144 hours
Analysis Population Description	Pharmacokinetic Analysis Results (PAS) - all treated patients with a valid measurement

	Group 1: Healthy Control	Group 2: Mild; Child-Pugh A	Group 3: Moderate; Child-Pugh B	Group 4: Severe; Child-Pugh C
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201
Number of Participants Analyzed [units: participants]	15	8	8	7
Pharmacokinetics (PK): CL/F (units: L/h)	**Median ± Standard Deviation**	**Median ± Standard Deviation**	**Median ± Standard Deviation**	**Median ± Standard Deviation**
	8.36 ± 2.71	7.56 ± 2.69	5.82 ± 1.77	5.48 ± 1.69

Pharmacokinetics (PK): Vz/F

Description	Apparent volume of distribution during terminal elimination phase (Vz/F) of siremadlin plasma - mean value reported from the below collection times.
Time Frame	pre-dose, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, and 144 hours
Analysis Population Description	Pharmacokinetic Analysis Results (PAS) - all treated patients with a valid measurement

	Group 1: Healthy Control	Group 2: Mild; Child-Pugh A	Group 3: Moderate; Child-Pugh B	Group 4: Severe; Child-Pugh C

Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201
Number of Participants Analyzed [units: participants]	15	8	8	7
Pharmacokinetics (PK): Vz/F (units: L)	**Median ± Standard Deviation**	**Median ± Standard Deviation**	**Median ± Standard Deviation**	**Median ± Standard Deviation**
	149 ± 35.5	147 ± 59.4	165 ± 26.4	171 ± 34.8

Pharmacokinetics (PK): AUC0-t

Description	Area Under Plasma Concentration from time zero to time "t" (AUC0-t) - siremadlin plasma - no values are reported for this endpoint since Tlast did not significantly differ between the Hepatic Impaired (HI) and healthy control groups.
Time Frame	pre-dose, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, and 144 hours
Analysis Population Description	Pharmacokinetic Analysis Results (PAS) - all treated patients with a valid measurement

	Group 1: Healthy Control	**Group 2: Mild; Child-Pugh A**	**Group 3: Moderate; Child-Pugh B**	**Group 4: Severe; Child-Pugh C**
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201
Number of Participants Analyzed [units: participants]	0	0	0	0
Pharmacokinetics (PK): AUC0-t (units: ng•h/mL)	**()**	**()**	**()**	**()**

Secondary Outcome Result(s)

Participants with Treatment Emergent Adverse Events (TEAEs)

Description	An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject
Time Frame	Adverse events are reported from the single dose of study medication plus 30 days post treatment, for a maximum timeframe of approximately 30 days.
Analysis Population Description	Safety Set - includes all treated patients

	Group 1: Healthy Control	**Group 2: Mild; Child-Pugh A**	**Group 3: Moderate; Child-Pugh B**	**Group 4: Severe; Child-Pugh C**
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201
Number of Participants Analyzed [units: participants]	15	8	8	7
Participants with Treatment Emergent Adverse Events (TEAEs) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Number of Participants with TEAEs	1 (6.67%)	0 (%)	0 (%)	1 (14.29%)
Number of Participants with TEAEs of Mild Intensity (Grade 1)	1 (6.67%)	0 (%)	0 (%)	1 (14.29%)
Number of Participants with TEAEs of Moderate Intensity (Grade 2)	0 (%)	0 (%)	0 (%)	0 (%)

Number of Participants with TEAEs of Severe Intensity (Grade 3)	0 (%)	0 (%)	0 (%)	0 (%)
Number of Participants with TEAEs of Life-Threatening Intensity (Grade 4)	0 (%)	0 (%)	0 (%)	0 (%)
Number of Participants with Treatment-Related TEAEs	1 (6.67%)	0 (%)	0 (%)	1 (14.29%)
Number of Participants with Serious TEAEs	0 (%)	0 (%)	0 (%)	0 (%)
Number of Participants with Serious Treatment-Related TEAEs	0 (%)	0 (%)	0 (%)	0 (%)
Number of Participants with TEAEs leading to Study Discontinuation	0 (%)	0 (%)	0 (%)	0 (%)
Number of Participants with TEAEs leading to Death	0 (%)	0 (%)	0 (%)	0 (%)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	Treatment-emergent adverse events
Source Vocabulary for Table Default	MedDRA (25.1)

Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Group 1: Healthy Control N = 15	Group 2: Mild; Child-Pugh A N = 8	Group 3: Moderate; Child-Pugh B N = 8	Group 4: Severe; Child-Pugh C N = 7	Overall N = 38
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201	Overall
Total Number Affected	0	0	0	0	0
Total Number At Risk	15	8	8	7	38

Serious Adverse Events

Time Frame	Treatment-emergent adverse events
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment

No data identified.

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Other (Not Including Serious) Adverse Events

Time Frame	Treatment-emergent adverse events
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Group 1: Healthy Control N = 15	**Group 2: Mild; Child-Pugh A N = 8**	**Group 3: Moderate; Child-Pugh B N = 8**	**Group 4: Severe; Child-Pugh C N = 7**	**Overall N = 38**
Arm/Group Description	Each healthy participant received a single 10 mg dose of HDM201	Each participant with mild Child-Pugh received a single 10 mg dose of HDM201	Each participant with moderate Child-Pugh received a single 10 mg dose of HDM201	Each participant with severe Child-Pugh received a single 10 mg dose of HDM201	Overall
Total # Affected by any Other Adverse Event	1	0	0	1	2
Total # at Risk by any Other Adverse Event	15	8	8	7	38
Nervous system disorders					
Headache	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)
Skin and subcutaneous tissue disorders					

Rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (2.63%)

Other Relevant Findings

Conclusion:

Siremadlin total exposure (AUClast and AUCinf) were approximately 1.10-, 1.46-1.48-, and 1.45-1.46-fold greater in participants with mild, moderate, and severe HI respectively compared to healthy participants.

Siremadlin peak (Cmax) exposures in participants with mild, moderate, and severe HI were comparable to healthy participants (GMR: 107%, 94% and 93%, respectively).

Time to reach maximum plasma concentration following a single dose administration (Tmax) was similar among all Hepatic impairment (HI) groups and in the healthy control group.

Single oral doses of 10 mg siremadlin were well tolerated when administered to participants with mild, moderate, or severe HI and to healthy matched participants in this study.

Date of Clinical Trial Report

12-Aug-2024