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Sponsor: Kadmon **Drug substance:** Belumosudil (KD025)	**Study Identifiers:** NCT04735822 **Study code:** KD025-111 (QSC203981)

Title of the study: A Two-Part, Phase I Study Designed to Evaluate the Taste Profile of Novel Belumosudil Oral Suspensions (Part 1) and Assess the Relative Bioavailability of the Selected Belumosudil Oral Suspension Formulation Compared with Oral Tablet Reference (Part 2) in Healthy Male Subjects

Study center: 1 center in the United Kingdom

Study period:

Date first participant enrolled: 26/Oct/2020

Date last participant completed: 03/Sep/2021

Study Status: Completed

Phase of development: I

Objectives:

The primary objective of Part 1 of the study were:

- To evaluate the taste attributes (smell, sweetness, bitterness, flavour, mouth feel/texture, grittiness and aftertaste) and overall acceptability of belumosudil in Bottle formulations

The primary objectives of Part 2 of the study were:

- To determine the relative bioavailability of the selected belumosudil suspension formulation (test) with the oral belumosudil Tablet (reference) in the fed state
- To determine the effect of food on the pharmacokinetic (PK) of belumosudil following administration of the selected belumosudil suspension formulation

There were no secondary objectives for Part 1 of the study.

The secondary objectives of Part 2 of the study were:

- To determine the PK of belumosudil and known metabolites (KD025m1, KD025m2) following administration of the selected belumosudil suspension formulation in the fed and fasted states and the oral belumosudil Tablet (reference) in the fed state
- To provide additional safety and tolerability information for belumosudil

Methodology: This was a single centre, open-label, randomised, two-part study in healthy male subjects.

Number of participants:

Part 1

Planned: 12

Enrolled: 12

Part 2

Planned: 18

Enrolled: 18

Evaluated:

Part 1

Taste/palatability: 12

Safety: 12

Part 2

Safety: 18

Pharmacokinetics: 18

Taste/palatability: 18

Diagnosis and criteria for inclusion:

Healthy male subjects between 18 and 55 years of age at the time of informed consent with a body weight ≥ 50 kg and body mass index between 18.0 and 32.0 kg/m^2 as measured at screening.

Study products

Part 1

Investigational medicinal product: Belumosudil

Formulation: 40 mg/mL (200 mg in 5 mL) dose of belumosudil Bottle formulation

Route of administration: Oral administration (sip and spit)

Part 2

Investigational medicinal product: Belumosudil

Formulations: 200mg tablet form/oral suspension

Routes of administration: Oral administration

Duration of treatment/participation:

Part 1

Subjects received 6 single oral doses of belumosudil administered on 6 separate occasions over the course of one day. The 'sip and spit' technique was used so no drug was swallowed.

Part 2

Subjects received a single oral dose of a belumosudil Tablet (Regimen G) or belumosudil Oral Suspension (Regimen H and I) with a minimum washout period of 3 days between each IMP dose.

Duration of observation: 3-7 days follow-up period

Criteria for evaluation:

Taste/Palatability, Part 1

Taste/palatability was assessed for each treatment in Part 1 and for Regimen H only in Part 2 using a taste/palatability questionnaire. The questionnaire asked subjects to rate the overall acceptability of taste/palatability as well as the acceptability of 7 taste attributes (smell, sweetness, bitterness, flavour, mouth feel/texture, grittiness and aftertaste) on a 9-point scale ("Dislike extremely", "Dislike very much", "Dislike moderately", "Dislike slightly", "Neither like nor dislike", "Like slightly", "Like moderately", "Like very much", "Like extremely").

Taste/palatability assessment data was summarised (ie number of subjects with an observation [n], mean, standard deviation, median, minimum and maximum) for each taste/palatability attribute and overall acceptability score by treatment. A breakdown of the number and percentages of subjects in each rating category was also presented for each of the taste/palatability attributes and overall acceptability.

Stacked bar charts were produced separately for each taste/palatability attribute and overall acceptability. For each treatment, a bar displayed the proportion of subjects (as a proportion of all subjects with data for that treatment) with a taste/palatability rating of Dislike (Grades 1-3), Neutral (Grades 4-6) and Like (Grades 7-9). The actual number of subjects with each rating is displayed on the figure.

Pharmacokinetics, Part 2

The following PK parameters for plasma concentrations of belumosudil, KD025m1 and KD025m2 were estimated where possible and appropriate for each subject and regimen by non-compartmental analysis methods using Phoenix® WinNonlin® software (v8.0, Certara USA, Inc., USA):

Tlag: time prior to the first measurable concentration

Tmax: time of maximum observed concentration

Cmax: maximum observed concentration

AUC(0-24): area under the curve from time zero to 24 h post-dose

AUC(0-last): area under the curve from time zero to the last measurable concentration

AUC(0-inf): area under the curve from time zero extrapolated to infinity

AUC%extrap: area under the curve from the time of the last measurable concentration to infinity as a percentage of the area under the curve extrapolated to infinity

T1/2: terminal elimination half-life

Lambda-z: first order rate constant associated with the terminal (log-linear) portion of the curve

CL/F: total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown (belumosudil only)

Vz/F: apparent volume of distribution based on the terminal phase calculated using AUC(0-inf) after a single extravascular administration where F (fraction of dose bioavailable) is unknown (belumosudil only)

Frel Cmax: Relative bioavailability based on Cmax

Frel AUC(0-last): Relative bioavailability based on AUC(0-last)

Frel AUC(0-inf): Relative bioavailability based on AUC(0-inf)

MPR Cmax: Metabolite to parent ratio based on Cmax (KD025m1 and KD025m2 only)

MPR AUC(0-last): Metabolite to parent ratio based on AUC(0-last) (KD025m1 and KD025m2 only)

MPR AUC(0-inf): Metabolite to parent ratio based on AUC(0-inf) (KD025m1 and KD025m2 only)

Safety

The evaluation of safety parameters comprised analysis of AEs, laboratory variables (haematology, clinical chemistry and urinalysis), vital signs, electrocardiograms (ECGs), body weight and physical examination findings.

Pharmacokinetic sampling times and bioanalytical methods:

Part 1: A single plasma PK sample was taken approximately 1 h post-final dose (prior to discharge from the clinical unit). This sample was retained for analysis only in the case of accidental swallowing of the formulation by a subject and/or for the purpose of investigating a treatment-emergent adverse event (TEAE) considered to be related to the IMP. No subjects reported accidentally swallowing the formulation and/or a TEAE considered to be related to the IMP in Part 1 of the study; therefore, the plasma PK sample was not required to be analysed for any subject, and was destroyed.

Part 2: All subjects remained on site until 72 h post-final dose for safety and PK assessments.

Bioanalytical methods: Protein precipitation extraction/ liquid chromatography followed by tandem mass spectrometric detection

Statistical methods:

Statistical Analysis of Taste/Palatability Data, Part 1

A Friedman test was used as an overall comparison to test if there is any difference between the 6 belumosudil in Bottle regimens for each of the 7 taste attributes (ie smell, sweetness, bitterness, flavour, mouth feel/texture, grittiness and aftertaste) as well as overall acceptability. If the Friedman test was significant at the 5% significance level, the following pairwise comparisons were performed using Wilcoxon signed rank tests:

- Regimen B vs Regimen A
- Regimen C vs Regimen A
- Regimen D vs Regimen A
- Regimen E vs Regimen A
- Regimen F vs Regimen A

The results of this statistical analysis were used in the interim decision meeting to inform the decision of what to dose in Part 2.

Statistical Analysis of Pharmacokinetic Data, Part 2

Formal statistical analysis was performed for the following plasma PK parameters of belumosudil, KD025m1 and KD025m2: Cmax, AUC(0 last) and AUC(0-inf).

The PK parameters underwent a natural logarithmic transformation and were analysed using mixed effect modelling techniques. The mixed effects model included terms for period, sequence and treatment as fixed effects and subject nested within sequence as a random effect. The adjusted means including differences from the pairwise comparisons listed above and their associated 90% confidence intervals (CIs) obtained from the model were back transformed on the log scale to obtain adjusted geometric mean ratios (GMRs) and 90% Cis of the ratios. These were presented together with the p-value from the pairwise comparison

and the intra-subject variability values (denoted as CVw in the results table).

The pairwise treatment comparisons of interest were:

- Relative Bioavailability: belumosudil Oral Suspension, fed [Regimen I] (test) vs belumosudil Tablet, fed [Regimen G] (reference)
- Food Effect: belumosudil Oral Suspension, fed [Regimen I] (test) vs belumosudil Oral Suspension, fasted [Regimen H] (reference)

Summary Results:

Taste/Palatability Results, Part 1

Vehicle 1 (sterile water – reference) was the lowest scoring vehicle, with a median score for overall acceptability of 3.0, indicating that the subject panel moderately disliked the product. The flavoured regimens (Vehicles 4 [orange low sucralose], 5 [tropical fruit blend low sucralose] and 6 [lemon low sucralose]) achieved median scores of 6.5, 7.0 and 7.0, respectively, indicating that addition of flavouring improved the overall taste/palatability profile of the IMP.

The taste/palatability attributes with the lowest median scores for Vehicle 1 were flavour, mouth feel/texture and grittiness (3.5, 3.0 and 3.5, respectively), indicating that these were the driver for the dislike. With the addition of a flavoured low sucralose vehicle (Vehicles 4, 5 and 6), the median scores for each of these attributes increased, ranging from 6.5 to 7.0 for flavour, 4.5 to 5.0 for mouth feel/texture and 4.0 to 5.5 for grittiness. Median scores also improved for all other taste/palatability attributes with the addition of a flavoured low sucralose vehicle, indicating the subjects preferred the taste profiles of these vehicles.

For each taste attribute, the Friedman's Test was statistically significant at the 5% significance level indicating that at least one of the novel formulations had a significantly different taste score to the other treatments ($p < 0.001$ for overall acceptability, smell, sweetness, bitterness, flavour and mouth feel/texture, $p = 0.041$ and $p = 0.001$ for grittiness and aftertaste, respectively).

For all pairwise comparisons and taste attributes, the median of the paired differences was positive indicating that use of a sweetener and/or flavour showed improved acceptability compared to the reference vehicle, sterile water.

In all taste attributes, the tropical fruit blend low sucralose or the lemon low sucralose vehicles showed either the greatest improvement or joint greatest improvement compared to the reference vehicle (based on median of paired differences).

Taste/Palatability Results, Part 2

Overall, the Oral Suspension (Regimen H) was rated either Grade 5 ('Neither Like Nor Dislike'), Grade 6 ('Like Slightly') or Grade 7 ('Like Moderately') by the majority of subjects. The overall taste profile scores for Regimen H were comparable to those for Regimen B in Part 1, which utilised the same sweetener combination (ie low sucralose).

Pharmacokinetic Results, Part 2

The key geometric mean (geometric coefficient of variation [CV%]) PK parameters for plasma belumosudil following dosing with belumosudil are summarised below:

Regimen Dose Level Status	G 200 mg Tablet Fed	H 200 mg Oral Suspension Fasted	I 200 mg Oral Suspension Fed
No. of Subjects Parameter	**N = 18**	**N = 18**	**N = 18**
Tlag[a] (h)	0.500 (0.00-2.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Tmax[a] (h)	3.00 (1.00-5.00)	1.50 (1.00-4.00)	2.00 (1.00-3.03)
Cmax (ng/mL)	1930 (26.1%)	1550 (33.3%)	1790 (25.1%)
AUC(0-24) (ng.h/mL)	9310 (37.5%)	7620 (44.9%)	9340 (34.6%)
AUC(0-last) (ng.h/mL)	9720 (39.3%)	8010 (48.4%)	9570 (37.6%)
AUC(0-inf) (ng.h/mL)	10200 (39.6%) [n = 16]	8430 (46.4%) [n = 13]	9500 (40.9%) [n = 15]
AUC%extrap (%)	2.601 (44.8%) [n = 16]	2.785 (50.4%) [n = 13]	1.918 (34.9%) [n = 15]
T1/2 (h)	9.393 (57.7%) [n = 16]	9.499 (43.5%) [n = 13]	6.788 (49.2%) [n = 15]
Lambda-z (1/h)	0.074 (57.7%) [n = 16]	0.073 (43.5%) [n = 13]	0.102 (49.2%) [n = 15]
CL/F (mL/min)	326 (39.6%) [n = 16]	395 (46.4%) [n = 13]	351 (40.9%) [n = 15]
Vz/F (L)	265 (62.6%) [n = 16]	325 (47.9%) [n = 13]	206 (27.6%) [n = 15]

n: number of subjects with an observation; N: number of subjects in the dataset

[a] Medium (range)

Following a single oral administration of belumosudil to healthy male volunteers as a Tablet reference in the fed state (Regimen G), concentrations of belumosudil were evident from between 0.5 h and 3 h in all subjects. Following dosing with an Oral Suspension in the fasted and fed states (Regimens H and I), concentrations were evident from 0.5 h in all subjects. Maximum plasma concentrations occurred between 1 h and 5 h post-dose.

Concentrations then declined in a biphasic manner and remained quantifiable for up to between 24 h and 72 h post-dose. Resultant elimination half-lives ranged between 4.84 h and 33.02 h, 5.36 h and 23.76 h and 2.38 h and 15.73 h, respectively. The geometric mean half-life ranged from 6.788 h to 9.499 h.

The key geometric mean (geometric CV%) PK parameters for plasma KD025m1 following dosing with belumosudil are summarised below:

Regimen Dose level Status	G 200 mg Tablet Fed	H 200 mg Oral Suspension Fasted	I 200 mg Oral Suspension Fed
No. of Subjects Parameter	**N = 18**	**N = 18**	**N = 18**
Tlag[a] (h)	1.00 (0.500-2.00)	0.00 (0.00-1.00) [n = 17]	0.500 (0.00-1.00) [n = 17]
Tmax[a] (h)	2.00 (1.00-4.03)	1.00 (0.500-1.50) [n = 17]	1.50 (0.500-3.00) [n = 17]
Cmax (ng/mL)	22.3 (37.9%)	19.0 (41.7%) [n = 17]	19.4 (27.6%) [n = 17]
AUC(0-24) (ng.h/mL)	45.3 (63.9%) [n = 15]	34.9 (104.8%) [n = 12]	49.4 (83.1%) [n = 17]
AUC(0-last) (ng.h/mL)	42.7 (50.7%) [n = 15]	30.3 (70.9%) [n = 12]	37.9 (53.2%) [n = 17]
T1/2 (h)	1.81, 2.88 [n = 2]	2.28, 2.67 [n = 2]	2.128 [n = 1]
Lambda-z (1/h)	0.24, 0.38 [n = 2]	0.26, 0.30 [n = 2]	0.326 [n = 1]
MPR Cmax	0.013 (40.6%)	0.014 (36.0%) [n = 17]	0.012 (31.7%) [n = 17]
MPR AUC(0-24)	0.005 (62.0%) [n = 15]	0.005 (87.7%) [n = 12]	0.006 (78.3%) [n = 17]
MPR AUC(0-last)	0.004 (52.1%) [n = 15]	0.004 (59.9%) [n = 12]	0.004 (49.9%) [n = 17]

n: number of subjects with an observation; N: number of subjects in the dataset; NC: not calculated

[a] Medium (range)

Following a single oral administration of belumosudil to healthy male volunteers as Tablet reference in the fed state (Regimen G), concentrations of KD025m1 were evident from between 0.5 h and 3 h in all subjects. Concentrations of KD025m1 were below the limit of quantification at all time points for two profiles. Following dosing with an Oral Suspension in the fasted and fed states (Regimens H, and I), concentrations were evident from 0.5 h and 1.5 h in all subjects.

Maximum plasma concentrations occurred between 1 h and 4.03 h post-dose.

Concentrations declined in a monophasic manner and remained quantifiable for up to between 1 h and 5 h post-dose. Resultant elimination half-lives ranged between 1.81 h and 2.88 h.

The geometric mean (geometric CV%) metabolite to parent ratios following Regimen G, Regimen H and Regimen I were 0.013 (40.6%), 0.014 (36.0%) and 0.012 (31.7%), respectively, for Cmax; 0.005 (62.0%), 0.005 (87.7%) and 0.006 (78.3%), respectively, for AUC(0-24) and 0.004 (52.1%), 0.004 (59.9%) and 0.004 (49.9%), respectively, for AUC(0-last).

The key geometric mean (geometric CV%) PK parameters for plasma KD025m2 following dosing with belumosudil are summarised below:

Regimen Dose level Status	G 200 mg Tablet Fed	H 200 mg Oral Suspension Fasted	I 200 mg Oral Suspension Fed
No. of Subjects Parameter	N = 18	N = 18	N = 18
Tlag[a] (h)	1.00 (0.500-2.00)	0.00 (0.00-0.00)	0.00 (0.00-1.00)
Tmax[a] (h)	3.00 (1.50-5.00)	1.50 (1.00-3.02)	2.00 (1.00-3.03)
Cmax (ng/mL)	406 (52.5%)	372 (56.4%)	319 (57.9%)
AUC(0-24) (ng.h/mL)	1280 (62.9%)	1130 (61.8%)	1180 (58.1%)
AUC(0-last) (ng.h/mL)	1200 (65.7%)	1080 (62.2%)	1120 (59.5%)
AUC(0-inf) (ng.h/mL)	1180 (75.3%) [n = 8]	1030 (59.8%) [n = 10]	926 (56.0%) [n = 10]
AUC%extrap (%)	5.607 (49.8%) [n = 8]	4.453 (60.7%) [n = 10]	5.388 (43.1%) [n = 10]
T1/2 (h)	2.466 (43.1%) [n = 8]	2.506 (87.4%) [n = 10]	2.539 (56.5%) [n = 10]
Lambda-z (1/h)	0.281 (43.1%) [n = 8]	0.277 (87.4%) [n = 10]	0.273 (56.5%) [n = 10]
MPR Cmax	0.232 (42.1%)	0.264 (44.1%)	0.196 (45.6%)
MPR AUC(0-24)	0.151 (40.2%)	0.164 (45.1%)	0.139 (37.7%)
MPR AUC(0-last)	0.136 (42.6%)	0.149 (47.0%)	0.129 (38.1%)
MPR AUC(0-inf)	0.136 (42.7%) [n = 7]	0.139 (49.0%) [n = 6]	0.117 (40.2%) [n = 7]

n: number of subjects with an observation; N: number of subjects in the dataset

[a] Medium (range)

Following a single oral administration of belumosudil to healthy male volunteers as Tablet reference in the fed state (Regimen G), concentrations of KD025m2 were evident from between 1 h and 3 h in all subjects. Following dosing with belumosudil Oral Suspension in the fasted and fed states (Regimens H and I), concentrations were evident from 0.5 h to 1 h in all subjects.

Maximum plasma concentrations occurred between 1 h and 5 h post-dose.

Elimination half-lives ranged between 1.39 h and 4.33 h, 0.96 h and 6.70 h and 0.95 h and 4.39 h, respectively.

The geometric mean (geometric CV%) metabolite to parent ratios following Regimen G, Regimen H and Regimen I were 0.232 (42.1%), 0.264 (44.1%) and 0.196 (45.6%) for Cmax, 0.151 (40.2%), 0.164 (45.1%) and 0.139 (37.7%) for AUC(0-24) and 0.136 (42.6%), 0.149 (47.0%) and 0.129 (38.1%) for AUC(0-last), 0.136 (42.7%), 0.139 (49.0%) and 0.117 (40.2%) for AUC(0-inf).

Administration of belumosudil oral suspension in the fasted state showed an earlier median Tmax (1.5 h) compared to the same dose in the fed state.

Comparison of the GMRs relating to peak (Cmax) and total exposure (AUC(0-last) and AUC(0-inf)) levels for belumosudil Oral Suspension in the fed state vs Tablet in the fed state indicated that levels of peak and total exposure to belumosudil and KD025m1 for the oral suspension were largely similar to that of the tablet reference, with the 90% CI for each parameter including 100%. The upper bound of the 90% CI for peak exposure was marginally below 100% (upper CI 94.39%); although it did exclude unity, this indicates that any true difference could be minimal and unlikely to be of clinical significance. Additionally, the change in formulation resulted in little to no change in AUC, indicating change in formulation had no notable impact on overall exposure to belumosudil or its two known metabolites.

Comparison of the GMRs relating to peak and total exposure for Oral Suspension fed vs fasted demonstrated a slight increase in for belumosudil after the fed regimen, averaging 15% to 19% greater exposure than that seen for the fasted regimen. For KD025m1, moderate increases in total exposure were observed, although this increase should be interpreted with caution due to the relatively sparse data available for KD025m1 parameter estimation across all regimens. The lower bound of the 90% CI for each parameter exceeded 100%. No notable changes based on food effect were observed for KD025m2.

The adjusted GMRs (90% CIs) of Cmax, AUC(0-last), AUC(0-inf) and AUC(0-24) for the assessment of relative bioavailability and food effect are shown below (ratio [90%] CIs):

Analyte	belumosudil	KD025m1	KD025m2
No. of Subjects Parameter	**N = 18**	**N = 18**	**N = 18**
Frel OS vs TAB Cmax[a] (%)	93.03 (84.68%, 102.19%)	87.79 (76.48%, 100.78%) [n = 17] vs [n = 18]	78.58 (65.42%, 94.39%)
Frel OS vs TAB AUC(0-last)[a] (%)	98.42 (89.80%, 107.87%)	93.06 (77.43%, 111.83%) [n = 17] vs [n = 15]	93.47 (81.02%, 107.85%)
Frel OS vs TAB AUC(0-24) (%) or AUC(0-inf)[a] (%)[a]	97.28 (86.77%, 109.06%) [n = 15] vs [n = 16	114.18 (88.95%, 146.57%) [n = 17] vs [n = 15]	92.68 (80.93%, 106.14%)
Food Effect Frel Cmax[b] (%)	115.68 (105.30%, 127.08%)	103.31 (89.75%, 118.91%) [n = 17] vs [n = 17]	85.75 (71.39%, 103.00%)
Food Effect Frel AUC(0-last)[b] (%)	119.48 (109.02%, 130.95%)	138.19 (112.99%, 169.01%) [n = 17] vs [n = 12]	103.63 (89.82%, 119.56%)
Food Effect Frel AUC(0-24) or AUC(0-inf)[b] (%)[c]	115.43 (102.29%, 130.26%) [n = 15] vs [n = 13]	161.78 (123.05%, 212.69%) [n = 17] vs [n = 12]	104.36 (91.13%, 119.52%)

n: number of subjects with an observation; N: number of subjects in the dataset; OS: Oral Suspension; TAB: Tablet

[a] Regimen I (200 mg belumosudil Oral Suspension, fed) compared to Regimen G (200 mg belumosudil Tablet, fed)

[b] Regimen I (200 mg belumosudil Oral Suspension, fed) compared to Regimen H (200 mg belumosudil Oral Suspension, fasted)

[c] AUC(0-inf) for belumosudil and AUC(0-24) for metabolites KD025m1 and KD025m2

Safety Results, Part 1

Tasting of belumosudil in Bottle formulation was well tolerated by healthy male subjects, with no TEAEs reported in Part 1 of the study. There were no deaths, serious adverse events (SAEs), severe AEs or AEs leading to subject withdrawal during Part 1 of this study.

No clinically significant laboratory, vital signs, ECG or physical examination findings were reported following dosing in Part 1.

Safety Results, Part 2

There were no deaths, SAEs, severe AEs or AEs leading to subject withdrawal during Part 2 of this study. The number of subjects reporting AEs was low for all regimens and all AEs were mild in severity.

Headache was the most frequently reported AE in Part 2 of the study: 3 (16.7%) subjects experienced a headache, comprising 2 (11.1%) and 1 (5.6%) subjects, following administration of Regimens H and I (Oral Suspension fasted and fed, respectively).

Two subjects reported AEs considered related to IMP; these were urticaria in 1 subject approximately 1.5 h post dosing with Regimen G (belumosudil oral Tablet, fed) and headache and nausea in 1 subject approximately 2.5 h post-dosing with Regimen I (belumosudil Oral Suspension, fed). These AEs occurred within 1 h of Tmax of belumosudil for each subject and are consistent with those AEs reported in previous belumosudil clinical studies. All other AEs were considered not related to IMP.

All AEs resolved prior to the end of the study.

No clinically significant laboratory, vital signs, ECG or physical examination findings were reported following dosing in Part 2.

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