Sponsor: Sanofi **Drug substance:** Belumosudil	**Study Identifiers:** NCT04166942 **Study code:** KD025-109 (POP17629)
Title of the study: A Single-dose, Open-label, Pharmacokinetic Study of KD025 in Participants with Normal Hepatic Function and Participants with Varying Degrees of Hepatic Impairment	
Study period: 11 December 2019 (date of first informed consent) to 06 June 2022 (date of the last participant's last assessment [scheduled or unscheduled]).	
Phase of development: Clinical Phase 1	
Objectives: The primary objective was: ・to assess the pharmacokinetic (PK) of belumosudil following a single oral dose of belumosudil in participants with mild, moderate, or severe hepatic impairment compared to healthy participants with normal hepatic function. The secondary objectives were: ・to evaluate the safety and tolerability of a single oral dose of belumosudil in participants with mild, moderate, or severe hepatic impairment, and in healthy participants with normal hepatic function. ・to assess the PK of the belumosudil metabolites following a single oral dose of belumosudil in participants with mild, moderate, or severe hepatic impairment compared to healthy participants with normal hepatic function.	

Methodology:

This was a Phase 1, open-label, non-randomized, parallel-group study to determine the effect of hepatic impairment on the PK, safety, and tolerability of a single oral dose of belumosudil compared to matched healthy participants with normal hepatic function.

Approximately 38 participants were to be enrolled into the following groups based on their hepatic function, as determined according to the Child-Pugh system.

- Group 1 (n = approximately 16): matched healthy participants with normal hepatic function
- Group 2 (n = 8): participants with mild hepatic impairment (Child-Pugh Class A [score of 5 or 6])
- Group 3 (n = 8): participants with moderate hepatic impairment (Child-Pugh Class B [score of 7 to 9])
- Group 4 (n = 6): participants with severe hepatic impairment (Child-Pugh Class C [score of 10 to 14]).

Healthy participants with normal hepatic function (Group 1) were demographically matched by age (±10 years), sex, and body mass index (BMI; ±20%) to participants with hepatic impairment (Groups 2, 3, and 4). Participants with normal hepatic function could be matched to multiple participants across the 3 hepatic impairment groups (mild, moderate, and severe), but could not be matched to more than 1 participant within the same impairment group.

Potential participants were screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Participants were admitted into the clinical research unit (CRU) on Day -1 and were confined to the CRU until discharge on Day 3. Participants returned to the CRU for a follow-up visit on Day 10 (approximately 9 days after the belumosudil dose).

On the morning of Day 1, a single oral dose of 200 mg belumosudil was administered with 240 mL of water, within 5 minutes of completing a standardized breakfast. Pharmacokinetic blood samples were obtained from predose until 48 hours postdose (Day 3).

Number of participants:

It was planned to study approximately 38 participants: 8 participants in each of the mild and moderate hepatic impairment groups, 6 participants in the severe hepatic impairment group, and approximately 16 matched participants with normal hepatic function.

A total of 36 participants were enrolled in the study in accordance with the protocol and protocol amendments: 8 participants in each of the mild and moderate hepatic impairment groups, 6 participants in the severe hepatic impairment group, and 14 matched participants with normal hepatic function. Data for all participants were included in the PK and safety analyses.

Diagnosis and main criteria for inclusion:

Participants of any race, aged between 18 and 75 years, inclusive, and with a BMI between 18.0 and 38.0 kg/m^2, inclusive.

The matched control participants with normal hepatic functions were to be in good health, as assessed by the investigator (or designee), and the participants with hepatic impairment were to have documented chronic stable liver disease and may have had medical findings consistent with their hepatic dysfunction.

Study products

A single dose of 200 mg belumosudil was administered orally as a tablet following a standard breakfast.

Duration of treatment: Single doses were administered in each group.

Criteria for evaluation:

The primary endpoints, PK endpoints of belumosudil derived from the concentration time profile following single-dose oral administration, were area under the concentration time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$), AUC from time 0 to the last measurable concentration (AUC_{0-t}),maximum observed concentration (C_{max}), time of C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), time of last measurable concentration (t_{last}), apparent total clearance (CL/F), and apparent volume of distribution during the terminal elimination phase (V_Z/F).

The secondary/safety endpoints were: incidence and severity of adverse events (AEs), clinical laboratory parameters (hematology, clinical chemistry, coagulation, and urinalysis), 12-lead electrocardiogram (ECG) parameters, vital signs parameters, and physical examinations.

The PK outcome endpoints of the belumosudil metabolites derived from the concentration-time profile following single-dose oral administration were as follows and were determined whenever possible: $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, t_{last}, and metabolite to parent ratios, adjusted for molecular weight.

Statistical methods:

Analysis populations:

The participant population included all participants who signed the informed consent form and had any study assessment recorded in the database per the protocol.

The safety population included all participants who received a dose of belumosudil.

The PK population included all participants who received a dose of belumosudil, did not receive excluded concomitant medications through the completion of PK sampling, and had sufficient concentration-time data to permit reliable estimation of PK parameters.

Statistical methodology:

All PK concentrations and parameters were listed.

Summary tables, mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by hepatic function and time postdose were provided for plasma PK concentrations. Summary tables by hepatic function were provided for all PK parameters, with the exception of terminal phase regression-related diagnostic parameters (λz, λz upper, λ z lower, λz number of points, R2-adj, and %AUCextrap), which were listed only.

A statistical analysis was conducted to evaluate the PK of belumosudil and metabolites following a single dose in participants with mild, moderate, or severe hepatic impairment (test hepatic functions) compared to their matched healthy participants with normal hepatic function (reference hepatic function) for primary PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}). All other PK parameters were regarded as secondary and were not participant to inferential statistical analysis.

All safety data for the safety population were listed.

Treatment-emergent AEs (TEAEs) were summarized by severity and relationship to the investigational medicinal product (IMP). The frequency of TEAEs was summarized by Medical Dictionary for Regulatory Activities system organ class and preferred term, and hepatic function. Summary and frequency TEAE tables were presented for all causalities and for those considered related to the IMP.

Serum biochemistry, hematology, and coagulation data were summarized by hepatic function. In addition, all serum biochemistry, hematology, and urinalysis data outside the clinical reference ranges were listed by parameter and treatment. Vital signs and ECG data were summarized by hepatic function, together with changes from baseline.

Summary Results:

Population characteristics:

A total of 36 participants were enrolled in the study in accordance with the protocol and protocol amendments: 8 participants in each of the mild and moderate hepatic impairment groups, 6 participants in the severe hepatic impairment group, and 14 matched participants with normal hepatic function. Male (72.2%) and female (27.8%) participants aged 36 to 70, inclusive, with a BMI between 22.6 and 38.0 kg/m^2, inclusive, were enrolled in the study.

Pharmacokinetic results:

The following PK analysis considerations were noted:

• One participant (moderate hepatic impairment) did not complete the 48-hour postdose sample due to early discharge following an SAE. The PK was not affected as concentrations of all analytes were below the limit of quantification (BLQ) by 36 hours postdose.

• One participant (mild hepatic impairment) had an embedded BLQ at 8 hours postdose for metabolite KD025m1. This concentration was excluded from descriptive statistics and PK analysis.

• Two participants (normal hepatic function and moderate hepatic impairment) had full BLQ profiles for KD025m1; therefore, no PK parameters were calculable.

• Seven participants had fewer than 3 consecutive quantifiable concentrations in their profiles; only C_{max}, t_{lag}, t_{max}, and t_{last} were reportable for:

o 4 participants with normal hepatic function and 2 participants with mild impairment for KD025m1

o 1 participant with moderate impairment for KD025m2

• For multiple participants, a terminal phase regression could not be determined due to poor fit (r2 adj. <0.7); regression-based parameters ($AUC_{0-\infty}$, $\%AUC_{extrap}$, $t_{1/2}$, CL/F, and V_z/F) were not calculable for:

o 1 participant with severe impairment and 1 participant with normal hepatic function for KD025

o 1 participant with mild impairment, 2 participants with moderate impairment, and 1 participant with severe impairment for KD025m1

Arithmetic mean (+SD) plasma concentration-time profiles of belumosudil are presented in Figure 1. The summary and statistical analysis of plasma PK parameters of belumosudil are presented in Table 1 and Table 2.

o 1 participant with severe impairment for KD025m2

・ Terminal phase regression-based parameters for the following participants and analytes were listed but flagged for exclusion from statistics because $\%AUC_{extrap}$ >30%:

o 1 participant with severe impairment for KD025

o 2 participants with normal hepatic function, 1 participant with mild impairment, 1 participant with moderate impairment for KD025m1

o 3 participants with severe impairment for KD025m2

・For several participants, the half-life was calculated over a span of time less than twice the resultant half-life. These half-life values are flagged and footnoted but included in statistics.

・Thirteen participants (2 with mild impairment, 5 with moderate impairment, and all 6 with severe impairment) were taking rifaximin and are flagged and footnoted.

Rifaximin is a non-absorbable rifampicin analog. Rifampicin is a strong CYP inducer and has been shown to decrease exposure of belumosudil by approximately 60% to 70% (KD025-107). Per label, rifaximin is not shown to have drug-drug interaction (DDI) effects in healthy volunteers, consistent with a non-absorbable compound, and DDI effects have not been reported in participants with hepatic impairment. However, in vitro, rifaximin has been shown to be a CYP3A4 inducer at high concentrations, which may result in a clinical DDI due to higher rifaximin exposure in participants with hepatic impairment. The potential for a clinical DDI effect has not been studied in participants with hepatic impairment. Rifaximin plasma concentration increases with Child-Pugh class, so participants with a greater degree of hepatic impairment may have higher rifaximin plasma levels than participants with mild hepatic impairment or healthy volunteers. If rifaximin levels were higher in moderately and severely impaired participants, higher levels of CYP induction could be expected, thus belumosudil exposure may be reduced. Rifaximin is a commonly used medication in participants with hepatic impairment; participants in this study were not in violation of the inclusion or exclusion criteria by taking this medication.

o 1 participant with moderate impairment showed a greatly reduced concentration profile and exposure, which may be consistent with rifaximin dosing. This participant's belumosudil and metabolite concentrations and PK parameters are also flagged for exclusion from statistics and are participant to sensitivity analysis due to atypical concentration profiles.

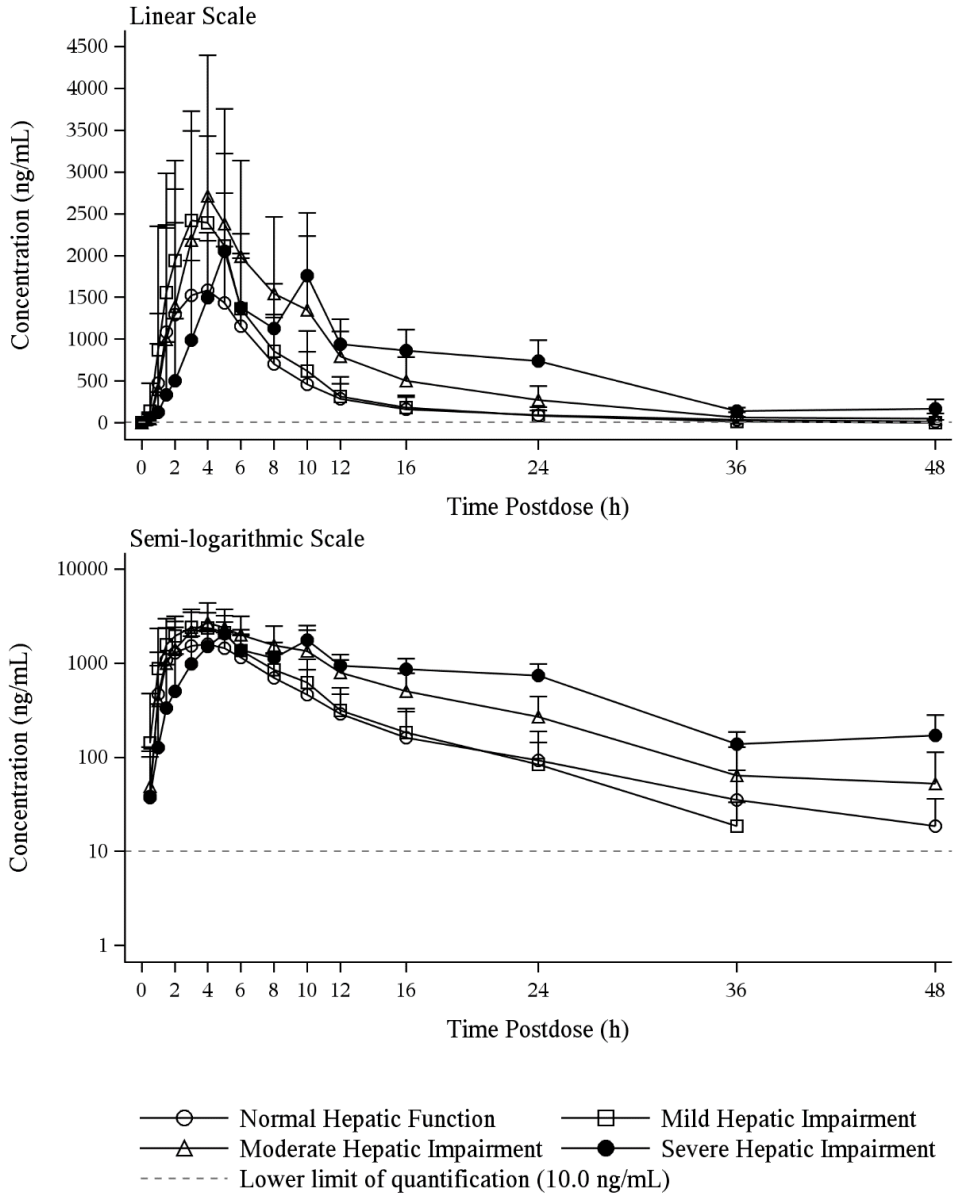
o 2 participants with severe impairment show greatly reduced concentration profiles and exposures, which may be consistent with rifaximin dosing. These participants' belumosudil and metabolite concentrations and PK parameters are also flagged for exclusion from statistics and are participant to sensitivity analysis.

Pharmacokinetic Analysis of Belumosudil

Arithmetic mean (+SD) plasma concentration-time profiles of belumosudil are presented in Figure 1. The summary and statistical analysis of plasma PK parameters of belumosudil are presented in Table 1.

Figure 1: Arithmetic Mean (+SD) Plasma Concentration-time Profile of Belumosudil

Population: Pharmacokinetic
Matrix: Plasma; Analyte: KD025
Treatment: 200 mg KD025



Reference: Table 14.2.1-1
Program Location: /cvn/projects/prj/ecb/programs/000000188368/dev/figures/f_pc.sas
Program Status: FINAL Program Run: 24NOV2022 Protocol Reference: KD025-109

Table 1: Summary of the Plasma Pharmacokinetic Parameters of Belumosudil

Matrix: Plasma; Analyte: KD025

Parameter	Normal Hepatic Function (N = 14)	Mild Hepatic Impairment (N = 8)	Moderate Hepatic Impairment (N = 8)	Severe Hepatic Impairment (N = 6)
$AUC_{(0-\infty)}$ (h*ng/mL)	12800 (52.9) [13]	16000 (45.3) [8]	23700 (61.2) [7]	30100 (14.7) [3]
$AUC_{(0-24)}$ (h*ng/mL)	11300 (49.5) [14]	15400 (44.6) [8]	21300 (57.7) [7]	23400 (20.3) [4]
AUC_{0-t} (h*ng/mL)	12000 (53.1) [14]	15800 (45.4) [8]	23100 (60.9) [7]	29600 (17.6) [4]
C_{max} (ng/mL)	2190 (36.4) [14]	2590 (30.7) [8]	2490 (69.8) [7]	2170 (33.6) [4]
t_{max} (h)	3.50 (1.50-6.00) [14]	2.98 (1.92-4.00) [8]	4.00 (3.00-8.00) [7]	5.02 (5.00-10.0) [4]
t_{last} (h)	48.0 (16.0-48.0) [14]	36.0 (16.0-48.0) [8]	48.0 (23.8-48.0) [7]	48.0 (48.0-48.0) [4]
$t_{1/2}$ (h)	8.58 (48.8) [13]	5.86 (45.2) [8]	6.30 (44.4) [7]	10.00 (40.7) [3]
CL/F (L/h)	15.6 (52.9) [13]	12.5 (45.3) [8]	8.42 (61.2) [7]	6.63 (14.7) [3]
V_z/F (L)	193 (57.9) [13]	105 (63.4) [8]	76.6 (49.5) [7]	95.7 (48.4) [3]
t_{lag} (h)	NC (NC) [14]	NC (NC) [8]	NC (NC) [7]	NC (NC) [4]

$AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CL/F = apparent total clearance; C_{max} = maximum observed concentration; CV = coefficient of variation (%);
n = number of participants with valid observations; NC = not calculated; $t_{1/2}$ = apparent terminal elimination half-life; t_{last} = time of the last quantifiable concentration; t_{max} = time of the maximum observed
concentration; Vz/F = apparent volume of distribution during the terminal phase; (%)AUCextrap = percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
Geometric mean (CV) [n] statistics presented; for t_{max}, and t_{last}, median (min-max) [n] statistics presented.

Following administration of a single oral dose of 200 mg belumosudil, the plasma concentration-time profiles of belumosudil in participants with normal hepatic function, and with mild, moderate, and severe hepatic impairment were characterized by steady absorption and bi-phasic disposition, with respective median t_{max} values of 3.50, 2.98, 4.00, and 5.02 hours and geometric mean $t_{1/2}$ values of 8.58, 5.86, 6.30, and 10.00 hours. The severe hepatic impairment group had delayed median t_{max} and longer geometric mean $t_{1/2}$ compared to other hepatic function groups.
Geometric mean CL/F values for belumosudil decreased as the severity of hepatic impairment increased, with values of 15.6, 12.5, 8.42, and 6.63 L/h for participants with normal hepatic function, and with mild, moderate, and severe hepatic impairment, respectively.
Geometric mean Vz/F values were generally lower for participants with hepatic impairment (76.6 to 105 L) than for participants with normal hepatic function (193 L).
Geometric mean PK exposure of belumosudil was higher in participants with hepatic impairment compared to participants with normal hepatic function. However, statistical analysis showed that the effect of mild and moderate impairment on belumosudil PK exposure was not statistically significant. The ratios of the geometric least squares mean (GLSM; 90% CI) for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were 1.36 (0.831, 2.21), 1.48 (0.960, 2.28), and 1.20 (0.907, 1.58), respectively, for the mild hepatic impairment group, and 1.51 (0.975, 2.33), 1.50 (0.973, 2.31), and 0.944 (0.600, 1.48), respectively, for the moderate hepatic impairment

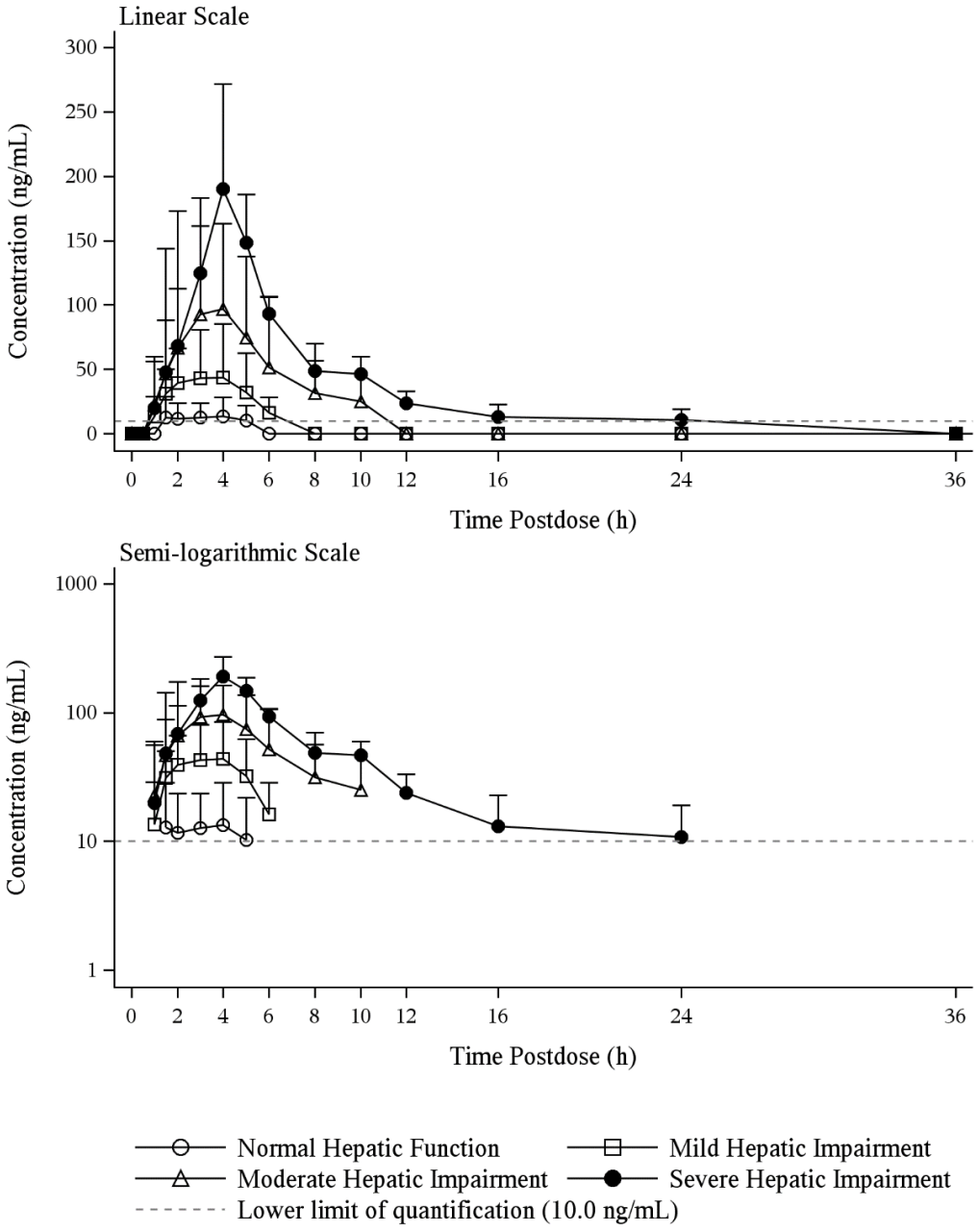
group, with 90% CIs spanning unity. However, severe hepatic impairment significantly increased the $AUC_{0-\infty}$ and AUC_{0-t} of belumosudil but had no apparent effect on its C_{max}, with the ratios of the GLSMs (90% CI) of 4.21 (2.20, 8.06), 3.23 (1.53, 6.81), and 1.32 (0.896, 1.96), respectively.
As assessed from the within-matched participants CV%, the variability was generally high for all comparisons for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, with values ranging from 23.5% to 54.9%.

Pharmacokinetic Analysis of Belumosudil Metabolites

Arithmetic mean (+SD) plasma concentration-time profiles of KD025m1 are presented in Figure 2. The summary and statistical analysis of plasma PK parameters of KD025m1 are presented in Table 2, respectively.

Figure 2: Arithmetic Mean (+SD) Plasma Concentration-time Profile of KD025m1

Population: Pharmacokinetic
Matrix: Plasma; Analyte: KD025m1
Treatment: 200 mg KD025



Reference: Table 14.2.1-1
Program Location: /cvn/projects/prj/ecb/programs/000000188368/dev/figures/f_pc.sas
Program Status: FINAL Program Run: 24NOV2022 Protocol Reference: KD025-109

Table 2: Summary of the Plasma Pharmacokinetic Parameters of KD025m1

Matrix: Plasma; Analyte: KD025m1

Parameter	Normal Hepatic Function (N = 14)	Mild Hepatic Impairment (N = 8)	Moderate Hepatic Impairment (N = 8)	Severe Hepatic Impairment (N = 6)
$AUC_{(0-\infty)}$ (h*ng/mL)	NC (NC) [2]	304 (21.0) [4]	681 (66.4) [4]	1180 (42.8) [3]
$AUC_{(0-24)}$ (h*ng/mL)	138 (36.0) [4]	315 (40.5) [6]	464 (105.3) [7]	1030 (30.6) [4]
AUC_{0-t} (h*ng/mL)	71.6 (58.7) [9]	242 (54.8) [6]	382 (141.1) [7]	1010 (32.7) [4]
C_{max} (ng/mL)	24.1 (50.4) [13]	43.9 (100.9) [8]	90.2 (78.2) [7]	180 (48.0) [4]
t_{max} (h)	3.00 (1.50-6.00) [13]	2.46 (1.48-4.00) [8]	3.95 (1.50-5.00) [7]	4.52 (4.00-6.00) [4]
t_{last} (h)	5.00 (1.95-10.0) [13]	6.00 (1.48-10.0) [8]	10.0 (5.00-24.0) [7]	24.0 (12.0-24.1) [4]
$t_{1/2}$ (h)	2.29 (18.8) [4]	2.46 (91.5) [5]	3.06 (33.4) [5]	5.36 (77.7) [3]
MR_{AUC}	0.00696 (24.1) [9]	0.0147 (70.3) [6]	0.0182 (91.6) [7]	0.0377 (26.1) [4]
t_{lag} (h)	NC (NC) [13]	NC (NC) [8]	NC (NC) [7]	NC (NC) [4]

$AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CL/F = apparent total clearance; C_{max} = maximum observed concentration; CV = coefficient of variation (%);
n = number of participants with valid observations; NC = not calculated; t1/2 = apparent terminal elimination half-life; t_{last} = time of the last quantifiable concentration; t_{max} = time of the maximum observed concentration; V_z/F = apparent volume of distribution during the terminal phase; (%)AUC_{extrap} = percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
Geometric mean (CV) [n] statistics presented; for tmax, and tlast, median (min-max) [n] statistics presented.

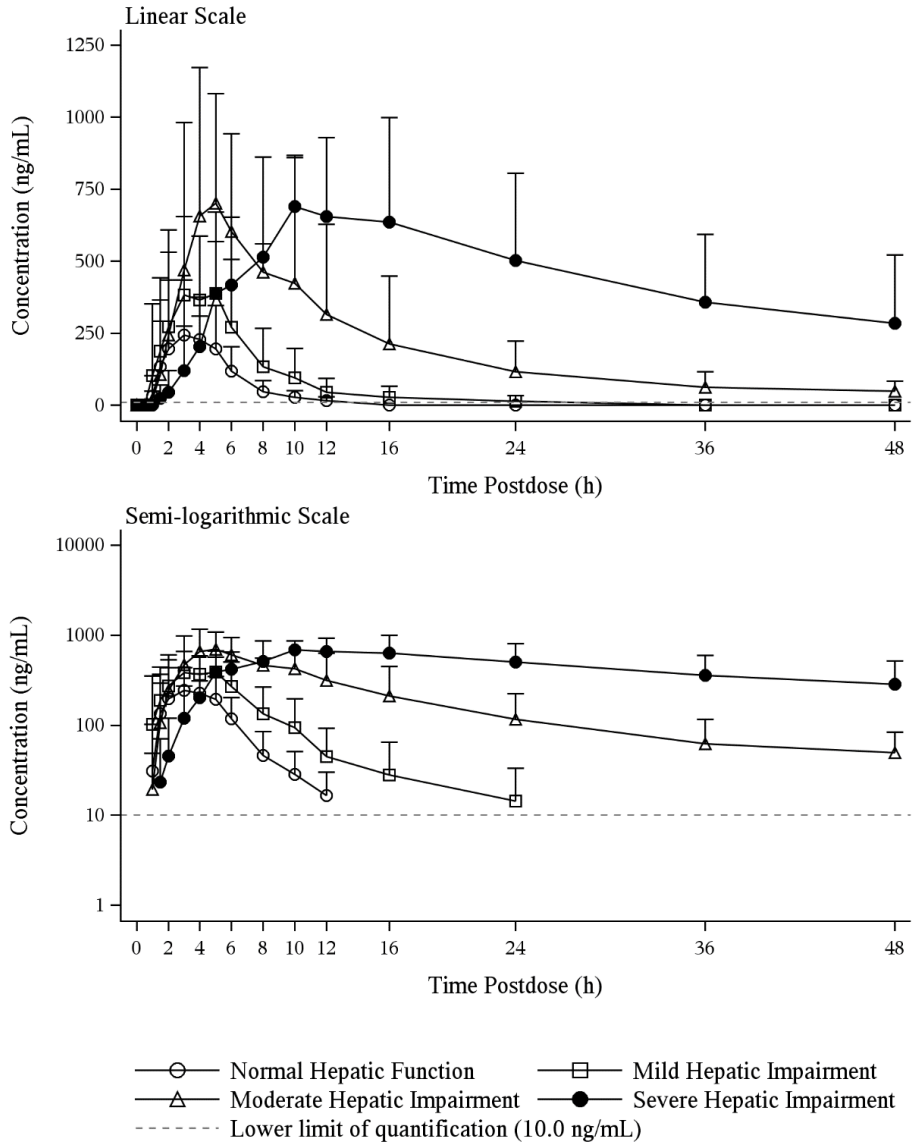
Following administration of a single oral dose of 200 mg belumosudil, the metabolite KD025m1 was steadily produced with median t_{max} values of 3.00, 2.46, 3.95, and 4.52 hours for participants with normal hepatic function, mild hepatic impairment, moderate hepatic impairment, and severe hepatic impairment, respectively.
The geometric mean $t_{1/2}$ of KD025m1 increased with increasing severity of hepatic impairment, with values of 2.29, 2.46, 3.06, and 5.36 hours in participants with normal hepatic function, and with mild, moderate, and severe hepatic impairment, respectively.
The $AUC_{0-\infty}$ was not calculable for KD025m1 in the normal hepatic function group due to limited quantifiable data. For hepatic impairment groups, geometric mean $AUC_{0-\infty}$ values increased from mild, moderate, to severe impairment. The AUC_{0-t} and C_{max} in participants with hepatic impairment were higher than in participants with normal hepatic function, and increased with increasing severity of hepatic impairment. Statistical analysis showed that the ratios of GLSMs (90% CI) for AUC_{0-t} and C_{max} were 3.15 (1.46, 6.79) and 1.63 (0.980, 2.70), respectively, in participants with mild hepatic impairment, 3.56 (1.53, 8.31) and 2.40 (1.36, 4.25), respectively, in participants with moderate hepatic impairment, and 18.6 (5.89, 58.4) and 8.59 (4.72, 15.6) in participants with severe hepatic impairment. These results indicated that hepatic impairment significantly increased KD025m1 exposure, especially in participants with severe hepatic impairment.
As assessed from the within-matched participants CV%, the variability was high for all comparisons for AUC_{0-t} and C_{max}, with values ranging from 37.2% (geometric CV%) to 96.1% (total CV% as participant matching could not be fitted in the model).

The geometric mean $MRAUC_{0-t}$ for KD025m1 was higher in participants with hepatic impairment compared to participants with normal hepatic function; however, the associated variability (based on geometric CV%) was also much higher in the mild and moderate hepatic impairment groups, although similar in the severe hepatic impairment group. The geometric mean MR_{AUC0-t} (CV%) was 0.00696 (24.1%), 0.0147 (70.3%), 0.0182 (91.6%), and 0.0377 (26.1%) for participants with normal hepatic function, mild hepatic impairment, moderate hepatic impairment, and severe hepatic impairment, respectively.

KD025m2
Arithmetic mean (+SD) plasma concentration-time profiles of KD025m2 are presented in Figure 3. The summary and statistical analysis of plasma PK parameters of KD025m2 are presented in Table 3

Figure 3: Arithmetic Mean (+SD) Plasma Concentration-time Profile of KD025m2

Population: Pharmacokinetic
Matrix: Plasma; Analyte: KD025m2
Treatment: 200 mg KD025



Reference: Table 14.2.1-1
Program Location: /cvn/projects/prj/ecb/programs/000000188368/dev/figures/f_pc.sas
Program Status: FINAL Program Run: 24NOV2022 Protocol Reference: KD025-109

Table 3: Summary of the Plasma Pharmacokinetic Parameters of KD025m2

Matrix: Plasma; Analyte: KD025m2

Parameter	Normal Hepatic Function (N = 14)	Mild Hepatic Impairment (N = 8)	Moderate Hepatic Impairment (N = 8)	Severe Hepatic Impairment (N = 6)
AUC(0-∞) (h*ng/mL)	1220 (66.8) [14]	2040 (120.4) [8]	7500 (117.5) [7]	NC (NC) [2]
AUC(0-24) (h*ng/mL)	1160 (61.7) [14]	1960 (114.0) [8]	5720 (102.2) [7]	11000 (38.3) [4]
AUC0-t (h*ng/mL)	1130 (64.8) [14]	1940 (123.3) [8]	6680 (121.9) [7]	18300 (62.9) [4]
Cmax (ng/mL)	335 (61.6) [14]	437 (73.1) [8]	660 (111.1) [7]	838 (18.8) [4]
tmax (h)	3.00 (1.50-6.00) [14]	2.98 (1.92-5.00) [8]	5.00 (4.00-10.0) [7]	11.0 (6.05-16.0) [4]
tlast (h)	14.0 (5.97-24.0) [14]	23.9 (5.88-48.0) [8]	48.0 (16.1-48.0) [7]	48.0 (48.0-48.0) [4]
t1/2 (h)	4.06 (114.0) [14]	4.47 (79.5) [8]	11.3 (57.4) [7]	17.7 (37.2) [3]
MRAUC	0.103 (68.8) [14]	0.135 (73.8) [8]	0.318 (70.5) [7]	0.680 (63.5) [4]
tlag (h)	NC (NC) [14]	NC (NC) [8]	NC (NC) [7]	NC (NC) [4]

$AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CL/F = apparent total clearance; C_{max} = maximum observed concentration; CV = coefficient of variation (%);
n = number of participants with valid observations; NC = not calculated; t1/2 = apparent terminal elimination half-life; t_{last} = time of the last quantifiable concentration; t_{max} = time of the maximum observed concentration; V_z/F = apparent volume of distribution during the terminal phase; (%)AUC_{extrap} = percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
Geometric mean (CV) [n] statistics presented; for t_{max}, and t_{last}, median (min-max) [n] statistics presented.

Following administration of a single oral dose of 200 mg belumosudil, the metabolite KD025m2 was steadily produced, with median t_{max} values of 3.00, 2.98, 5.00, and 11.00 hours for participants with normal hepatic function, mild hepatic impairment, moderate hepatic impairment, and severe hepatic impairment, respectively.
The geometric mean $t_{1/2}$ of KD025m2 was similar between participants with normal hepatic function and participants with mild hepatic impairment, with values of 4.06 and 4.47 hours, respectively. The geometric mean $t_{1/2}$ was much longer for participants with moderate and severe hepatic impairment, with values of 11.3 and 17.7 hours, respectively.
Geometric mean PK exposure of KD025m2 was higher in participants with hepatic impairment compared to participants with normal hepatic function. Statistical analysis showed that the effect of mild impairment on the $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} of KD025m2 was not apparent, with the respective ratio of GLSMs (90% CI) of 1.68 (0.748, 3.79), 1.70 (0.793, 3.65), and 1.15 (0.676, 1.96), respectively, and 90% CIs spanning the unity of 1. However, moderate and severe hepatic impairment significantly increased the PK exposure of KD025m2; the ratios of GLSMs (90% CI) for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were 5.06 (2.73, 9.35), 4.95 (2.68, 9.15), and 1.70 (1.00, 2.88), respectively, in participants with moderate hepatic impairment, and for AUC_{0-t} and C_{max} were 15.3 (7.34, 32.0) and 2.55 (1.51, 4.31), respectively, in participants with severe hepatic impairment ($AUC_{0-\infty}$ was not calculated for the severe group).
As assessed from the within-matched participants CV%, the variability was high for all comparisons for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, with values ranging from 32.2% (geometric CV%) to 105.9% (total CV% as participant matching could not be fitted in the model).

The geometric mean MRAUC for KD025m2 was generally similar between normal hepatic function and mild hepatic impairment groups, with values (CV%) of 0.103 (68.8%) and 0.135 (73.8%), respectively. The geometric mean MRAUC was the highest in participants with severe hepatic impairment, followed by participants with moderate hepatic impairment, with values (CV%) of 0.680 (63.5%) and 0.318 (70.5%), respectively.

Safety results:

There were no reports of deaths, no reports of AEs related to study drug, and no participants discontinued due to an AE during the study.
Overall, 1 participant (12.5%) in the moderate hepatic impairment group reported a total of 2 TEAEs; 1 of which was classified as an SAE. Additionally, 2 participants reported AEs of urinary tract infection on Day -1, which were not considered treatment-emergent as they were prior to dose administration.
There were no clinically significant changes in clinical chemistry, hematology, coagulation, or urinalysis throughout the duration of the study.
During all parts of the study, there were no clinically significant changes in the vital signs parameters for individual participants. Although transient changes in blood pressure and pulse rate were noted at isolated timepoints for some participants, none of these findings were clinically important.
There were no clinically significant changes in the 12-lead ECG parameters for individual participants.
There were no clinically significant findings in the physical examinations performed throughout the study.

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