Sponsor: Sanofi **Drug substance(s):** Belumosudil	**Study Identifiers:** U1111-1277-6732; NCT05806567 **Study code:** INT17676 (KD025-112)

Title of the study:

A three-part, sequential, non-randomized, open-label study designed to evaluate the effect of oral Belumosudil on UGT1A1, P-gp, BCRP and OATP1B1 inhibition in the fed state in healthy male subjects

Study center(s):

This study was conducted at 1 center that enrolled participants in the USA.

Study period:

27 July 2022 to 28 October 2022

Study Status: Completed

Phase of development: 1

Objectives:

Primary:

Part 1:

To determine the effect of multiple doses of REZUROCK™ (belumosudil) tablet on the single dose oral PK of the UGT1A1 victim drug, ISENTRESS® (raltegravir).

Part 2:

To determine the effect of multiple doses of REZUROCK (belumosudil) tablet on the single dose oral PK of the P-gp victim drug, PRADAXA® (dabigatran etexilate).

Part 3:

To determine the effect of multiple doses of REZUROCK (belumosudil) tablet on the single dose oral PK of the OATP1B1/BCRP victim drug, CRESTOR® (rosuvastatin calcium).

Secondary:

Part 1:

To provide single dose PK data on the victim drug raltegravir and its metabolite, raltegravir glucuronide, following administration of raltegravir alone and in combination with REZUROCK (belumosudil) tablet.

Part 2:

To provide single dose PK data on the victim drug dabigatran etexilate, alone and in combination with REZUROCK (belumosudil) tablet.

Part 3:

To provide single dose PK data on the victim drug rosuvastatin, alone and in combination with REZUROCK (belumosudil) tablet.

Parts 1, 2, and 3

To determine the PK of belumosudil and known metabolites (KD025m1, KD025m2) following single and multiple oral doses of REZUROCK (belumosudil) tablet in healthy participants in the fed state.

Parts 1, 2, and 3

To provide additional safety and tolerability information for REZUROCK (belumosudil) tablet when coadministered with the UGT1A1 victim drug, raltegravir (Part 1), the P-gp victim drug, dabigatran etexilate (Part 2), and the OATP1B1/BCRP victim drug, rosuvastatin (Part 3).

Methodology:

Part 1 was a single-center, nonrandomized, open-label, single-period design to assess the effect of multiple doses of belumosudil on the single-dose PK of raltegravir (a UGT1A1-sensitive substrate), and 19 healthy male participants were to be enrolled.

Part 2 was a single-center, nonrandomized, open-label, single-period design to assess the effect of multiple doses of belumosudil on the single-dose PK of dabigatran etexilate (a P-gp-sensitive substrate), and 19 healthy male participants were to be enrolled.

Part 3 was a single-center, nonrandomized, open-label, single-period design to assess the effect of multiple doses of belumosudil on the single-dose PK of rosuvastatin (a BCRP/OATP1B1-sensitive substrate), and 15 healthy male participants were to be enrolled.

Throughout this clinical study report, the term “study intervention” refers to the following:

• Perpetrator investigational medicinal product (IMP): REZUROCK (belumosudil) tablets, 200 mg

• Victim IMPs: ISENTRESS (raltegravir) film-coated tablets (400 mg), PRADAXA (dabigatran etexilate) capsules (75 mg), and CRESTOR (rosuvastatin calcium) tablets (10 mg)

Parts 1, 2, and 3 Study Design

In each study part, participants underwent preliminary screening procedures for the study at the screening visit (Days -28 to -2 of each study part). Participants were admitted to the clinical unit on the morning of the day prior to first dose of study intervention (ie, on Day -1).

Enrolled participants were dosed with perpetrator and victim IMPs as follows:

• Part 1 (Regimen A [raltegravir + belumosudil]): Participants received a single dose of the victim IMP raltegravir on the morning of Days 1 and 7. Additionally, participants received a single dose of the perpetrator belumosudil tablet on the morning of Days 3 to 8 (once daily [QD]). On Day 7, the victim and perpetrator IMPs were administered simultaneously.

• Part 2 (Regimen B [dabigatran etexilate + belumosudil]): Participants received a single dose of the victim IMP dabigatran etexilate on the morning of Days 1 and 9. Additionally, participants received a single dose of the perpetrator belumosudil tablet on the morning of Days 5 to 12 (QD). On Day 9, the victim and perpetrator IMPs were administered simultaneously.

• Part 3 (Regimen C [rosuvastatin calcium + belumosudil]): Participants received a single dose of the victim IMP rosuvastatin on the morning of Days 1 and 10. Additionally, participants received a single dose of the perpetrator belumosudil tablet on the morning of Days 6 to 13 (QD). On Day 10, the victim and perpetrator IMPs were administered simultaneously.

On the evening before each dose, participants were provided with a light snack and were required to fast from all food and drink (except water) for a minimum of 10 hours until the following morning. All study interventions were administered in the fed state, following completion of a standard breakfast (with dosing planned to occur 30 minutes after the start of the breakfast).

In each study part, blood samples were collected at regular intervals for the PK analysis of plasma concentrations of the following analytes: raltegravir and raltegravir glucuronide (Part 1); unconjugated dabigatran (Part 2); rosuvastatin (Part 3); and belumosudil and known metabolites (KD025m1, KD025m2) (Parts 1, 2, and 3). The following safety assessments were also performed in Parts 1, 2, and 3: incidence of adverse events (AEs), vital signs, electrocardiograms (ECGs), physical examinations, and laboratory safety tests.

All participants remained on site until 48 hours postfinal dose for safety and PK assessments, and a follow-up phone call was to take place at 3 to 7 days postfinal dose to ensure the ongoing wellbeing of the participants.

Number of participants:

Part 1 (Regimen A): It was planned to enroll 19 participants in Part 1. 19 participants were enrolled and were administered Regimen A (raltegravir + belumosudil), and all enrolled participants completed the study.

All 19 enrolled participants were included in the safety and PK populations and analysis sets.

Part 2 (Regimen B): It was planned to enroll 19 participants in Part 2. 19 participants were enrolled and were administered Regimen B (dabigatran etexilate + belumosudil), and all enrolled participants completed the study.

All 19 enrolled participants were included in the safety and PK populations and analysis sets.

Part 3 (Regimen C): It was planned to enroll 15 participants in Part 3; however, 1 participant was determined to be ineligible to dose on Day 1. Therefore, 14 participants were enrolled and were administered Regimen C (rosuvastatin calcium + belumosudil), and all enrolled participants completed the study.

All 14 enrolled participants were included in the safety and PK populations and analysis sets.

Diagnosis and criteria for inclusion:

This study enrolled healthy male participants aged 18 to 55 years inclusive, at time of signing informed consent, with a body mass index (BMI) 18.0 to 32.0 kg/m^2 and body weight ≥50 kg as measured at screening. In Part 1, participants identified to be poor metabolizers for UGT1A1 and in Part 3, participants identified to carry reduced or predicted reduced function genes for SLCO1B1 (OATP1B1) were excluded from the study.

Study products

Part 1 (Regimen A):

Victim IMP: ISENTRESS (raltegravir) film coated tablets, for oral use, 400 mg (expressed as the free phenol equivalent)

Part 2 (Regimen B):

Victim IMP: PRADAXA (dabigatran etexilate) capsules, for oral use, 75 mg (expressed as the free drug equivalent)

Part 3 (Regimen C):

Victim IMP: CRESTOR (rosuvastatin calcium) tablets, 10 mg (expressed as the free drug equivalent)

Parts 1, 2, and 3 (Regimens A, B, and C, respectively):

Perpetrator IMP: REZUROCK (belumosudil) tablet, 200 mg (expressed as the free base equivalent)

All study interventions were administered orally in the fed state.

Duration of study intervention:

In Part 1, participants received a single dose of raltegravir on 2 separate occasions (morning of Days 1 and 7), and belumosudil QD for 6 consecutive days (morning of Days 3 to 8). In Part 2, participants received a single dose of dabigatran etexilate on 2 separate occasions (morning of Days 1 and 9), and belumosudil QD for 8 consecutive days (morning of Days 5 to 12). In Part 3, participants received a single dose of rosuvastatin on 2 separate occasions (morning of Days 1 and 10), and belumosudil QD for 8 consecutive days (morning of Days 6 to 13).

Criteria for evaluation:

Primary:

Part 1:

• PK parameters: $AUC_{(0\text{-}last)}$ and $AUC_{(0\text{-}inf)}$ for raltegravir, as applicable, following administration of the test (raltegravir + belumosudil) and reference (raltegravir alone) treatments.

• Results of the formal statistical analysis of the PK parameters $AUC_{(0\text{-}last)}$ and $AUC_{(0\text{-}inf)}$ for raltegravir in the test treatment (raltegravir + belumosudil) compared to the reference treatment (raltegravir alone), where possible and appropriate.

Part 2:

• PK parameters: $AUC_{(0\text{-}last)}$ and $AUC_{(0\text{-}inf)}$ for unconjugated dabigatran, as applicable, following administration of the test (dabigatran etexilate + belumosudil) and reference (dabigatran etexilate alone) treatments.

• Results of the formal statistical analysis of the PK parameters $AUC_{(0\text{-}last)}$ and $AUC_{(0\text{-}inf)}$ for unconjugated dabigatran in the test treatment (dabigatran etexilate + belumosudil) compared to the reference treatment (dabigatran etexilate alone), where possible and appropriate.

Part 3:

• PK parameters: $AUC_{(0\text{-}last)}$ and $AUC_{(0\text{-}inf)}$ for rosuvastatin, as applicable, following administration of the test (rosuvastatin + belumosudil) and reference (rosuvastatin alone) treatments.

• Results of the formal statistical analysis of the PK parameters $AUC_{(0\text{-}last)}$ and $AUC_{(0\text{-}inf)}$ for rosuvastatin in the test treatment (rosuvastatin + belumosudil) compared to the reference treatment (rosuvastatin alone), where possible and appropriate.

Secondary:

Part 1:

• PK parameters: T_{max}, C_{max}, and $T_{1/2}$ for raltegravir, as applicable, following administration of the test (raltegravir + belumosudil) and reference (raltegravir alone) treatments.

• PK parameters: $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}inf)}$, T_{max}, C_{max}, and $T_{1/2}$ for raltegravir glucuronide, as applicable, following administration of the test (raltegravir + belumosudil) and reference (raltegravir alone) treatments.

• Results of the formal statistical analysis of the PK parameter C_{max} for raltegravir in the test treatment (raltegravir + belumosudil) compared to the reference treatment (raltegravir alone), where possible and appropriate

• Results of the formal statistical analysis of the PK parameters C_{max}, $AUC_{(0\text{-}last)}$, and $AUC_{(0\text{-}inf)}$ for raltegravir glucuronide in the test treatment (raltegravir + belumosudil) compared to the reference treatment (raltegravir alone), where possible and appropriate.

Part 2:

• PK parameters: T_{max}, C_{max}, and $T_{1/2}$ for unconjugated dabigatran, as applicable, following administration of the test (dabigatran etexilate + belumosudil) and reference (dabigatran etexilate alone) treatments.

• Results of the formal statistical analysis of the PK parameter C_{max} for unconjugated dabigatran in the test treatment (dabigatran etexilate + belumosudil) compared to the reference treatment (dabigatran etexilate alone), where possible and appropriate.

Part 3:

• PK parameters: T_{max}, C_{max}, and $T_{1/2}$ for rosuvastatin, as applicable, following administration of the test (rosuvastatin + belumosudil) and reference (rosuvastatin alone) treatments.

• Results of the formal statistical analysis of the PK parameter C_{max} for rosuvastatin in the test treatment (rosuvastatin + belumosudil) compared to the reference treatment (rosuvastatin alone), where possible and appropriate.

Parts 1, 2, and 3:

• PK parameters: T_{max}, C_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}tau)}$, and $T_{1/2}$, for belumosudil, KD025m1, and KD025m2 as applicable.

Parts 1, 2, and 3:

• To provide additional safety and tolerability information for belumosudil by assessing: AEs, vital signs, ECGs, physical examinations, and laboratory safety tests following administration of the 3 victim drugs (raltegravir [Part 1], dabigatran etexilate [Part 2] and rosuvastatin [Part 3]) alone and in combination with belumosudil.

Statistical methods:

Formal statistical analysis was performed on the PK parameters maximum observed concentration (C_{max}) and area under the curve from time 0 to the time of last measurable concentration ($AUC_{(0\text{-}last)}$) for Regimens A, B, and C (Parts 1, 2 and 3), and area under the curve from time 0 extrapolated to infinity ($AUC_{(0\text{-}inf)}$) for Regimen B (Part 2) only, separately for each regimen/part and included the following pairwise treatment comparisons (test versus reference, ie, victim + perpetrator IMPs versus victim IMP alone): • Regimen A (Part 1): raltegravir + belumosudil (Day 7) versus raltegravir alone (Day 1) for parent raltegravir and its metabolite raltegravir glucuronide • Regimen B (Part 2): dabigatran + belumosudil (Day 9) versus dabigatran alone (Day 1) for unconjugated dabigatran • Regimen C (Part 3): rosuvastatin + belumosudil (Day 10) versus rosuvastatin alone (Day 1) for rosuvastatin The PK parameters underwent a natural logarithmic transformation and were analyzed using a mixed effect modelling technique. Adjusted geometric mean ratios and 90% confidence intervals (CIs) of the ratios were obtained for each comparison. The ratio was defined as test/reference. In addition, the intraparticipant variability were also presented. Additional PK parameters were estimated for plasma raltegravir, raltegravir glucuronide, unconjugated dabigatran, and rosuvastatin, belumosudil and known metabolites (KD025m1 and KD025m2) where possible and appropriate. No formal statistical analyses were performed for the PK data for plasma belumosudil and known metabolites (KD025m1 and KD025m2), or for the safety data during this study. No formal interim analyses were performed for this study.

Summary Results:

Demographic and other baseline characteristics:

Overall, 52 healthy male participants between 19 and 54 years of age inclusive were entered into the study; all had a body weight of at least 50 kg and were within the reference range for BMI (18.0 to 32.0 kg/m^2) as required by the protocol. No participants were current smokers and all had an alcohol consumption of between 0 and 2 units per week.

Exposure:

For Regimen A, all 19 participants received the planned total of 2 oral doses of raltegravir and 6 oral doses of belumosudil over 8 days: single doses of 400 mg raltegravir on Days 1 and 7, and QD doses of 200 mg belumosudil on Days 3 to 8. The cumulative dose of belumosudil received by each participant was 1200 mg and duration of exposure was 6 days.

For Regimen B, all 19 participants received the planned total of 2 oral doses of dabigatran etexilate and 8 oral doses of belumosudil over 12 days: single doses of 75 mg dabigatran etexilate on Days 1 and 9, and QD doses of 200 mg belumosudil on Days 5 to 12. The cumulative dose of belumosudil received by each participant was 1600 mg and duration of exposure was 8 days.

Although 15 participants were planned to be administered Regimen C, 1 participant was determined to be ineligible to dose on Part 3 Day 1. All 14 participants received the planned total of 2 oral doses of rosuvastatin calcium and 8 oral doses of belumosudil over 13 days: single doses of 10 mg rosuvastatin calcium on Days 1 and 10, and QD doses of 200 mg belumosudil on Days 6 to 13. The cumulative dose of belumosudil received by each participant was 1600 mg and duration of exposure was 8 days.

Pharmacokinetic results:

The statistical analysis results for the assessment of the effect of multiple doses of belumosudil on the single dose oral PK endpoints $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$ (Regimen B [dabigatran etexilate + belumosudil; Part 2] only) and C_{max} for raltegravir, raltegravir glucuronide, unconjugated dabigatran and rosuvastatin are presented below.

Regimen (Part)/analyte	Parameter	Victim IMP + belumosudil		Victim IMP alone		Ratio (%)[b]	90% CI (%)[c]	CVw (%)[d]
		n	Adj geo mean[a]	n	Adj geo mean[a]			
Regimen A (Part 1)/raltegravir	$AUC_{(0\text{-last})}$ (ng.h/mL)	18	1500	18	1570	95.23	(65.99, 137.42)	70.1
	C_{max} (ng/mL)	18	447	18	512	87.28	(60.80, 125.29)	68.9
Regimen A (Part 1)/raltegravir glucuronide	$AUC_{(0\text{-last})}$ (ng.h/mL)	19	859	19	1420	60.38	(42.87, 85.03)	66.9
	C_{max} (ng/mL)	19	207	19	359	57.58	(42.51, 78.00)	58.1
Regimen B (Part 2)/unconjugated dabigatran	$AUC_{(0\text{-last})}$ (ng.h/mL)	19	682	19	317	215.41	(167.03, 277.81)	47.6
	$AUC_{(0\text{-inf})}$ (ng.h/mL)	16	822	16	398	206.47	(160.20, 266.11)	42.7
	C_{max} (ng/mL)	19	99.5	19	42.1	236.06	(178.61, 311.98)	52.8
Regimen C (Part 3)/rosuvastatin	$AUC_{(0\text{-last})}$ (ng.h/mL)	10	62.6	10	13.6	461.59	(332.25, 641.26)	41.8
	C_{max} (ng/mL)	11	10.6	11	2.96	359.21	(231.34, 557.75)	61.9

$AUC_{(0\text{-inf})}$: area under the curve from time 0 extrapolated to infinity; $AUC_{(0\text{-last})}$: area under the curve from time 0 to the time of last measurable concentration; C_{max}: maximum observed concentration; CI: confidence interval; IMP: investigational medicinal product; n: number of participants with an observation.

Victim investigational medicinal products = Regimen A (Part 1): raltegravir 400 mg single dose (Days 1 and 7); Regimen B (Part 2): dabigatran etexilate 75 mg single dose (Days 1 and 9); Regimen C (Part 3): rosuvastatin calcium 10 mg single dose (Days 1 and 10).

Perpetrator investigational medicinal products = belumosudil 200 mg QD, Days 3 to 8 for Regimen A (Part 1), Days 5 to 12 for Regimen B (Part 2), and Days 6 to 13 for Regimen C (Part 3).

Results obtained from mixed modelling of natural log transformed PK parameters with terms for treatment as a fixed effect and participant as a random effect. Only participants who have evaluable parameter estimates for both treatments have been included. $AUC_{(0\text{-inf})}$ is excluded where there are insufficient evaluable estimates.

a Adj geo mean = adjusted geometric mean.

b Ratio of adj geo means (test/reference ie, victim + perpetrator/victim alone).

c Confidence intervals for ratio of adj geo means.

d CVw = intraparticipant variability.

For Regimen A (Part 1), geometric mean (geometric coefficient of variation [CV%]) values for plasma PK parameters for raltegravir and raltegravir glucuronide are presented below.

Treatment (Day) Number of participants	Raltegravir alone (Day 1) N = 19		Raltegravir + belumosudil (Day 7) N = 19	
Analyte Parameter	**Raltegravir**	**Raltegravir glucuronide**	**Raltegravir**	**Raltegravir glucuronide**
T_{max}[a] (h)	3.000 (1.00-12.00)	4.000 (1.00-12.00)	3.000 (2.00-12.00) [n = 18]	4.000 (2.00-12.00)
C_{max} (ng/mL)	520 (136.7%)	359 (102.3%)	447 (86.6%) [n = 18]	207 (118.1%)
$AUC_{(0-24)}$ (ng.h/mL)	1970 (170.6%) [n = 17]	1710 (151.5%) [n = 17]	1790 (49.0%) [n = 11]	1090 (95.8%) [n = 12]
$AUC_{(0-last)}$ (ng.h/mL)	1640 (188.4%)	1420 (164.9%)	1500 (111.7%) [n = 18]	859 (163.8%)
$AUC_{(0-inf)}$ (ng.h/mL)	1510 (226.5%) [n = 8]	1290 (160.1%) [n = 8]	1860 (33.5%) [n = 6]	1170 (83.1%) [n = 7]
$T_{1/2}$ (h)	1.434 (58.4%) [n = 8]	1.541 (38.4%) [n = 8]	3.865 (84.7%) [n = 6]	3.919 (94.1%) [n = 7]
MPR C_{max}	N/A	0.506 (46.4%)	N/A	0.299 (41.0%) [n = 18]
MPR $AUC_{(0-24)}$	N/A	0.641 (39.5%) [n = 16]	N/A	0.380 (33.0%) [n = 11]
MPR $AUC_{(0-last)}$	N/A	0.634 (41.0%)	N/A	0.376 (42.4%) [n = 18]
MPR $AUC_{(0-inf)}$	N/A	0.698 (54.8%) [n = 6]	N/A	0.303 (24.5%) [n = 5]

$AUC_{(0-24)}$: area under the curve from time 0 to 24 hours post-dose; $AUC_{(0-inf)}$: area under the curve from time 0 extrapolated to infinity; $AUC_{(0-last)}$: area under the curve from time 0 to the time of last measurable concentration; C_{max}: maximum observed concentration; MPR $AUC_{(0-24)}$: metabolite to parent ratio based on $AUC_{(0-24)}$; MPR $AUC_{(0-inf)}$: metabolite to parent ratio based on $AUC_{(0-inf)}$; MPR $AUC_{(0-last)}$: metabolite to parent ratio based on $AUC_{(0-last)}$; MPR C_{max}: metabolite to parent ratio based on C_{max}; n: number of participants with an observation; n: number of participants with an observation; N: number of participants in the dataset; N/A: not applicable; QD: once daily; $T_{1/2}$: terminal elimination half-life; T_{max}: time of maximum observed concentration.

Regimen A (Part 1): raltegravir 400 mg single dose (Days 1 and 7) and belumosudil 200 mg QD (Days 3 to 8).

a Median (range).

For Part 1 (Regimen A), peak and overall exposure levels of raltegravir were comparable when raltegravir was dosed with belumosudil tablet compared to dosing alone. However, for peak and overall exposure levels of raltegravir glucuronide, a notable decrease was observed when raltegravir was dosed with belumosudil compared to dosing alone. Belumosudil coadministration did not change the median time of maximum observed concentration (T_{max}) of either raltegravir or raltegravir glucuronide. The geometric mean terminal elimination half-life ($T_{1/2}$) values increased following belumosudil coadministration, from approximately 1.4 hours (raltegravir) or 1.5 hours (raltegravir glucuronide) on Day 1 to approximately 3.9 hours (both analytes) on Day 7.

For Regimen B (Part 2), geometric mean (geometric CV%) values for plasma PK parameters for unconjugated dabigatran are presented below.

Treatment (Day) Number of participants	Dabigatran etexilate alone (Day 1) N = 19	Dabigatran etexilate + belumosudil (Day 9) N = 19
Parameter		
T_{max}[a] (h)	3.000 (2.00-4.00)	2.000 (1.50-8.00)
C_{max} (ng/mL)	42.1 (70.9%)	99.5 (110.1%)
$AUC_{(0\text{-}last)}$ (ng.h/mL)	317 (67.6%)	682 (86.5%)
$AUC_{(0\text{-}inf)}$ (ng.h/mL)	371 (52.2%) [n = 17]	801 (73.2%) [n = 17]
$T_{1/2}$ (h)	8.128 (18.3%) [n = 18]	8.293 (24.8%) [n = 18]

$AUC_{(0\text{-}inf)}$: area under the curve from time 0 extrapolated to infinity; $AUC_{(0\text{-}last)}$: area under the curve from time 0 to the time of last measurable concentration; C_{max}: maximum observed concentration; n: number of participants with an observation; N: number of participants in the dataset; QD: once daily; $T_{1/2}$: terminal elimination half-life; T_{max}: time of maximum observed concentration.
Regimen B (Part 2): dabigatran etexilate 75 mg single dose (Days 1 and 9) and belumosudil 200 mg QD (Days 5 to 12).
a Median (range).

For Part 2 (Regimen B), peak and overall exposure levels of unconjugated dabigatran (following administration of dabigatran etexilate) were increased by 2.36- and 2.06-fold, respectively, when dosed with belumosudil compared to dosing alone. Median Tmax and geometric mean $T_{1/2}$ were similar following administration of dabigatran etexilate alone or with belumosudil.

For Regimen C (Part 3), geometric mean (geometric CV%) values for plasma PK parameters for rosuvastatin are presented below.

Treatment (Day) Number of participants	Rosuvastatin calcium alone (Day 1) N = 14	Rosuvastatin calcium + belumosudil (Day 10) N = 14
Parameter		
T_{max}[a] (h)	6.000 (2.00-10.00) [n = 11]	2.500 (1.50-4.00)
C_{max} (ng/mL)	2.96 (79.1%) [n = 11]	9.49 (49.5%)
$AUC_{(0\text{-}last)}$ (ng.h/mL)	13.6 (75.3%) [n = 10]	54.0 (43.9%)
$AUC_{(0\text{-}inf)}$ (ng.h/mL)	25.4, 39.3[b] [n = 2]	54.1 (30.1%) [n = 13]
$T_{1/2}$ (h)	4.050 (46.4%) [n = 5]	2.748 (20.4%) [n = 13]

$AUC_{(0\text{-}inf)}$: area under the curve from time 0 extrapolated to infinity; $AUC_{(0\text{-}last)}$: area under the curve from time 0 to the time of last measurable concentration; C_{max}: maximum observed concentration; n: number of participants with an observation; N: number of participants in the dataset; QD: once daily; $T_{1/2}$: terminal elimination half-life; T_{max}: time of maximum observed concentration.
Regimen C (Part 3): rosuvastatin calcium 10 mg single dose (Days 1 and 10) and belumosudil 200 mg QD (Days 6 to 13).
a Median (range).
b Individual participant value(s).

For Part 3 (Regimen C), peak and overall exposure levels of rosuvastatin (following administration of rosuvastatin calcium) were increased by 3.59- and 4.62-fold, respectively, when dosed with belumosudil compared to dosing alone. Additionally, belumosudil coadministration resulted in an earlier median Tmax (decrease from approximately 6 hours postdose on Day 1 to 2.5 hours postdose on Day 10), and geometric mean $T_{1/2}$ decreased from 4.1 to 2.7 hours, although this change should be interpreted with caution due to the low number of reliable estimates (n = 5) on Day 1 compared with Day 10 (n = 13).

For Regimen A (Part 1), geometric mean (geometric CV%) values for PK parameters for belumosudil, KD025m1 and KD025m2 following oral doses of 200 mg belumosudil, alone and coadministered with 400 mg raltegravir (a prototypical UGT1A1 substrate) are presented below.

Treatment (Day)	Belumosudil alone (Day 3)			Raltegravir + belumosudil (Day 8)		
Analyte Number of participants Parameter	Belumosudil N = 19	KD025m1 N = 19	KD025m2 N = 19	Belumosudil N = 19	KD025m1 N = 19	KD025m2 N = 19
T_{max}[a] (h)	2.00 (1.00-4.00)	2.00 (1.00-3.00) [n = 17]	2.00 (1.00-4.00)	2.00 (1.50-4.00)	1.50 (1.00-4.00)	3.00 (1.50-4.00)
C_{max} (ng/mL)	2130 (36.6%)	21.4 (45.9%) [n = 17]	278 (100.2%)	2760 (14.7%)	18.6 (41.7%)	368 (65.8%)
$AUC_{(0\text{-}tau)}$ (ng.h/mL)	9330 (38.3%)	96.6 (12.0%) [n = 5]	961 (73.2%) [n = 17]	13 000 (21.9%)	90.7 (18.7%) [n = 3]	1260 (64.4%)
$AUC_{(0\text{-}last)}$ (ng.h/mL)	9200 (39.0%) [n = 18]	47.6 (41.6%) [n = 13]	879 (75.9%) [n = 18]	13 700 (22.6%)	36.9 (50.6%) [n = 13]	1210 (69.4%)
$T_{1/2}$ (h)	5.841 (27.0%) [n = 16]	1.621 (27.1%) [n = 3]	3.695 (48.3%) [n = 14]	8.303 (30.2%) [n = 15]	2.335 (25.0%) [n = 3]	4.746 (61.7%) [n = 15]

$AUC_{(0\text{-}last)}$: area under the curve from time 0 to the time of last measurable concentration; $AUC_{(0\text{-}tau)}$: area under the curve for the defined interval between doses (tau); Cmax: maximum observed concentration; n: number of participants with an observation; N: number of participants in the dataset; QD: once daily; $T_{1/2}$: terminal elimination half-life; T_{max}: time of maximum observed concentration.
Regimen A (Part 1): raltegravir 400 mg single dose (Days 1 and 7) and belumosudil 200 mg QD (Days 3 to 8).
a Median (range).

In Part 1, following single and repeated administration of belumosudil, median T_{max} of belumosudil, KD025m1 and KD025m2 was attained at approximately 1.5 to 3 hours postdose, and exposures (C_{max} and AUC) of belumosudil and KD025m2 increased by between 1.30- and 1.49-fold following multiple dosing.

Geometric mean $T_{1/2}$ for belumosudil increased following repeated administration of belumosudil compared to a single dose, from approximately 6 hours on Day 3 to approximately 8 hours on Day 8; geometric mean $T_{1/2}$ for KD025m1 was approximately 1.6 to 2 hours on Days 3 and 8, and geometric mean $T_{1/2}$ for KD025m2 increased slightly from approximately 4 hours on Day 3 to approximately 5 hours on Day 8.

For Regimen B (Part 2), geometric mean (geometric CV%) values for PK parameters for belumosudil, KD025m1 and KD025m2 following oral doses of 200 mg belumosudil, alone and coadministered with 75 mg dabigatran etexilate (a prototypical P-gp substrate) are presented below.

Treatment (Day)	Belumosudil alone (Day 5)			Dabigatran etexilate + belumosudil (Day 12)		
Analyte Number of participants Parameter	Belumosudil N = 19	KD025m1 N = 19	KD025m2 N = 19	Belumosudil N = 19	KD025m1 N = 19	KD025m2 N = 19
T_{max}[a] (h)	2.000 (1.50-6.00)	1.750 (1.50-4.00) [n = 14]	2.000 (1.50-6.00) [n = 18]	2.000 (1.00-6.00)	1.500 (0.50-30.00) [n = 15]	2.000 (1.50-30.00)
C_{max} (ng/mL)	1710 (113.5%)	19.5 (44.6%) [n = 14]	184 (122.1%) [n = 18]	2180 (142.1%)	18.9 (49.0%) [n = 15]	236 (117.8%)
$AUC_{(0\text{-}tau)}$ (ng.h/mL)	8490 (92.6%)	80.6, 184[b] [n = 2]	746 (63.3%) [n = 16]	11 000 (98.5%)	281[b] [n = 1]	991 (63.0%) [n = 17]
$AUC_{(0\text{-}last)}$ (ng.h/mL)	8430 (96.0%)	35.3 (86.1%) [n = 8]	692 (66.4%) [n = 16]	12 000 (93.8%)	38.4 (94.9%) [n = 7]	921 (68.4%) [n = 17]
$T_{1/2}$ (h)	6.199 (31.4%) [n = 11]	1.878[b] [n = 1]	2.858 (54.9%) [n = 14]	10.371 (34.6%) [n = 13]	N/C	4.450 (63.3%) [n = 11]

$AUC_{(0\text{-}last)}$: area under the curve from time 0 to the time of last measurable concentration; $AUC_{(0\text{-}tau)}$: area under the curve for the defined interval between doses (tau); Cmax: maximum observed concentration; n: number of participants with an observation; N: number of participants in the dataset; N/C: not calculated; QD: once daily; $T_{1/2}$: terminal elimination half-life; T_{max}: time of maximum observed concentration.
Regimen B (Part 2): dabigatran etexilate 75 mg single dose (Days 1 and 9) and belumosudil 200 mg QD (Days 5 to 12).
a Median (range).
b Individual participant value(s).

In Part 2, following single and repeated administration of belumosudil, median T_{max} of belumosudil, KD025m1 and KD025m2 was attained at approximately 1.5 to 2 hours postdose, and exposures (C_{max} and AUC) of belumosudil and KD025m2 increased by between 1.27- and 1.42-fold following multiple dosing.

Where sufficient estimates were available, geometric mean $T_{1/2}$ for belumosudil increased following repeated administration of belumosudil compared to a single dose, from approximately 6 hours on Day 5 to approximately 10 hours on Day 12; geometric mean $T_{1/2}$ for KD025m2 increased slightly from approximately 3 hours on Day 5 to approximately 4 hours on Day 12.

For Regimen C (Part 3), geometric mean (geometric CV%) values for PK parameters for belumosudil, KD025m1 and KD025m2 following oral doses of 200 mg belumosudil, alone and coadministered with 10 mg rosuvastatin calcium (a prototypical BCRP/OATP1B1 substrate) are presented below.

Treatment (Day)	Belumosudil alone (Day 6)			Rosuvastatin calcium + belumosudil (Day 13)		
Analyte Number of participants Parameter	Belumosudil N = 14	KD025m1 N = 14	KD025m2 N = 14	Belumosudil N = 14	KD025m1 N = 14	KD025m2 N = 14
T_{max}[a] (h)	2.000 (1.50-4.00)	1.500 (1.00-3.00) [n = 12]	2.000 (2.00-4.00) [n = 12]	2.000 (1.00-3.00) [n = 13]	1.500 (1.00-3.00) [n = 12]	2.000 (1.50-3.00) [n = 12]
C_{max} (ng/mL)	2080 (20.7%)	17.1 (35.4%) [n = 12]	215 (69.3%) [n = 12]	2510 (29.0%) [n = 13]	16.8 (43.3%) [n = 12]	265 (78.6%) [n = 12]
$AUC_{(0\text{-}tau)}$ (ng.h/mL)	9710 (27.8%)	96.9, 120[b] [n = 2]	598 (72.4%) [n = 12]	12 900 (26.6%) [n = 13]	116 (46.3%) [n = 3]	937 (76.6%) [n = 12]
$AUC_{(0\text{-}last)}$ (ng.h/mL)	9710 (27.8%)	32.0 (61.4%) [n = 7]	557 (75.4%) [n = 12]	13 600 (27.4%) [n = 13]	41.2 (67.6%) [n = 5]	872 (83.0%) [n = 12]
$T_{1/2}$ (h)	4.901 (25.1%) [n = 8]	1.63, 3.18[b] [n = 2]	1.973 (42.0%) [n = 8]	9.102 (26.7%) [n = 12]	1.495[b] [n = 1]	6.337 (93.3%) [n = 6]

$AUC_{(0\text{-}last)}$: area under the curve from time 0 to the time of last measurable concentration; $AUC_{(0\text{-}tau)}$: area under the curve for the defined interval between doses (tau); Cmax: maximum observed concentration; n: number of participants with an observation; N: number of participants in the dataset; QD: once daily; $T_{1/2}$: terminal elimination half-life; T_{max}: time of maximum observed concentration.
Regimen C (Part 3): rosuvastatin calcium 10 mg single dose (Days 1 and 10) and belumosudil 200 mg QD (Days 6 to 13).
a Median (range).
b Individual participant value(s).

In Part 3, following single and repeated administration of belumosudil, median Tmax of belumosudil, KD025m1 and KD025m2 was attained at approximately 1.5 to 2 hours postdose, and exposures (C_{max} and AUC) of belumosudil and KD025m2 increased by between 1.21- and 1.57-fold following multiple dosing.

Where sufficient estimates were available, geometric mean $T_{1/2}$ for belumosudil increased following repeated administration of belumosudil compared to a single dose, from approximately 5 to 9 hours; and geometric mean $T_{1/2}$ for KD025m2 increased from approximately 2 to 6 hours.

Safety results:

Overall, the perpetrator IMP, belumosudil, was well tolerated when coadministered with the victim IMPs raltegravir, dabigatran etexilate, and rosuvastatin calcium. No serious adverse events or treatment emergent adverse events (TEAEs) leading to participant withdrawal or death were reported, and the overall number of TEAEs and number of participants reporting TEAEs was low. Only 2 (3.8%) participants reported 1 TEAE each during the study, both of which were Grade 1 (mild) in severity and resolved without medication or intervention. Only 1 event (headache) was judged by the Investigator to be related to the perpetrator IMP (belumosudil); no TEAEs were judged to be related to the victim IMPs. There were no clinically significant findings in the clinical laboratory evaluations, vital signs measurements, ECGs or physical examination assessments for any regimen, and no trends were observed in these data. No new potential safety signals were observed after review of the data generated in this study.

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