Sponsor: Sanofi **Drug substance(s):** Belumosudil	**Study Identifiers:** IND 125890; NCT03640481; EudraCT Number: 2024-000203-67 **Study code:** DRI17633 (KD025-213)

Title of the study:

A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 (belumosudil) in Subjects with Chronic Graft Versus Host Disease (cGVHD) After at Least 2 Prior Lines of Systemic Therapy (The ROCKstar Study)

Study center(s):

33 clinical sites in the United States (US)

Study period:

Initiation Date: 11 October 2018

End Date of Reporting Period: 19 February 2020

Study Status: Terminated. The sponsor has decided to prematurely terminate the study due to the challenges encountered in recruiting adolescent participants. This decision was made without any safety concerns.

Phase of development: 2

Objectives:

Primary:

The primary objective of this study was to evaluate the efficacy and safety of belumosudil, at dose levels of 200 mg once daily (QD) and 200 mg twice daily (BID), in subjects with cGVHD who had previously been treated with at least 2 prior lines of systemic therapy.

Secondary:

The secondary objectives of this study were to evaluate the following:

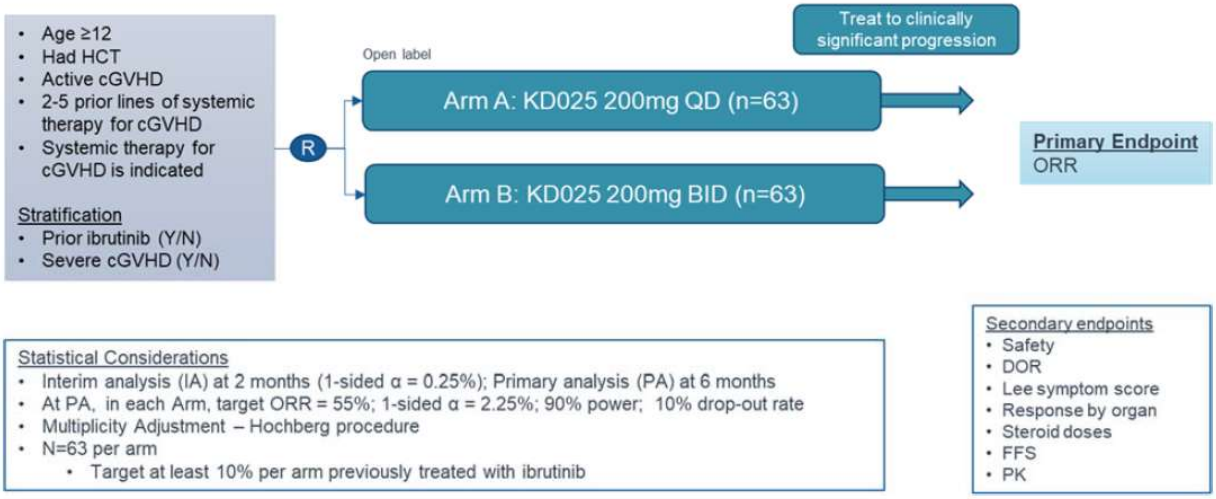
- To evaluate percentage of subjects who had a best response of partial response (PR) and percentage of subjects who had a best response of complete response (CR);
- To evaluate Duration of Response (DOR);
- To evaluate Time to Response (TTR);
- To evaluate response by organ system;
- To evaluate changes in National Institutes of Health (NIH) cGVHD global severity rating (GSR) using the Clinician-Reported Global cGVHD Activity Assessment;
- To evaluate changes in symptom burden/bother using the Lee Symptom Scale Score (LSS);
- To evaluate Failure-Free Survival (FFS);
- To evaluate Time to Next Treatment (TTNT);
- To evaluate Overall Survival (OS);
- To evaluate changes in corticosteroid dose;
- To evaluate changes in calcineurin inhibitor (CNI) dose;
- To evaluate changes in symptom activity using the cGVHD Activity Assessment Patient Self-Report; and
- To assess pharmacokinetics (PK) of belumosudil in subjects with cGVHD.

Methodology:

This was a Phase 2, randomized, multicenter, open-label study designed to evaluate the efficacy and safety of belumosudil in subjects with active cGVHD after at least 2 prior lines of systemic therapy. The study design is illustrated in Figure S1 below.

Sample size was based on the primary efficacy endpoint of ORR, with 1 planned interim analysis (0.0025 1-sided alpha spending) and a true ORR of 55%.

Figure S1. KD025-213 Study Schema



BID = twice daily; cGVHD = chronic graft versus host disease; DOR = Duration of Response; FFS = Failure-Free Survival; HCT = hematopoietic cell transplantation; IA = interim analysis; ORR = Overall Response Rate; PA = primary analysis; PK = pharmacokinetics; QD = once daily; R = randomization; Y/N = yes/no.

Source: Clinical Study Protocol Amendment 1 (Appendix 16.1.1)

A target of ≥10% of the enrolled population having previously received ibrutinib as a therapy for cGVHD was set.

After confirmation of eligibility during a 14-day screening period, eligible subjects were randomized (1:1) to 1 of 2 treatment arms:

- Arm A: belumosudil 200 mg QD; or
- Arm B: belumosudil 200 mg BID.

These doses were selected based upon the data from Study KD025-208.

Randomization was stratified according to prior cGVHD treatment with ibrutinib (yes/no) and severe cGVHD (yes/no).

Number of study participants: Screened: 221 subjects Randomized: 135 subjects Randomized but not dosed: 3 subjects Discontinued study as of 19 February 2020: 13 subjects Discontinued treatment as of 19 February 2020: 62 subjects
Diagnosis and criteria for inclusion: Subjects who consented and/or provided assent documented with a signed Institutional Review Board-approved informed consent/assent form as applicable, and met all of the eligibility criteria were enrolled. The study population consisted of adults and adolescents who: ● Had undergone allogeneic hematopoietic cell transplantation; ● Had previously received at least 2 prior lines of systemic therapy for cGVHD; ● Had received glucocorticoid therapy with a stable dose for at least 2 weeks prior to screening; and ● Had persistent cGVHD manifestations and for whom systemic therapy for cGVHD was indicated.
Study products: Belumosudil (KD025) was supplied as 200 mg tablets
Duration of treatment: Subjects received belumosudil treatment in 28-day cycles until clinically significant progression of cGVHD (defined as progression that required the addition of new systemic therapy for cGVHD), histologic recurrence of underlying malignancy, unacceptable toxicity, Investigator decision, subject preference/withdrawal of consent, loss of follow-up, Sponsor decision, or death (whichever occurred first).
Criteria for evaluation: Efficacy: The primary population for efficacy analyses was the modified Intent-to-Treat (mITT) Population, which was defined as all randomized subjects who received at least 1 dose of study drug. The primary efficacy endpoint was the ORR, as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD and as assessed by Investigators. Responders included subjects that achieved a response (PR+CR). The secondary efficacy endpoints were the following: ● DOR; ● TTR; ● Response rate by organ system; ● Change in cGVHD GSR based on the Clinician-Reported Global cGVHD Activity Assessment; ● Change in LSS; ● FFS; ● TTNT;

- OS;
- Change in corticosteroid dose;
- Change in CNI dose;
- Change in symptom activity based on the cGVHD Activity Assessment Patient Self-Report; and
- PK of belumosudil in subjects with cGVHD.

Safety:

Safety was a secondary endpoint. The primary safety outcome was the percent of subjects in each arm that experienced adverse events (AEs). See below for the safety endpoints and additional details of safety assessments:

- AEs and serious AEs (SAEs);
- Hematological and clinical chemistry parameters;
- Vital signs;

o Change from baseline in systolic blood pressure, diastolic blood pressure, and heart rate;

and

- 12-lead electrocardiograms (ECGs);

o Mean and maximum change from baseline in QTcF.

Statistical methods:

Primary Endpoint:

The primary efficacy endpoint was the ORR, as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD and as assessed by Investigators.

The overall response was assessed using scores from 9 individual organ systems (skin, eyes, mouth, esophagus, upper gastrointestinal [GI], lower GI, liver, lungs, and joints and fascia) and the GSR. Response was assessed with respect to the baseline (Cycle [C] 1, D1) cGVHD assessment. The overall response at each assessment time point was categorized as CR, PR, or Lack of Response (LR), where LR included the response status of unchanged, mixed, or progression. Response was assessed on D1 of C2 through C5, then on D1 of every other cycle thereafter and at the End of Treatment visit.

The ORR was defined as the proportion of subjects with a best response meeting the overall response criteria assessment of CR or PR at any post-baseline response assessment.

If a treated subject was lost to follow-up without a response assessment, the subject was counted as a non-responder.

Point estimates, confidence intervals (CIs) (Clopper-Pearson [exact] method), and unadjusted and Hochberg adjusted p-values corresponding to the null hypothesis of ORR ≤30% versus the alternative hypothesis of ORR >30% by treatment arms are reported.

The number and percentage of subjects who had a best response of PR and number and percentage of subjects who had a best response of CR are also reported.

Secondary Endpoints:

Duration of Response:

The DOR was reported only for subjects who responded and statistics included:

- Kaplan-Meier plots and descriptive statistics of DOR; and
- Landmark analyses.

Time to Response:

TTR was measured as the time from first treatment to the time of first documentation of response. Descriptive statistics and plots of cumulative number and percentage of responders over time are provided. TTR analyses were only conducted for the Responder Population.

Response by organ system:

The best response (CR or PR) for the 9 individual organ systems (skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs, and joints and fascia) plus GSR were summarized.

TTR at the organ level was also evaluated. Descriptive statistics and plots of cumulative number and percentage of responders over time are provided.

Change in Lee Symptom Scale Score:

The LSS was assessed on the same schedule as response assessments. The questionnaire consisted of 30 items over 7 domains: skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, and emotional distress. Each question was scored 0, 1, 2, 3, or 4.

A domain score was calculated for each domain by taking the mean of all items completed if more than 50% were answered and normalizing to a 0 to 100 scale. A summary score was calculated as average of all non-missing domain scores if more than 50% of them were non-missing. A higher score indicated more bothersome symptoms. A 7-point or greater reduction on the summary score of cGVHD Symptom Scale was considered to be clinically meaningful.

The analyses included the following:

- Descriptive statistics of absolute score and change from baseline score (summary score and domain scores) were summarized as continuous variables by treatment arm and visit;
- Number and percentage of subjects with a 7-point reduction (7-PtR) from baseline (C1D1);
- Number and percentage of subjects with a 7-PtR from baseline on 2 consecutive assessments; and
- Duration of a 7-PtR (DO7-PtR) (defined as time from documentation of the first 7-PtR to the first documentation of <7-PtR). If there were multiple episodes, the DO7-PtR was measured as the sum of DO7-PtR from all episodes.

These analyses were performed on the mITT, Responder, and Non-Responder Populations.

Failure-Free Survival:

FFS was defined as the time from the first dose of belumosudil to the time of the first event; events included the initiation of new systemic cGVHD therapy, non-relapse mortality, and recurrent malignancy (ie, underlying disease). FFS was censored by last response assessment or Long-Term Follow-Up assessment, whichever was the latest and available. Kaplan-Meier plots, descriptive statistics of FFS, and the landmark analyses at 6, 12, 18, and 24 months are provided. In addition, the number of events for each of the 3 components of FFS are provided.

Time to Next Treatment:

TTNT was measured as the time from the first dose of belumosudil to the time of new systemic cGVHD treatment, censored by the last response assessment or Long-Term Follow-Up assessment, whichever was the latest and available. TTNT was analyzed by the Kaplan-Meier survival method as well as with landmark analyses.

Overall Survival:

OS was defined as time from the first dose of belumosudil to the date of death due to any cause. Kaplan-Meier plots, descriptive statistics of OS, and the landmark analyses at 6, 12, 18, and 24 months are provided.

Change in corticosteroid dose:

Corticosteroid doses are presented as mg/kg/day prednisone equivalent dose. Descriptive statistics for the mITT, Responder, and Non-Responder Populations and subgroups defined by baseline corticosteroid dose level (upper and lower 50th percentiles) are provided for the following:

- Systemic corticosteroid dose over time;
- Change and percent change from baseline (C1D1) to the greatest corticosteroid dose reduction during the belumosudil treatment period;
- Number and percentage of subjects who reduced systemic corticosteroid dose during the belumosudil treatment period; and
- Number and percentage of subjects who ever discontinued systemic corticosteroid usage during the belumosudil treatment period.

Change in CNI dose:

CNIs included systemic tacrolimus and cyclosporine. Descriptive statistics are provided for the following:

- Number and percentage of subjects who reduced CNI dose during the belumosudil treatment period; and
- Number and percentage of subjects who ever discontinued CNI during the belumosudil treatment period.

Safety:

Safety assessments included AEs, SAEs, vital sign measurements, clinical laboratory evaluations (hematology and chemistry), and ECGs. Clinically significant PE findings were captured as AEs.

Safety analyses further included assessments of the defined stopping rules, namely:

1. Secondary graft failure in >10% of subjects;

2. Histological recurrence of underlying malignancy within 6 months of randomization in >20% of subjects; and/or

3. Withdrawal due to study drug-related AEs in >20% of subjects.

Summary Results:

Population:

Table S1 presents a summary of the mITT Population.

Table S1. Summary of Study Population − mITT Population

	Arm A 200 mg QD N=66	Arm B 200 mg BID N=66	Overall N=132
Age (years)			
n	66	66	132
Median (min, max)	53.0 (21, 77)	57.0 (21, 77)	55.5 (21, 77)
Sex - n (%)			
Female	24 (36.4)	33 (50.0)	57 (43.2)
Male	42 (63.6)	33 (50.0)	75 (56.8)
Number of prior lines of systemic cGVHD therapy			
Median	3.0	4.0	3.0
Prior ibrutinib	22 (33.3)	23 (34.8)	45 (34.1)
Prior ruxolitinib [1]	20 (30.3)	18 (27.3)	38 (28.8)
Refractory to the last systemic cGVHD treatment prior to enrollment to study (SD or PD) [2]	45/56 (80.4)	34/53 (64.2)	79/109 (72.5)
Time from cGVHD diagnosis to enrollment (months) [3]			
n	66	66	132
Median (min, max)	25.2 (1.9, 162.4)	30.2 (3.7, 144.1)	28.9 (1.9, 162.4)
Severe NIH cGVHD at screening - n (%) [4]	46 (69.7)	43 (65.2)	89 (67.4)
Prior aGVHD - n (%)	42 (63.6)	51 (77.3)	93 (70.5)
Summary of organs involved at baseline - n (%)			
Skin	55 (83.3)	55 (83.3)	110 (83.3)
Eyes	48 (72.7)	49 (74.2)	97 (73.5)
Mouth	30 (45.5)	41 (62.1)	71 (53.8)
Esophagus	19 (28.8)	12 (18.2)	31 (23.5)
Upper GI	13 (19.7)	10 (15.2)	23 (17.4)
Lower GI	6 (9.1)	7 (10.6)	13 (9.8)
Liver	9 (13.6)	4 (6.1)	13 (9.8)
Lung	24 (36.4)	23 (34.8)	47 (35.6)
Joints and fascia	51 (77.3)	49 (74.2)	100 (75.8)
GSR			
n	66	66	132
Median (min, max)	7.0 (0, 9)	7.0 (2, 10)	7.0 (0, 10)
Number of organs involved at baseline			
n	66	66	132
Median (min, max)	3.5 (0, 7)	4.0 (1, 7)	4.0 (0, 7)
≥4	33 (50.0)	35 (53.0)	68 (51.5)

Table S1. Summary of Study Population − mITT Population (Continued)

	Arm A 200 mg QD N=66	Arm B 200 mg BID N=66	Overall N=132
Concomitant systemic cGVHD therapies - n (%) [5,6]	66 (100)	66 (100)	132 (100)
Prednisone	63 (95.5)	65 (98.5)	128 (97.0)
Tacrolimus	23 (34.8)	25 (37.9)	48 (36.4)
Sirolimus	18 (27.3)	18 (27.3)	36 (27.3)
MMF	11 (16.7)	2 (3.0)	13 (9.8)
ECP [7]	19 (28.8)	22 (33.3)	41 (31.1)

Statistical notes:

1. Ruxolitinib prior therapy included prior therapy with ruxolitinib phosphate (21 [15.9%] subjects total) and ruxolitinib (17 [12.9%] subjects total).
2. The percentages of refractory were based on the number of subjects in the mITT Population whose best response to the last systemic cGVHD treatment prior to enrollment in the study was CR, PR, SD, or PD. The following formula was used: (PD+SD)/(PD+SD+CR+PR). Subjects with missing or unknown status were excluded.
3. Time from cGVHD diagnosis to enrollment (months) = (date of informed consent – date of cGVHD diagnosis +1)/365.25*12.
4. "Severe" was defined as at least 1 organ with an NIH Activity Assessment score of 3 or lung score of ≥2 at baseline.
5. Medications were coded using WHO Drug Dictionary, version March 2017, B2 Format.
6. A subject with multiple medications within a medication type or preferred term was counted only once for that medication type or preferred term.
7. ECP was coded as "photopheresis."
8. The results presented are based on the data cut-off date of 19 February 2020.

aGVHD = acute graft versus host disease; BID = twice daily; cGVHD = chronic graft versus host disease; CR = complete response; ECP = extracorporeal photopheresis; GI = gastrointestinal; GSR = global severity rating; max = maximum; min = minimum; mITT = modified Intent-to-Treat; MMF = mycophenolate mofetil; NIH = National Institutes of Health; PD = progressive disease; PR = partial response; QD = once daily; SD = stable disease; WHO = World Health Organization.
Sources: Post-text Tables 2.1.1, 2.1.3, 2.1.4, 2.1.5, 3.1.3, and 3.1.4

Table S2 summarizes subject disposition and follow-up duration for all informed consent subjects. In total, 132 subjects were included in the mITT Population: 66 subjects in Arm A and 66 subjects in Arm B.

As of the cut-off date for this analysis (19 February 2020), the median follow-up duration was 7.9 months: 8.0 months for Arm A and 7.9 months for Arm B. In total, 62 (47.0%) subjects have discontinued from treatment and 70 (53.0%) subjects remain on treatment with belumosudil. The most common reasons for treatment discontinuation were progression of disease under study (cGVHD) (16 [12.1%] subjects) and withdrawal by subject (14 [10.6%] subjects).

Table S2. Subject Disposition and Follow-Up Duration – All Informed Consent Subjects

	Arm A 200 mg QD n (%)	Arm B 200 mg BID n (%)	Overall n (%)
Informed consent - n	-	-	221
Screen failed - n	-	-	86
Randomized - n	67	68	135
Randomized but never dosed - n	1	2	3
mITT Population	66 (100)	66 (100)	132 (100)
Responder Population	48 (72.7)	49 (74.2)	97 (73.5)
Non-Responder Population	18 (27.3)	17 (25.8)	35 (26.5)
Safety Population	66 (100)	66 (100)	132 (100)

Treatment ongoing	33 (50.0)	37 (56.1)	70 (53.0)
Discontinued from treatment	33 (50.0)	29 (43.9)	62 (47.0)
Study ongoing	58 (87.9)	61 (92.4)	119 (90.2)
Discontinued from study	8 (12.1)	5 (7.6)	13 (9.8)
Duration of follow-up for the mITT Population (months)			
n	66	66	132
Median (min, max)	8.0 (0.6, 15.4)	7.9 (0.9, 15.7)	7.9 (0.6, 15.7)
Statistical notes: 1. The results presented are based on the data cut-off date of 19 February 2020. BID = twice daily; max = maximum; min = minimum; mITT = modified Intent-to-Treat; QD = once daily. Sources: Post-text Tables 1.1.1 and 4.1.1			

Overall, subjects had a median age of 55.5 years and were predominantly male (75 [56.8%] subjects), White (112 [84.8%] subjects), and not Hispanic or Latino (110 [83.3%] subjects). In total, 103 (78.0%) subjects had a Karnofsky Performance Scale score ≥80.

All subjects received a previous allogeneic transplant. Indications for the most recent transplant received by subjects included acute myelogenous leukemia (AML) (53 [40.2%] subjects), acute lymphoblastic leukemia (19 [14.4%] subjects), other (18 [13.6%] subjects), myelodysplastic syndrome (13 [9.8%] subjects), chronic myelogenous leukemia (8 [6.1%] subjects), myelofibrosis (5 [3.8%] subjects), chronic lymphocytic leukemia (4 [3.0%] subjects), non-Hodgkin lymphoma (4 [3.0%] subjects), diffuse large B-cell lymphoma (3 [2.3%] subjects), Hodgkin lymphoma (3 [2.3%] subjects), and multiple myeloma (2 [1.5%] subjects). The majority of subjects had prior acute graft versus host disease (93 [70.5%] subjects): 42 (63.6%) subjects in Arm A and 51 (77.3%) subjects in Arm B. The median time to cGVHD diagnosis from the most recent transplant was 6.8 months: 6.9 months in Arm A and 6.7 months in Arm B. The median time from cGVHD diagnosis to study enrollment was 28.9 months: 25.2 months in Arm A and 30.2 months in Arm B.

The overall median number of prior lines of systemic cGVHD therapy was 3.0 prior lines: 3.0 prior lines for Arm A and 4.0 prior lines for Arm B. In total, 79 (72.5%) subjects with known status were refractory to the last systemic cGVHD treatment prior to enrollment in the study (stable disease or progressive disease): 45 (80.4%) subjects in Arm A and 34 (64.2%) subjects in Arm B.

In total, 68 (51.5%) subjects had 4 organs involved at baseline: 33 (50.0%) subjects in Arm A and 35 (53.0%) subjects in Arm B. The most common organs involved at baseline included skin (110 [83.3%] subjects), joints and fascia (100 [75.8%] subjects), eyes (97 [73.5%] subjects), and mouth (71 [53.8%] subjects). Lung involvement was present in 35.6% of subjects. Of the subjects with lung involvement, 38.3% had a baseline lung NIH score of 2.

All 132 (100%) subjects were taking a concomitant cGVHD medication. The most common concomitant cGVHD medications taken were prednisone (128 [97.0%] subjects), tacrolimus (48 [36.4%] subjects), extracorporeal photopheresis (41 [31.1%] subjects), and sirolimus (36 [27.3%] subjects).

Efficacy:

The primary efficacy endpoint of this study was ORR as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD, as assessed by Investigators.

Table S3 summarizes the ORR interim analysis for the mITT Population. The primary efficacy endpoint was met at the pre-specified interim analysis with a cut-off date 2 months after last subject, first visit (17 October 2019) with an ORR (99.75% CI) of 65.2% (51.7, 77.1).

Table S3. Overall Response Rate Interim Analysis− mITT Population

	Arm A 200 mg QD N=66	Arm B 200mg BID N=66	Overall N=132
ORR (CR or PR) - n (%)	42 (63.6)	44 (66.7)	86 (65.2)
CR	2 (3.0)	1 (1.5)	3 (2.3)
PR	40 (60.6)	43 (65.2)	83 (62.9)

Exact method			
99.75% CI of ORR	(44.3, 80.2)	(47.4, 82.6)	(51.7, 77.1)

Statistical notes:
1. 2-sided, exact CI was calculated using the Clopper Pearson method.
2. The results presented are based on the data cut-off date of 17 October 2019.

BID = twice daily; CI = confidence interval; CR = complete response; mITT = modified Intent-to-Treat; ORR = Overall Response Rate; PR = partial response; QD = once daily.
Source: Post-text Table 5.1.1 (Interim)

For the primary analysis, (cut-off date 6 months after last subject, first visit), the ORR (95% CI) with belumosudil was 73.5% (65.1, 80.8): 72.7% (60.4, 83.0) in Arm A and 74.2% (62.0, 84.2) in Arm B. Across both arms, 4 (3.0%) subjects achieved CR and 93 (70.5%) subjects achieved PR. There were no notable differences in ORR according to arm (dose level).

The primary endpoint ORR results are summarized in Table S4 below.

Table S4. Overall Response Rate Analysis − mITT Population

	Arm A 200 mg QD N=66	Arm B 200 mgBID N=66	Overall N=132
ORR (CR or PR) - n (%)	48 (72.7)	49 (74.2)	97 (73.5)
CR	3 (4.5)	1 (1.5)	4 (3.0)
PR	45 (68.2)	48 (72.7)	93 (70.5)
Exact method			
95% CI of ORR	(60.4, 83.0)	(62.0, 84.2)	(65.1, 80.8)

Statistical notes:
1. 2-sided, exact CI was calculated using the Clopper-Pearson method.
2. The results presented are based on the data cut-off date of 19 February 2020.

BID = twice daily; CI = confidence interval; CR = complete response; mITT = modified Intent-to-Treat; ORR = Overall Response Rate; PR = partial response; QD = once daily.
Source: Post-text Table 5.1.1

ORR (95% CI) within 6 months of belumosudil treatment was 71.2% (62.7, 78.8): 69.7% (57.1, 80.4) in Arm A and 72.7% (60.4, 83.0) in Arm B. Across both arms, 3(2.3%) subjects achieved a CR and 91 (68.9%) subjects achieved a PR. Results of key secondary endpoints are summarized in Table S5 below.

Table S5. Key Secondary Endpoint Results

	Arm A 200 mg QD N=66	Arm B 200 mg BID N=66	Overall N=132
Median DOR (weeks) (95% CI)			
Number of responders	48	49	97
Primary median [1]	21.1 (9.4, NA)	32.0 (12.6, NA)	22.1 (16.1, NA)
Secondary median [2]	21.1 (9.4, NA)	32.0 (12.6, NA)	22.1 (16.1, NA)
Tertiary median [3]	NA (NA, NA)	NA (NA, NA)	NA (NA, NA)
Quaternary median [4]	NA (16.1, NA)	NA (NA, NA)	NA (NA, NA)
TTR (weeks)			
n	48	49	97
TTR median (min, max)	4.4 (3.7, 40.6)	4.4 (3.7, 40.1)	4.4 (3.7, 40.6)
Total response (CR+PR) by organ system [5] - n (%)			
Skin	16/55 (29.1)	22/55 (40.0)	38/110 (34.5)
Eyes	14/48 (29.2)	24/49 (49.0)	38/97 (39.2)
Mouth	15/30 (50.0)	21/41 (51.2)	36/71 (50.7)

Esophagus	7/19 (36.8)	5/12 (41.7)	12/31 (38.7)
Upper GI	7/13 (53.8)	4/10 (40.0)	11/23 (47.8)
Lower GI	3/6 (50.0)	5/7 (71.4)	8/13 (61.5)
Liver	3/9 (33.3)	1/4 (25.0)	4/13 (30.8)
Lungs	5/24 (20.8)	4/23 (17.4)	9/47 (19.1)
Joints and fascia	36/51 (70.6)	33/49 (67.3)	69/100 (69.0)
GSR	26/66 (39.4)	35/66 (53.0)	61/132 (46.2)
TTNT			
Failure event: new cGVHD systemic therapy	13 (19.7)	13 (19.7)	26 (19.7)
Kaplan-Meier estimate (months)			
Median (95% CI)	NA (NA, NA)	NA (NA, NA)	NA (NA, NA)
FFS [6]			
Failure event: new cGVHD systemic therapy	13 (19.7)	13 (19.7)	26 (19.7)
Failure event: non-relapse mortality	3 (4.5)	2 (3.0)	5 (3.8)
Failure event: recurrent malignancy	4 (6.1)	0 (0)	4 (3.0)
Kaplan-Meier estimate (months) (95% CI)			
Median	NA (10.2, NA)	NA (NA, NA)	NA (NA, NA)
6 months	0.74 (0.61, 0.83)	0.81 (0.70, 0.89)	0.77 (0.69, 0.84)
12 months	0.62 (0.44, 0.76)	0.74 (0.60, 0.84)	0.69 (0.58, 0.77)
OS [7]			
Event: death	5 (7.6)	3 (4.5)	8 (6.1)
Kaplan-Meier estimate of OS (months) (95% CI)			
Median	NA (NA, NA)	NA (NA, NA)	NA (NA, NA)
12 months	0.92 (0.82, 0.97)	0.93 (0.78, 0.98)	0.93 (0.85, 0.96)

Table S5. Key Secondary Endpoint Results (Continued)

	Arm A 200 mg QD N=66	Arm B 200 mg BID N=66	Overall N=132
Corticosteroid dosing for the mITT Population			
Median greatest reduction (%) (min, max)	-25.0 (-100, 0)	-50.0 (-100, 33.3)	-33.3 (-100, 33.3)
Subjects who reduced dose - n (%)	35 (53.0)	41 (62.1)	76 (57.6)
Subjects who discontinued corticosteroid usage - n (%)	11 (16.7)	13 (19.7)	24 (18.2)
Lee Symptom Score for the mITT Population			
Subjects with a 7-PtR from baseline	36 (54.5)	40 (60.6)	76 (57.6)
Subjects with a 7-PtR from baseline on 2 consecutive assessments	26 (39.4)	22 (33.3)	48 (36.4)

Statistical notes:

1. The primary definition of DOR was the time from first documentation of response to the time of first documentation of deterioration from best response (eg, CR to PR or PR to LR).
2. The secondary definition of DOR was the time from first documentation of response to the time of first documentation of LR.
3. The tertiary definition of DOR was the time from first documentation of response to the time of initiation of new systemic cGVHD therapy (which was reviewed and confirmed by a clinical team review).
4. The quaternary definition of DOR was the time from first documentation of response to the time of first documentation of LR (as the secondary definition) but with durations summed for multiple responses/LR episodes.
5. The denominator is the number of subjects who had organ involvement.
6. In FFS analysis, only 1 event per subject was included (the earliest event).
7. OS was defined as the time from first dose of belumosudil to the date of death due to any reason.
8. The results presented are based on the data cut-off date of 19 February 2020.

BID = twice daily; cGVHD = chronic graft versus host disease; CI = confidence interval; CR = complete response; 7-PtR = 7-point reduction; DOR = Duration of Response; FFS = Failure-Free Survival; GI = gastrointestinal; GSR = global severity rating; LR = Lack of Response; max = maximum; min = minimum; mITT = modified Intent-to-Treat; NA = not applicable; OS = Overall Survival; PR = partial response; QD = once daily; TTNT = Time to Next Treatment; TTR = Time to Response.

Sources: Post-text Tables 5.2.1.1, 5.2.1.2, 5.2.1.3, 5.2.1.4, 5.3.1, 5.4.1.1, 5.5.1.1, 5.6.1.1, 5.8.1, 5.8.2, and 5.9.1

Subgroups:

Responses were observed across key subgroups, including subjects with severe cGVHD, heavily pre-treated subjects, subjects previously treated with ibrutinib and/or ruxolitinib, and geriatric subjects.

When analyzed by subgroup, there was a trend of a >15% difference in overall response (95% CI) between the subgroups that had a duration of cGVHD before enrollment in the >50th percentile (>28.9 months) (65.2% [52.4, 76.5] of subjects) and ＞50th percentile (＞28.9 months) (81.8% [70.4, 90.2] of subjects). Additionally, there was a trend of >15% difference in overall response (95% CI) between the subgroup that had a baseline glomerular filtration rate (GFR) <60 mL/min/1.73m3 (57.1% [37.2, 75.5] of subjects) and the subgroups that had a baseline GFR ≥60 to <90 mL/min/1.73m3 (78.7% [66.3, 88.1] of subjects) and that had a baseline GFR ≥90 mL/min/1.73m3 (76.7% [61.4, 88.2] of subjects).

Table S6 summarizes subgroup analyses of ORR for the mITT Population.

Table S6. Subgroup Analyses of ORR − mITT Population

	Arm A 200 mg QD N=66 n (%)	Arm B 200 mg BID N=66 n (%)	Overall N=132 n (%)
Prior ibrutinib ORR (CR or PR)			
Yes	16 (72.7)	17 (70.8)	33 (71.7)
No	32 (72.7)	32 (76.2)	64 (74.4)
NIH severity ORR (CR or PR)			
Severe	34 (73.9)	30 (69.8)	64 (71.9)
Non-severe	14 (70.0)	19 (82.6)	33 (76.7)
Number of organs involved at baseline ORR (CR or PR)			
<4	25 (78.1)	25 (80.6)	50 (79.4)
≥4	23 (69.7)	24 (68.6)	47 (69.1)
Number of prior lines of therapy ORR (CR or PR)			
≤3	28 (77.8)	23 (74.2)	51 (76.1)
>3	20 (66.7)	26 (74.3)	46 (70.8)

Duration of cGVHD before enrollment ORR (CR or PR)			
≤50th percentile	18 (58.1)	25 (71.4)	43 (65.2)
>50th percentile	30 (85.7)	24 (77.4)	54 (81.8)
Gender ORR (CR or PR)			
Male	31 (73.8)	23 (69.7)	54 (72.0)
Female	17 (70.8)	26 (78.8)	43 (75.4)
Age ORR (CR or PR)			
<65 years	39 (79.6)	34 (73.9)	73 (76.8)
≥65 years	9 (52.9)	15 (75.0)	24 (64.9)
Race ORR (CR or PR)			
White	39 (70.9)	41 (71.9)	80 (71.4)
Non-White	9 (81.8)	8 (88.9)	17 (85.0)

Statistical notes:
1. These percentages were calculated based on the number of subjects in the specific subgroup in the mITT Population.
2. The results presented are based on the data cut-off date of 19 February 2020.

BID = twice daily; cGVHD = chronic graft versus host disease; CR = complete response; mITT = modified Intent-to-Treat; NIH = National Institutes of Health; ORR = Overall Response Rate; PR = partial response; QD = once daily.
Source: Post-text Table 5.13.1

Logistic regression modeling:

All the univariate logistic regression models (response ~ an individual factor, for a factor of arm or potential prognostic factors used in the subgroup analyses) did not find any factor that has strong influence on response rate; therefore, no further modeling activity was conducted.

Safety:

The overall median duration of treatment was 6.7 months: 6.7 months for Arm A and 6.7 months for Arm B. Overall, 6.1% of subjects received more than 12 months of belumosudil treatment. The median relative dose intensity (RDI) was 99.7%. In total, 110 (83.3%) subjects had an RDI >95%: 54 (81.8%) subjects in Arm A and 56 (84.8%) subjects in Arm B.

In total, 130 (98.5%) subjects experienced at least 1 treatment-emergent AE (TEAE): 65 (98.5%) subjects in Arm A and 65 (98.5%) subjects in Arm B. A total of 35 (26.5%) subjects experienced at least 1 TEAE that led to dose interruption: 19 (28.8%) subjects in Arm A and 16 (24.2%) subjects in Arm B. The most common TEAE that led to dose interruption by preferred term (PT) was pneumonia (7 [5.3%] subjects): 4 (6.1%) subjects in Arm A and 3 (4.5%) subjects in Arm B. A total of 5 (3.8%) subjects experienced at least 1 TEAE that led to dose reduction: 2 (3.0%) subjects in Arm A and 3 (4.5%) subjects in Arm B. The most common TEAE that led to dose reduction by PT was fatigue (2 [1.5%] subjects).

Key safety results are summarized in Table S7 below.

Table S7. Key Safety Results − Safety Population

	Arm A 200 mg QD N=66 n (%)	Arm B 200 mg BID N=66 n (%)	Overall N=132 n (%)
Subjects with at least 1 TEAE	65 (98.5)	65 (98.5)	130 (98.5)
Subjects with TEAEs by maximum severity			
Grade 1: mild	5 (7.6)	4 (6.1)	9 (6.8)
Grade 2: moderate	25 (37.9)	31 (47.0)	56 (42.4)

Table S7. Key Safety Results − Safety Population (Continued)

	Arm A 200 mg QD N=66 n (%)	Arm B 200 mg BID N=66 n (%)	Overall N=132 n (%)
Grade 3: severe	29 (43.9)	26 (39.4)	55 (41.7)
Grade 4: life-threatening	2 (3.0)	3 (4.5)	5 (3.8)
Grade 5: fatal	4 (6.1)	1 (1.5)	5 (3.8)
TEAEs by PT occurring in >20% subjects overall			
Fatigue	26 (39.4)	16 (24.2)	42 (31.8)
Diarrhea	20 (30.3)	18 (27.3)	38 (28.8)
Nausea	17 (25.8)	17 (25.8)	34 (25.8)
Cough	19 (28.8)	13 (19.7)	32 (24.2)
Dyspnea	20 (30.3)	11 (16.7)	31 (23.5)
Upper respiratory tract infection	14 (21.2)	16 (24.2)	30 (22.7)
Edema peripheral	17 (25.8)	11 (16.7)	28 (21.2)
Subjects with at least 1 study drug-related TEAE	47 (71.2)	36 (54.5)	83 (62.9)
Study drug-related TEAEs by PT occurring in >10% of subjects overall			
Fatigue	14 (21.2)	11 (16.7)	25 (18.9)
Nausea	8 (12.1)	7 (10.6)	15 (11.4)
Subjects with at least 1 Grade ≥3 TEAE	35 (53.0)	30 (45.5)	65 (49.2)
Grade ≥3 TEAEs by PT occurring in 5% of subjects overall			
Pneumonia	5 (7.6)	5 (7.6)	10 (7.6)
Hypertension	3 (4.5)	4 (6.1)	7 (5.3)
Subjects with at least 1 study drug-related Grade ≥3 TEAE	11 (16.7)	9 (13.6)	20 (15.2)
Study drug-related Grade ≥3 TEAEs by PT occurring in >1% of subjects overall			
Fatigue	0 (0)	2 (3.0)	2 (1.5)
GGT increased	2 (3.0)	0 (0)	2 (1.5)
Headache	0 (0)	2 (3.0)	2 (1.5)
Hypertension	0 (0)	2 (3.0)	2 (1.5)
Nausea	1 (1.5)	1 (1.5)	2 (1.5)
Subjects with at least 1 serious TEAE	27 (40.9)	18 (27.3)	45 (34.1)
Serious TEAEs by PT occurring in >2% subjects overall			
Pneumonia	6 (9.1)	4 (6.1)	10 (7.6)
Pyrexia	4 (6.1)	0 (0)	4 (3.0)
Dyspnea	1 (1.5)	2 (3.0)	3 (2.3)
Lung infection	1 (1.5)	2 (3.0)	3 (2.3)
Sepsis	2 (3.0)	1 (1.5)	3 (2.3)
Subjects with at least 1 study drug-related serious TEAE	6 (9.1)	1 (1.5)	7 (5.3)
Subjects with TEAE leading to dose discontinuation	14 (21.2)	9 (13.6)	23 (17.4)
Subjects with study drug-related TEAE leading to dose discontinuation	8 (12.1)	5 (7.6)	13 (9.8)
Subjects with TEAE leading to death	4 (6.1)	1 (1.5)	5 (3.8)

Statistical notes:
1. MedDRA version 20.0.
2. Definitely related, probably related, and possibly related were all considered as related to belumosudil.
3. A subject with multiple events within a category was counted only once in that category.
4. A subject with multiple conditions within a PT was counted only once for that PT.
5. The results presented are based on the data cut-off date of 19 February 2020.

BID = twice daily; cGVHD = graft versus host disease; GGT = gamma glutamyl transferase; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; TEAE = treatment-emergent adverse event.
Sources: Post-text Tables 6.1.1, 6.2.2, 6.3.1, 6.4.2, 6.5.1, 6.5.3, 6.6.2, and 6.7.1

In total, 5 subjects experienced a serious TEAE that led to treatment discontinuation: 4 subjects in Arm A (cellulitis; aspiration; septic shock; multiple organ dysfunction syndrome) and 1 subject in Arm B (sepsis and microangiopathic hemolytic anemia).

Table S8. Deaths Within 28 Days of Study Treatment − Safety Population

Treatment Arm (Dose)	Primary Cause of Death (Preferred Term)	Relationship to Study Drug	Study Day	Time From Last Dose (Day)
Arm A (200 mg QD)				
	Hemothorax	Not related	30	5
	Aspiration	Not related	47	12
	Respiratory failure	Not related		
	Septic shock	Unlikely related	17	4
	Multiple organ dysfunction syndrome	Possibly related		
	Acute myeloid leukemia recurrent	Not related	56	17
Arm B (200 mg BID)				
	Cardiac arrest	Unlikely related	26	15

Statistical notes:
1. MedDRA version 20.0.
2. Study Day = start date or end date − start date of study treatment (+1 for assessments on or after the first study drug administration).
3. The results presented are based on the data cut-off date of 19 February 2020.

BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily. Sources: Post-text Data Listings 6.1.1, 6.1.2, and 6.1.3

In the event of any of the following safety findings occurring in either treatment arm, after at least 10 subjects had been enrolled into the mITT Population in that arm, enrollment would have been
paused for assessment of safety:
1. Secondary graft failure in >10% of subjects;
2. Histological recurrence of underlying malignancy within 6 months of randomization in >20% of subjects; and/or
3. Withdrawal due to related AEs in >20% of subjects.

These stopping criteria were assessed on an ongoing basis by the Medical Monitor and shared with the study Steering Committee. As of the cut-off date, the rates for these stopping rules were:

- No subjects had secondary graft failure;
- 3.0% of subjects had histological recurrence of underlying malignancy within 6 months of randomization; and
- 9.8% of subjects withdrew due to AEs related to the study drug.

The Sponsor had the right to terminate or to stop the study at any time.
Adverse events of special interest have been added to the analysis identified based upon relevance to subjects with advanced cGVHD, the mechanism of action of belumosudil, and results from prior belumosudil studies (clinical and nonclinical).

In total, 75 (56.8%) subjects experienced at least 1 of 61 different infection AEs, including the following Customized MedDRA Queries (CMQ) infections: bacterial infections (16 [12.1%] subjects), fungal infections (9 [6.8%] subjects), and viral infections (24

[18.2%] subjects). Both bacterial and fungal infections occurred more in Arm A. Most of these infection AEs were mild to moderate in severity (79.2% of subjects).

In total, 49 (37.1%) subjects experienced a Grade ≥3 infection AE: 5 (3.8%) subjects experienced a Grade 3 CMQ bacterial infection and 5 (3.8%) subjects experienced a Grade ≥3 CMQ viral infection. No Grade ≥3 CMQ fungal infections occurred. The most common Grade ≥3 infections by PT included cellulitis (2 [1.5%] subjects), rhinovirus infection (2 [1.5%] subjects), and influenza (2 1.5%] subjects). No cytomegalovirus reactivation was reported.

In total, 28 (21.2%) subjects experienced the following increased liver enzymes (broad): gamma glutamyl transferase (GGT) increased (15 [11.4%] subjects), aspartate aminotransferase (AST) increase (12 [9.1%] subjects), alanine aminotransferase (ALT) increased (10 [7.6%] subjects), transaminases increased (unspecified) (2 [1.5%] subjects), bilirubin conjugated increased (1 [0.8%] subject), and LFT increased (unspecified) (1 [0.8%] subject). Most of these events were mild or moderate in severity. In total, 5 (3.8%) subjects experienced Grade 3 TEAEs of liver investigations, signs, and symptoms (broad): 3 (4.5%) subjects in Arm A and 2 (3.0%) subjects in Arm B. Of these subjects, 1 subject had cGVHD liver involvement at baseline (1 AST elevation and 1 GGT elevation). No Grade ≥3 elevations in ALT, AST, or bilirubin were reported based on laboratory values. No subjects satisfied the criteria for Hy's Law.

In total, 10 (7.6%) subjects experienced at least 1 CMQ cytopenia: 4 (6.1%) subjects in Arm A and 6 (9.1%) subjects in Arm B. The most common cytopenia by PT was platelet count decreased (7 [5.3%] subjects). Additionally, 2 (1.5%) subjects experienced at least 1 Grade ≥3 CMQ cytopenia; both subjects were in Arm A. The most common Grade ≥3 CMQ cytopenia by PT was platelet count decreased (2 [1.5%] subjects) followed by white blood cell count decreased (1 [1.5%] subject).

No subjects experienced any impaired wound healing.

Four subjects, all in Arm A, had a relapse of their underlying malignancy. One subject experienced a Grade 2 plasma cell myeloma, 1 subject experienced Grade 3 acute lymphocytic leukemia, and 2 subjects experienced AML (Grade 4 and Grade 5). The Grade 4 and Grade 5 AML recurrent AEs occurred 50 days and 55 days after initiation of study drug, respectively. The Grade 2 plasma cell myeloma occurred 93 days after initiation of study drug. None of these events were determined to be related to the study drug, as assessed by the Investigator.

Five subjects experienced second neoplasms while participating in the study. All 6 of these were AEs and were considered mild or moderate in severity and unrelated to the study drug.

Seven subjects experienced hypotension AEs. Three of these events were Grade 3 in severity. Most were considered to be unrelated to the study drug; however, 1 event was considered possibly related to the study drug. Five additional subjects experienced systolic blood pressure below 90 mmHg while receiving study drug. These instances were not reported as AEs.

Grade 4 post-baseline chemistry values included low glucose (1 [0.8%] subject in Arm B), low calcium (1 [0.8%] subject in Arm B), and high potassium (1 [0.8%] subject in Arm A).

Subjects in Arm A experienced the most Grade ≥3 post-baseline hematology values. Grade 4 post-baseline hematology values included low lymphocytes (2 [1.5%] subjects; 1 subject in each arm) and low platelets (1 [1.5%] subject in Arm A).

No subject developed clinically significant changes in vital signs or ECGs while taking the study drug.

Overall, belumosudil was well tolerated at both dose levels, 200 mg QD and 200 mg BID, with a safety profile consistent with that expected in this population of cGVHD subjects and their underlying disorders.

Issue date: 04-Jun-2024

Sponsor: Sanofi **Drug substance(s):** Belumosudil	**Study Identifiers:** IND 125890; NCT03640481; EudraCT Number: 2024-000203-67 **Study code:** DRI17633 (KD025-213)

Title of the study:

A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 (belumosudil) in Subjects with Chronic Graft Versus Host Disease (cGVHD) After at Least 2 Prior Lines of Systemic Therapy (The ROCKstar Study)

Study center(s):

34 sites in the United States

Study period:

Initiation Date: 11 October 2018

End Date of Reporting Period (Database Lock): 01 September 2022

Study Status: Terminated. The sponsor has decided to prematurely terminate the study due to the challenges encountered in recruiting adolescent participants. This decision was made without any safety concerns.

Phase of development: 2

Objectives:

Primary:

The primary objective of this study was to evaluate the efficacy and safety of belumosudil, at dose levels of 200 mg once daily (QD) and 200 mg twice daily (BID), in subjects with cGVHD who had previously been treated with at least 2 prior lines of systemic therapy.

Secondary:

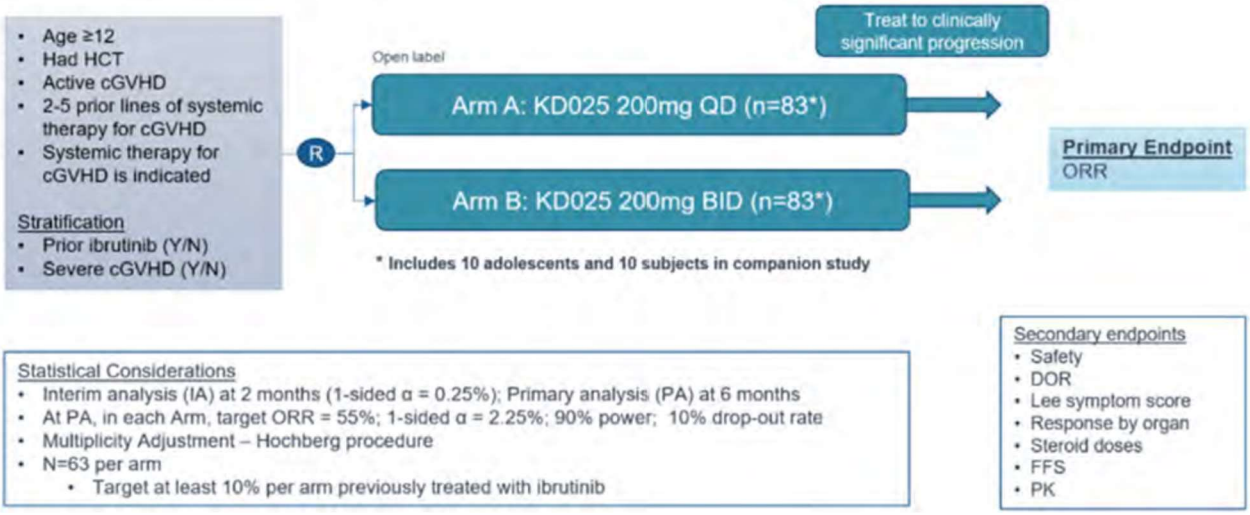
The secondary objectives of this study were to evaluate the following:

- To evaluate percentage of subjects who had a best response of partial response (PR) and percentage of subjects who had a best response of complete response (CR);
- To evaluate Duration of Response (DOR);
- To evaluate Time to Response (TTR);
- To evaluate response by organ system;
- To evaluate changes in National Institutes of Health (NIH) cGVHD global severity rating (GSR) using the Clinician-Reported Global cGVHD Activity Assessment;
- To evaluate changes in symptom burden/bother using the Lee Symptom Scale Score (LSS);
- To evaluate Failure-Free Survival (FFS);
- To evaluate Time to Next Treatment (TTNT);
- To evaluate Overall Survival (OS);
- To evaluate changes in corticosteroid dose;
- To evaluate changes in calcineurin inhibitor (CNI) dose;
- To evaluate changes in symptom activity using the cGVHD Activity Assessment Patient Self-Report; and
- To assess pharmacokinetics (PK) of belumosudil in subjects with cGVHD.

Methodology:

This was a Phase 2, randomized, multicenter, open-label study designed to evaluate the efficacy and safety of belumosudil in subjects with active cGVHD after at least 2 prior lines of systemic therapy. The study design is illustrated in Figure S1 below. Sample size was based on the primary efficacy endpoint of ORR, with 1 planned interim analysis (0.0025 1-sided alpha spending) and a true ORR of 55%.

Figure S1. KD025-213 Study Schema



Under KD025-213 Clinical Study Protocol Amendment 4 dated 21 April 2022, remaining eligible adolescents were to enroll into the study at the following dose: belumosudil 200 mg QD. There was no more randomization, and therefore, no stratification factors were applied.

Any adolescent taking a PPI or a strong CYP3A4 inducer began C1D1 at the following escalated dose: belumosudil 200 mg BID. BID = twice daily; C = Cycle; cGVHD = chronic graft versus host disease; CYP = cytochrome P450; D = Day; DOR = Duration of Response; FFS = Failure-Free Survival; HCT = hematopoietic cell transplantation; IA = interim analysis; ORR = Overall Response Rate; PA = primary analysis; PK = pharmacokinetics; PPI = proton-pump inhibitor; QD = once daily;

R = randomization; Y/N = yes/no.

Source: Clinical Study Protocol Amendment 4 (Appendix 16.1.1)

A target of ≥ 10% of the enrolled population having previously received ibrutinib as a therapy for cGVHD was set.

After confirmation of eligibility during a 14-day screening period, eligible subjects were randomized (1:1) to 1 of 2 treatment arms:

- Arm A: belumosudil 200 mg QD; or
- Arm B: belumosudil 200 mg BID.

These doses were selected based upon the data from study KD025-208.

Randomization was stratified according to prior cGVHD treatment with ibrutinib (yes/no) and severe cGVHD (yes/no).

Number of study adult participants: Planned: 166 subjects Randomized: 156 subjects Randomized but not dosed: 4 subjects Discontinued study as of 01 September 2022 (database lock): 152 subjects Discontinued treatment as of 01 September 2022 (database lock): 152 subjects
Diagnosis and criteria for inclusion: Subjects who consented and/or provided assent documented with a signed Institutional Review Board-approved informed consent/assent form as applicable, and met all of the eligibility criteria were enrolled. The study population consisted of adults and adolescents who: ● Had undergone allogeneic hematopoietic cell transplantation; ● Had previously received at least 2 prior lines of systemic therapy for cGVHD; ● Had received glucocorticoid therapy with a stable dose for at least 2 weeks prior to screening; and ● Had persistent cGVHD manifestations and for whom systemic therapy for cGVHD was indicated.
Study products Belumosudil (KD025) was supplied as 200 mg tablets
Duration of treatment: Subjects received belumosudil treatment in 28-day cycles until clinically significant progression of cGVHD (defined as progression that required the addition of new systemic therapy for cGVHD), histologic recurrence of underlying malignancy, unacceptable toxicity, Investigator decision, subject preference/withdrawal of consent, loss of follow-up, Sponsor decision, or death (whichever occurred first).

Criteria for evaluation:

Efficacy: The primary population for efficacy analyses was the modified Intent-to-Treat (mITT) Population, which was defined as all randomized subjects who received at least 1 dose of study drug.
The primary efficacy endpoint was the ORR, as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD and as assessed by Investigators. Responders included subjects that achieved a response (PR+CR).
The secondary efficacy endpoints were the following:

- DOR;
- TTR;
- Response rate by organ system;
- Change in cGVHD GSR based on the Clinician-Reported Global cGVHD Activity Assessment;
- Change in LSS;
- FFS;
- TTNT;
- OS;
- Change in corticosteroid dose;
- Change in CNI dose;
- Change in symptom activity based on the cGVHD Activity Assessment Patient Self-Report; and
- PK of belumosudil in subjects with cGVHD.

Safety: Safety was a secondary endpoint. The primary safety outcome was the percent of subjects in each arm that experienced adverse events (AEs). See below for the safety endpoints and additional details of safety assessments:

- AEs and serious AEs (SAEs);
- Hematological and clinical chemistry parameters;
- Vital signs;

o Change from baseline in systolic blood pressure, diastolic blood pressure, and heart rate;

and

- 12-lead electrocardiograms (ECGs);

o Mean and maximum change from baseline in corrected QT interval using Fridericia's formula.

Statistical methods:

Primary Endpoint:

The primary efficacy endpoint was the ORR, as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD and as assessed by Investigators.

The overall response was assessed using scores from 9 individual organ systems (skin, eyes, mouth, esophagus, upper gastrointestinal [GI], lower GI, liver, lungs, and joints and fascia) and the GSR. Response was assessed with respect to the baseline (Cycle [C] 1, Day [D] 1) cGVHD assessment. The overall response at each assessment time point was categorized as CR, PR, or Lack of Response (LR), where LR included the response status of unchanged, mixed, or progression. Response was assessed on D1 of C2 through C5, then on D1 of every other cycle thereafter and at the End of Treatment visit.

The ORR was defined as the proportion of subjects with a best response meeting the overall response criteria assessment of CR or PR at any post-baseline response assessment.

If a treated subject was lost to follow-up without a response assessment, the subject was counted as a non-responder.

Point estimates, confidence intervals (CIs) (Clopper-Pearson [exact] method), and unadjusted and Hochberg adjusted p-values corresponding to the null hypothesis of ORR ≤30% versus the alternative hypothesis of ORR >30% by treatment arms are reported. The number and percentage of subjects who had a best response of PR and number and percentage of subjects who had a best response of CR are also reported.

Secondary Endpoints:

Duration of Response:

The DOR was reported only for subjects who responded and statistics included:

- Kaplan-Meier plots and descriptive statistics of DOR; and
- Landmark analyses.

Time to Response:

TTR was measured as the time from first treatment to the time of first documentation of response.

Descriptive statistics and plots of cumulative number and percentage of responders over time are provided. TTR analyses were only conducted for the Responder Population.

Response by organ system:

The best response (CR or PR) for the 9 individual organ systems (skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs, and joints and fascia) plus GSR were summarized.

TTR at the organ level was also evaluated. Descriptive statistics and plots of cumulative number and percentage of responders over time are provided.

Change in Lee Symptom Scale Score:
The LSS was assessed on the same schedule as response assessments. The questionnaire consisted of 30 items over 7 domains: skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, and emotional distress. Each question was scored 0, 1, 2, 3, or 4. A domain score was calculated for each domain by taking the mean of all items completed if more than 50% were answered and normalizing to a 0 to 100 scale. A summary score was calculated as average of all non-missing domain scores if more than 50% of them were non-missing. A higher score indicated more bothersome symptoms. A 7-point or greater reduction on the summary score of cGVHD Symptom Scale was considered to be clinically meaningful.
The analyses included the following:

- Descriptive statistics of absolute score and change from baseline score (summary score and domain scores) were summarized as continuous variables by treatment arm and visit;
- Number and percentage of subjects with a ≥7-point reduction (7-PtR) from baseline (C1D1);

- Number and percentage of subjects with a 7-PtR from baseline on 2 consecutive assessments;

and

- Duration of a 7-PtR (DO7-PtR) (defined as time from documentation of the first ≥7-PtR to the first documentation of <7-PtR). If there were multiple episodes, the DO7-PtR was measured as the sum of DO7-PtR from all episodes.

These analyses were performed on the mITT, Responder, and Non-Responder Populations.

Failure-Free Survival:

FFS was defined as the time from the first dose of belumosudil to the time of the first event; events included the initiation of new systemic cGVHD therapy, non-relapse mortality, and recurrent malignancy (ie, underlying disease). FFS was censored by last response assessment or Long-Term Follow-Up assessment, whichever was the latest and available. Kaplan-Meier plots, descriptive statistics of FFS, and the landmark analyses at 6, 12, 18, and 24 months are provided. In addition, the number of events for each of the 3 components of FFS are provided.

Time to Next Treatment:

TTNT was measured as the time from the first dose of belumosudil to the time of new systemic cGVHD treatment, censored by the last response assessment or Long-Term Follow-Up assessment, whichever was the latest and available. TTNT was analyzed by the Kaplan-Meier survival method as well as with landmark analyses.

Overall Survival:

OS was defined as time from the first dose of belumosudil to the date of death due to any cause. Kaplan-Meier plots, descriptive statistics of OS, and the landmark analyses at 6, 12, 18, and 24 months are provided.

Change in corticosteroid dose:

Corticosteroid doses are presented as mg/kg/day prednisone equivalent dose. Descriptive statistics for the mITT, Responder, and Non-Responder Populations and subgroups defined by baseline corticosteroid dose level (upper and lower 50th percentiles) are provided for the following:

- Systemic corticosteroid dose over time;
- Change and percent change from baseline (C1D1) to the greatest corticosteroid dose reduction during the belumosudil treatment period;
- Number and percentage of subjects who reduced systemic corticosteroid dose during the belumosudil treatment period; and
- Number and percentage of subjects who ever discontinued systemic corticosteroid usage during the belumosudil treatment period.

Change in CNI dose:

CNIs included systemic tacrolimus and cyclosporine. Descriptive statistics are provided for the following:

- Number and percentage of subjects who reduced CNI dose during the belumosudil treatment period; and
- Number and percentage of subjects who ever discontinued CNI during the belumosudil treatment period.

Safety:

Safety assessments included AEs, SAEs, vital sign measurements, clinical laboratory evaluations (hematology and chemistry), and ECGs. Clinically significant physical examination findings were captured as AEs. Safety analyses further included assessments of the defined stopping rules, namely:

1. Secondary graft failure in >10% of subjects;

2. Histological recurrence of underlying malignancy within 6 months of randomization in >20% of subjects; and/or

3. Withdrawal due to study drug-related AEs in >20% of subjects.

Summary Results:

Efficacy:

The primary efficacy endpoint of this study was the ORR, as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD and as assessed by Investigators.

the ORR (95% CI) with belumosudil was 73.5% (65.1, 80.8): 72.7% (60.4, 83.0) in Arm A and 74.2% (62.0, 84.2) in Arm B. By comparison, the ORR for the primary analysis (database lock 01 September 2022) was slightly increased with the ORR (95% CI) with belumosudil being 75.0% (67.3, 81.7): 74.0% (62.8, 83.4) in Arm A and 76.0% (64.7, 85.1) in Arm B. Across both arms, 6 (3.9%) subjects achieved a CR and 108 (71.1%) subjects achieved a PR. The ORR (95% CI) within 6 months of belumosudil treatment was 72.4% (64.5, 79.3): 71.4% (60.0, 81.2) in Arm A and 73.3% (61.9, 82.9) in Arm B.

Across both arms, 3 (2.0%) subjects achieved a CR and 107 (70.4%) subjects achieved a PR.

The primary and secondary DOR amongst responders was slightly increased compared to results reported in the KD025-213 CSR dated 16 July 2020 with a median DOR of 26.0 weeks: 23.9 weeks for Arm A and 32.0 weeks for Arm B.

The TTR and responses observed across all organ systems were consistent with what was reported in the KD025-213 CSR dated 16 July 2020. The median TTR was 4.43 weeks: 4.43 weeks in Arm A and 4.43 weeks in Arm B.

The median Kaplan Meier estimate of FFS (95% CI) was 16.6 (12.85, 24.18) months: 16.3 (10.15, 26.48) months for Arm A. The median Kaplan-Meier estimate of FFS was 17.2 months for Arm B. The Kaplan-Meier estimate of FFS (95% CI) at 18 and 24 months was 0.49 (0.40, 0.57) and 0.43 (0.35, 0.52), respectively. The most common failure event at 24 months was initiation of new systemic therapy for cGVHD (61 [40.1%] subjects): 31 (40.3%) subjects in Arm A and 30 (40.0%) subjects in Arm B. In total, 5 (3.3%) subjects had a failure event of recurrent malignancy at 24 months and all subjects were in Arm A. In total, 13 (8.6%) subjects had a failure event of non-relapse mortality at 24 months: 4 (5.2%) subjects in Arm A and 9 (12.0%) subjects in Arm B.

The Kaplan-Meier estimate of TTNT (95% CI) at 18 and 24 months was 0.58 (0.49, 0.66) and 0.53 (0.44, 0.61), respectively. The overall Kaplan-Meier estimate of OS (95% CI) at 6, 12, 18, and 24 months was comparable to (0.96 [0.91, 0.98], 0.91 [0.85, 0.95], 0.87 [0.80, 0.92], and 0.85 [0.77, 0.90], respectively).

In the mITT Population, more subjects had a corticosteroid dose reduction during treatment with belumosudil with 105 (69.1%) subjects overall reporting a corticosteroid dose reduction. In total, 44 (28.9%) subjects discontinued corticosteroid usage: 21 (27.3%) subjects in Arm A and 23 (30.7%) subjects in Arm B. The median percent change from baseline to the greatest reduction was -53.14%: -50.00% for Arm A and -66.67% for Arm B. Corticosteroid dose reductions and discontinuations were demonstrated among both responders and non-responders.

In total, 58 (38.2%) subjects were taking a CNI at baseline. Of these subjects, 30 (51.7%) subjects reduced their CNI dose, and 16 (27.6%) subjects discontinued their CNI dose altogether.

Safety:

The overall median treatment duration was 10.53 months: 9.20 months for Arm A and 11.93 months for Arm B. In total, 38 (25.0%) subjects had a treatment duration of ≥24 months. The overall cumulative exposure was 179.09 patient years. The median relative dose intensity (RDI) was 99.38%. In total, 118 (77.6%) subjects had an RDI >95%: 60 (77.9%) subjects in Arm A and 58 (77.3%) subjects in Arm B.

In total, 151 (99.3%) subjects experienced at least 1 treatment-emergent AE (TEAE): 76 (98.7%) subjects in Arm A and 75 (100%) subjects in Arm B. The most common TEAEs by preferred term (PT) (>20% of subjects) were diarrhea (59 [38.8%] subjects), fatigue (57 [37.5%] subjects), nausea (47 [30.9%] subjects), headache (44 [28.9%] subjects), cough (42 [27.6%] subjects), dyspnea (42 [27.6%] subjects), edema peripheral (40 [26.3%] subjects), upper respiratory tract infection (40 [26.3%] subjects), vomiting (35 [23.0% subjects]), and arthralgia (33 [21.7%] subjects).

In total, 94 (61.8%) subjects experienced at least 1 Grade ≥3 TEAE. The most common Grade ≥3 TEAEs that occurred in ≥2 subjects overall by PT were pneumonia (16 [10.5%] subjects), hypertension (11 [7.2%] subjects), and hyperglycemia (7 [4.6%] subjects).

In total, 66 (43.4%) subjects experienced a serious TEAE: 36 (46.8%) subjects in Arm A and 30 (40.0%) subjects in Arm B. The most common serious TEAEs that occurred overall by PT were pneumonia (14 [9.2%] subjects) and pyrexia (4 [2.6%] subjects).

In total, 109 (71.7%) subjects experienced at least 1 study drug-related TEAE: 59 (76.6%) subjects in Arm A and 50 (66.7%) subjects in Arm B. The most common study drug-related TEAEs occurring overall by PT were fatigue (33 [21.7%] subjects), diarrhea (19 [12.5%] subjects), headache (18 [11.8%] subjects), nausea (17 [11.2%] subjects), aspartate aminotransferase (AST) increased (16 [10.5%] subjects), and alanine aminotransferase (ALT) increased (12 [7.9%] subjects).

In total, 31 (20.4%) subjects experienced at least 1 study drug-related Grade ≥3 TEAE: 17 (22.1%) subjects in Arm A and 14 (18.7%) subjects in Arm B. The most common study drug-related Grade 3 TEAEs that occurred by PT were hypertension (4 [2.6%] subjects), fatigue (4 [2.6%] subjects), and pneumonia (3 [2.0%] subjects).

In total, 12 (7.9%) subjects experienced at least 1 study drug-related serious TEAE: 7 (9.1%) subjects in Arm A and 5 (6.7%) subjects in Arm B.

In total, 7 subjects experienced a serious TEAE that led to treatment discontinuation: 2 subjects in Arm A (cellulitis, aspiration, and respiratory failure) and 5 subjects in Arm B (diarrhea, sepsis, rhinovirus infection, microangiopathic hemolytic anemia, and Coronavirus Disease 2019).

In total, 28 (18.4%) subjects died: 14 (18.2%) subjects in Arm A and 14 (18.7%) subjects in Arm B. Of these, 18 subjects died during Long-Term Follow-Up: 9 subjects in each Arm. Ten (6.6%) subjects experienced a serious TEAE that led to death during the study: 5 (6.5%) subjects in Arm A and 5 (6.7%) subjects in Arm B.

In total, 97 (63.8%) subjects experienced at least 1 infection AE, including the following Customized Medical Dictionary for Regulatory Activities Query (CMQ) infections: bacterial infections (20 [13.2%] subjects), fungal infections (12 [7.9%] subjects), and viral infections (27 [17.8%] subjects). Bacterial and fungal infections occurred more frequently in Arm A. Most of these infection AEs were mild to moderate in severity (74.6% of subjects).

In total, 33 (21.7%) subjects experienced a Grade ≥3 infection AE: 7 (4.6%) subjects experienced a Grade ≥3 CMQ bacterial infection, and 8 (5.3%) subjects experienced a Grade ≥3 CMQ viral infection. No Grade ≥3 CMQ fungal infections occurred. The most common Grade ≥3 infections by PT included rhinovirus infection (5 [3.3%] subjects), cellulitis (3 [2.0%] subjects), and influenza (2 [1.3%] subjects).

In total, 43 (28.3%) subjects experienced the following liver-related investigations, signs, and symptoms (Standardized Medical Dictionary for Regulatory Activities Query [SMQ]) (broad): AST increased (21 [13.8%] subjects), ALT increased (18 [11.8%] subjects), gamma-glutamyl transferase (GGT) increased (18 [11.8%] subjects), blood alkaline phosphatase increased (11 [7.2%] subjects), hypoalbuminemia (6 [3.9%] subjects), transaminases increased (unspecified) (3 [2.0%] subjects), liver function test increased (unspecified) (2 [1.3%] subjects), and bilirubin conjugated increased (1 [0.7%] subject). Most of these events were mild or moderate in severity. In total, 7 (4.6%) subjects experienced Grade ≥3 TEAEs of liver investigations, signs, and symptoms (SMQ) (broad): 3 (3.9%) subjects in Arm A and 4 (5.3%) subjects in Arm B. Of these subjects, 1 subject had cGVHD liver involvement at baseline (1 AST elevation and 1 GGT elevation). All of these TEAEs were considered to be related to the study drug.

In total, 17 (11.2%) subjects experienced at least 1 CMQ cytopenia: 5 (6.5%) subjects in Arm A and 12 (16.0%) subjects in Arm B. The most common cytopenia by PT was platelet count decreased (8 [5.3%] subjects). Additionally, 6 (3.9%) subjects experienced at least 1 Grade ≥3 CMQ cytopenia: 3 (3.9%) subjects in Arm A and 3 (4.0%) subjects in Arm B. The most common Grade ≥3 CMQ cytopenias by PT were neutropenia and platelet count decreased, which were both reported by 2 (1.3%) subjects.

Nine subjects experienced hypotension AEs. Three of these events were Grade 3 in severity. Most were considered to be unrelated to the study drug; however, 1 event was considered possibly related to the study drug.

Grade 4 post-baseline chemistry values included low calcium (3 [4.0%] subjects in Arm B), high GGT (3 [2.0%] subjects: 1 [1.3%] subject in Arm A and 2 [2.7%] subjects in Arm B), high glucose (3 [2.0%] subjects: 1 [1.3%] subject in Arm A and 2 [2.7%] subjects in Arm B), high AST (1 [1.3%] subject in Arm B), low glucose (1 [1.3%] subject in Arm B), and high potassium (1 [1.3%] subject in Arm A).

Overall, subjects in Arm A had more Grade 2 or 3 low lymphocyte values at baseline and post-baseline compared to subjects in Arm B. Grade 4 post-baseline hematology values included low lymphocytes (4 [2.6%] subjects: 3 [3.9%] subjects in Arm A and 1 [1.3%] subject in Arm B), and low platelets (1 [1.3%] subject in Arm A). Overall, the data suggest that belumosudil was well tolerated at both dose levels, 200 mg QD and 200 mg BID, with a safety profile consistent with that expected in this population of cGVHD subjects and their underlying disorders.
Issue date: 04-Jun-2024

Sponsor: Sanofi **Drug substance(s):** belumosudil	**Study Identifiers:** IND 125890; NCT03640481; EudraCT Number: 2024-000203-67 **Study code:** DRI17633 (KD025-213)

Title of the study:

A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 (belumosudil) in Subjects with Chronic Graft Versus Host Disease (cGVHD) After at Least 2 Prior Lines of Systemic Therapy (The ROCKstar Study)

Study center(s):

This study was conducted at 30 centers that randomized participants in the United States.

Study period:

Study initiation (first adolescent participant first visit): 20 July 2021

Study completion (last patient last visit for adolescent cohort): 11 December 2023

Study Status: Terminated. The sponsor has decided to prematurely terminate the study due to the challenges encountered in recruiting adolescent participants. This decision was made without any safety concerns.

Phase of development: Phase 2

Objectives:

Primary

- Evaluate the efficacy of belumosudil at dose levels of 200 mg QD and 200 mg BID in participants with cGVHD who were previously treated with at least 2 prior lines of systemic therapy

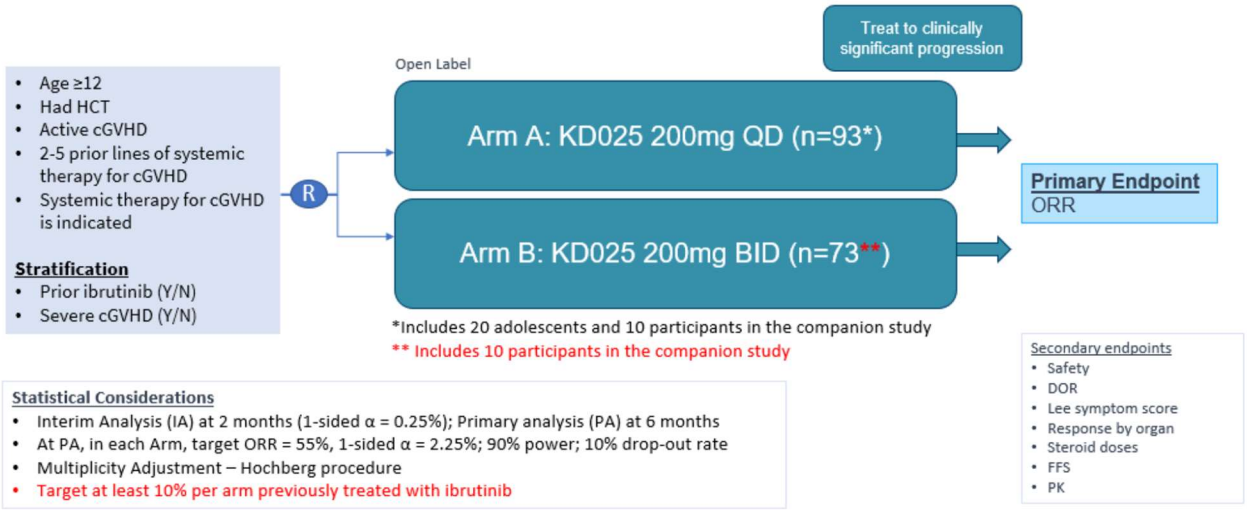
Secondary

- Duration of response
- Changes in the Lee Symptom Scale Score
- Response by organ system
- Time to response
- Time to next treatment
- Percentage of participants who had a best response of PR and percentage of participants who had a best response of CR
- Change in corticosteroid dose
- Change in calcineurin inhibitor dose
- Failure-free survival
- Overall survival
- Change in cGVHD global severity rating using the Clinician-Reported Global cGVHD Activity Assessment
- Change in symptom activity using the cGVHD Activity Assessment Patient Self-Report
- Pharmacokinetic of belumosudil in participants with cGVHD
- Safety

Methodology:

This was a Phase 2, randomized, multi-center, open-label, study designed to evaluate the efficacy and safety of belumosudil in participants with active cGVHD after at least 2 prior lines of systemic therapy. The study design is illustrated in Figure 1.

Figure 1 - KD025-213 study schema



Abbreviations: BID=twice a day, cGVHD=chronic graft versus host disease, DOR=duration of response, FFS=Failure-Free Survival, HCT=hematopoietic cell transplantation, IA=interim analysis, ORR=Overall Response Rate, PA=primary analysis, PK=pharmacokinetics, QD=once a day, R=randomization, Y/N=yes/no.

A target of ≥10% of the enrolled population having previously received ibrutinib as a therapy for cGVHD was set.

After confirmation of eligibility during a 14-day screening period, eligible participants were randomized (1:1) to one of two treatment arms:

- Arm A: belumosudil 200 mg once a day (QD)

- Arm B: belumosudil 200 mg twice a day (BID)

These doses were selected based upon the data from study KD025-208.

Randomization was stratified according to prior cGVHD treatment with ibrutinib (Yes/No) and severe cGVHD (Yes/No).

With amendment 2 of the protocol, the sample size was increased from approximately 126 participants, with additional participants enrolled as follows:

- 20 adolescents

- 20 adults into a site-specific companion study to collect biospecimens. These participants were randomized (1:1) to Arm A or Arm B.

With protocol amendment 4, there were no more randomization and stratification factors applied for adolescent group, and remaining eligible adolescent participants were enrolled into the study at the belumosudil 200 mg QD dose arm. The expected sample size in each Arm was therefore: Arm A, N = 93 with addition of 20 adolescents and 10 adults and Arm B, N = 73 with addition of 10 adults.

Number of study participants: Planned: Approximately 20 adolescent participants. Screened: 3 adolescent participants. Enrolled: 3 adolescent participants. Enrolled but not dosed: 0 adolescent participants. Discontinued the study: 3 adolescent participants. Discontinued the treatment: 2 adolescent participants. Completed the treatment based on sustained response: 1 participant.
Diagnosis and criteria for inclusion: Participants who consented and/or provided assent documented with a signed Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent/assent form as applicable and met all of the eligible criteria were enrolled. The study population was adults and adolescents who: ・have undergone allogenic hematopoietic cell transplantation (HCT). ・have previously received at least 2 lines of systemic therapy for cGVHD. ・have persistent cGVHD manifestations and systemic therapy for cGVHD is indicated.
Study products Belumosudil was provided as 200 mg tablets to be taken orally.
Duration of treatment: Participants were to receive belumosudil treatment in 28-day cycles until clinically significant progression of cGVHD (defined as progression requiring addition of new systemic therapy for cGVHD), histologic recurrence of underlying malignancy, unacceptable toxicity, Investigator decision, participant preference/withdrawal of consent, lost to follow-up, Sponsors decision, or death (whichever occurred first).

Criteria for evaluation:

Primary:

The ORR (including PR and CR). Responses were defined by the 2014 NIH Consensus Development Project on clinical trials in cGVHD

Secondary:

- Duration of response
- Changes in the Lee Symptom Scale Score
- Response rate by organ system
- Time to response
- Time to next treatment
- Percentage of participants who had a best response of PR and percentage of participants who had a best response of CR
- Change in corticosteroid dose
- Change in calcineurin inhibitor dose
- Failure-free survival
- Overall survival
- Change in cGVHD global severity rating as based on the Clinician-Reported Global cGVHD Activity Assessment
- Change in symptom activity as based on cGVHD Activity Assessment Patient Self-Report
- Pharmacokinetics
- Percentage of participants in each arm experiencing AEs

Abbreviations: AE=adverse event, BID=twice a day, cGVHD=chronic graft versus host disease, CR=complete response, NIH=National Institutes of Health, ORR=overall response rate, PR=partial response, QD=once a day.

Statistical methods:

Primary Endpoint:

The primary efficacy endpoint was the overall response rate (ORR), with response status as assessed by Investigators based upon the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD.

Response was assessed using individual scores from ten systems (skin, eyes, mouth, esophagus, upper gastrointestinal, lower gastrointestinal, liver, lungs, joints and fascia, and Global Severity Rating [GSR]). Response was assessed with respect to the baseline (Cycle 1, Day 1 [C1D1]) cGVHD assessment. The overall response at each assessment time point was categorized as complete response (CR), partial response (PR), or lack of response (LR), where LR includes the response status of unchanged, mixed, or progression.

The ORR was defined as the proportion of participants with a best response meeting the overall response criteria assessment of CR or PR at any postbaseline response assessment.

If a treated participant was lost to follow up without response assessment, this participant was to be counted as a nonresponder. Any response on and after new systemic cGVHD treatment was to be censored as nonresponse.

Point estimates, various confidence intervals (Clopper-Pearson [exact] method), and raw and Hochberg adjusted p-values corresponding to the null hypothesis of ORR ≤30% versus alternative hypothesis of ORR >30% by treatment arms was to be reported.

The number and percentage of participants who had a best response of PR and number and percentage of participants who had a best response of CR were also to be reported.

Secondary Endpoints:

Duration of response:

The duration of response (DOR) was reported only for responders and statistics included:

・Kaplan-Meier plots and descriptive statistics of DOR; and

・Landmark analyses.

Lee Symptom Scale Score:

Lee cGVHD Symptom Scale Score was assessed with protocol amendment 2 on Day 1 of every Cycle and at end of treatment (EOT). With protocol amendment 5, the assessment was scheduled on Day 1 of Cycles 2, 3, 5, 7, and then every other 3 treatment cycles (Cycle 10 Day 1 [C10D1], Cycle 13 Day 1 [C13D1], etc). The questionnaire consisted of 30 items over 7 domains: skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, and mental and emotional distress. Each question was scored 0, 1, 2, 3 or 4.

A domain score was calculated for each domain by taking the mean of all items completed if more than 50% were answered and normalizing to a 0 to 100 scale. A summary score was calculated as average of all nonmissing domain scores if more than 50% of them were non-missing. A higher score indicated more bothersome symptoms. A 7-point difference on the summary score of cGVHD symptom scale was considered to be clinically meaningful.

The analyses included the following:

・Both score and change-from-baseline values (summary score and domain scores) were summarized as continuous variables by visit.

・Number and percent of participants with a ≥7-point reduction (7-PtR) from baseline (C1D1).

・Number and percent of participants with a 7-PtR from baseline on 2 consecutive assessments.

・Duration of a 7-PtR (DO7-PtR) (defined as time from documentation of the first ≥7-PtR to the first documentation of less than 7-PtR). If there were multiple episodes, the DO7-PtR was measured as the sum of DO7-PtR from all episodes.

These analyses were performed on modified intent-to-treat (mITT), responder, and nonresponder populations.

Response by organ system:

The best response (CR, PR) for the 9 individual organs (skin, eyes, mouth, esophagus, upper gastrointestinal (GI), lower GI, liver, lungs, and joints and fascia) plus GSR were summarized.

Time to response (TTR) at the organ level was also evaluated. Descriptive statistics and plots of cumulative number and percentage of responders over time (4, 8, 12, 16, 24, 32, 40, ≥48 weeks) were provided.

Time to response:

Time to response was measured as the time from first treatment to the time of first documentation of response. Descriptive statistics and plots of cumulative number and percent of responders over time (4, 8, 12, 16, 24, 32, 40, ≥48 weeks) were provided. Time to response analyses were only conducted for the responder population.

Time to next therapy:

The time to next therapy (TTNT) was measured as the time from first treatment to the time of new systemic cGVHD treatment, censored by last response assessment or long term follow up assessment, whichever was the latest and available. The TTNT was analyzed by the Kaplan-Meier survival method as well as the landmark analysis at 6, 12, 18, and 24 months.

Corticosteroid dose:

Corticosteroid doses were presented as mg/kg/day prednisone equivalent dose. Descriptive statistics for the mITT population, responder/nonresponder populations and subgroups defined by baseline corticosteroid dose level (upper and lower 50 percentiles) were provided for the following:

- Systemic corticosteroid dose over time.
- Change and percentage change from baseline (C1D1) to the greatest corticosteroid dose reduction during the belumosudil treatment period.
- Number and percentage of participants who reduced systemic corticosteroid dose during the belumosudil treatment period.
- Number and percentage of participants who ever discontinued systemic corticosteroid usage for over 28 days during the belumosudil treatment period.

Calcineurin inhibitor doses:

Calcineurin inhibitor (CNI) doses include systemic tacrolimus and cyclosporine. Descriptive statistics are provided for the following:

- Number and percentage of participants who reduced CNI dose during the belumosudil treatment period.
- Number and percentage of participants who ever discontinued CNI during the belumosudil treatment period.

Failure-free survival:

Failure-free survival (FFS) was defined as the time from the first dose of belumosudil to the time of the first event; events included the absence of new cGVHD systemic therapy, nonrelapse mortality, and recurrent malignancy (ie, underlying disease). Failure-free survival was censored by last response assessment or long term follow up assessment, whichever was the latest and available. Kaplan-Meier plots, descriptive statistics of FFS and the landmark FFS at 6, 12, 18, and 24 months are provided. In addition, analyses for the 3 components of FFS were provided.

Overall survival:

Overall survival (OS) was defined as time from first dose of belumosudil to the date of death due to any cause. Kaplan- Meier plots, descriptive statistics of OS, and the landmark OS at 6, 12, 18, and 24 months were provided.

Change in cGVHD severity using the Clinician-Reported Global cGVHD Activity Assessment:

The Clinician-reported global cGVHD Activity Assessment was a 0 to 10 point numeric rating scale with a score of 0 indicating "cGVHD symptoms not at all severe" and a score of 10 being "most severe cGVHD symptoms possible". With protocol amendment 2, the activities were assessed on Cycle 1 (C1D1, baseline) and then again at Day 1 of every cycle. With protocol amendment 5, this assessment was scheduled on Day 1 of Cycles 2, 3, 5, 7, and then every other 3 treatment cycles (C10D1, C13D1, etc).

Summary Results:

Demographic and other baseline characteristics:

The study included 2 male and 1 female adolescent participants. One male participant was Black or African American Hispanic or Latino with severe baseline cGVHD. The other 2 participants were White not Hispanic or Latino with no severe cGVHD at baseline. None of the 3 participants had received prior treatment with ibrutinib.

Exposure:

One participant in the 200 mg QD arm had a maximum treatment duration of 27.6 months with a relative dose intensity of 94.5%. The other participant in the same arm had a treatment duration of 3.7 months with a relative dose intensity of 100%. The participant in the 200 mg BID arm had a treatment duration of 8 months with a relative dose intensity of 89.2%.

Efficacy results:

Primary efficacy results:

Overall response rate:

One participant in the 200 mg QD arm with a treatment duration of 27.6 months first achieved a PR at Cycle 3 Day 1. The participant continued the treatment and achieved PR at EOT. The other participant in the same treatment arm received only 4 cycles of treatment and showed unchanged response before the study was terminated early by the Sponsor.

The participant in the BID dose arm first achieved a PR at Cycle 2 Day 1 (C2D1) followed by PR at Day 1 of Cycles 4 and 5 and at EOT (Table 1).

Table 1 - Overall response by subject by visit, adolescent participants (mITT population)

Treatment	Visit	Study day	cGVHD overall response
KD025 200 mg QD	Cycle 2, Day 1	26	Lack of response-unchanged
	Cycle 3 Day 1	53	Partial response
	Cycle 4 Day 1	82	Partial response
	Cycle 5 Day 1	109	Partial response
	Cycle 7 Day 1	165	Lack of response-mixed
	Cycle 9 Day 1	222	Partial response
	Cycle 11 Day 1	278	Partial response
	Cycle 13 Day 1	334	Lack of response-mixed
	Cycle 15 Day 1	390	Lack of response-mixed
	Cycle 17 Day 1	446	Lack of response-mixed
	Cycle 19 Day 1	501	Lack of response-mixed
	Cycle 21 Day 1	557	Partial response
	Cycle 23 Day 1	613	Partial response
	Cycle 25 Day 1	671	Partial response
	Cycle 27 Day 1	725	Partial response
	Cycle 29 Day 1	781	Partial response

	End of treatment	840	Partial response
KD025 200 mg BID	Cycle 2 Day 1	29	Partial response
	Cycle 3 Day 1	57	Lack of response-unchanged
	Cycle 4 Day 1	85	Partial response
	Cycle 5 Day 1	113	Partial response
	Cycle 7 Day 1	169	Lack of response-mixed
	Cycle 9 Day 1[a]	225	Lack of response-unchanged
	End of treatment	253	Partial response
KD025 200 mg QD	Cycle 2 Day 1	29	Lack of response-unchanged
	Cycle 3 Day 1	57	Lack of response-unchanged
	End of treatment	113	Lack of response-unchanged

Abbreviations: BID=two times a day, cGVHD=chronic graft versus host disease, ID=identification, mITT=modified intent-to-treat, QD=once a day.

Source: Appendix 16.2.6 Efficacy response data, Listing 16.2.6.1.

a The response assessment was performed on or after initiation of new systemic therapy for cGVHD.

Secondary efficacy results:

Duration of response:

Duration of response was reported only for the 2 participants who achieved a PR. The participant in the QD arm of belumosudil showed primary and secondary DOR for 113 days each with documented LR. The same participant showed tertiary DOR for 820 days (censored due to study terminated by Sponsor) and quaternary DOR for 510 days (censored due to completed treatment due to sustained response). The participant in the BID arm of belumosudil showed primary and secondary DOR for 29 days each with documented LR.

The same participant showed 180 days tertiary DOR and 114 days quaternary DOR with documented LR.

Change in Lee Symptom Scale Score:

The participant in the BID arm of belumosudil had a baseline score of 1. The 2 participants in the QD arm of belumosudil had baseline scores of 8 and 4 respectively. None of the participants had at least 7-PtR in the score from baseline.

Response rate by organ system:

The participant in the BID arm had an overall response of PR at C2D1. This participant showed CR for organs such as eyes and esophagus. One participant in the QD arm had an overall PR at Cycle 3 Day 1. This participant showed PR for skin and CR for mouth. The other participant in the QD arm received only 4 cycles of treatment with overall LR (unchanged) (Appendix 16.2.6 Efficacy response data).

Time to response:

The TTR was conducted for 2 participants who showed a response. The participant in the QD arm showed a TTR of 53 days compared with a TTR of 29 days shown by the participant in BID arm.

Change in corticosteroid dose:

One participant in the QD arm showed a decrease in systemic corticosteroid dosing during the belumosudil treatment period. The dosing reduced from 40.5 mg QD on C1D1 to 2.5 mg QD on C10D1. The other participant in the QD arm showed a stable usage of systemic corticosteroid dose of 5 mg QD during the belumosudil treatment period.

Change in calcineurin inhibitor dose:

One participant in the QD arm decreased the dose of CNI. The dose was reduced from 1 mg BID on C1D1 to 0.5 mg QD on Cycle 4 Day 1 (C4D1).

Failure-free survival:

Both participants in the QD arm did not have any FFS event and they discontinued from the study after 872 days (stopped by Investigator based on sustained response) and 113 days (when the study was terminated by the Sponsor), respectively. The participant in the BID arm had initiated a new systemic therapy for cGVHD on study day 208 (having initially shown

a PR at Cycles 2, 4, and 5 but subsequently unchanged and then response seen again at EOT

visit).

Change in symptom activity based on the cGVHD Activity Assessment Patient Self-Report:

One participant in the QD arm had an overall severity ranging from mild to moderate. The other participant in the QD arm had an overall severity of mild during the study. The participant in the BID arm had an overall severity of mild, except on Cycle 5 Day 1 when moderate severity was reported.

Safety results:

Adverse events:

One participant in the QD arm experienced 6 serious adverse events (SAEs) of steroid induced diabetes, hypersensitivity, face edema, rash, pneumonia, and hypoxia. All SAEs were CTCAE Grade 3 except for steroid induced diabetes, which was Grade 2. The SAE of hypoxia was considered possibly related to belumosudil by the Investigator (considered not related by the Sponsor) and was ongoing until the EOT.

The other 2 participants did not experience any SAEs. No adverse events led to study treatment discontinuation and there were no deaths reported during the study.

Vital signs:

One participant in the QD arm and the participant in the BID arm showed an increase in pulse rate from C1D1 onwards, which gradually decreased by the EOT.

Electrocardiogram:

One participant in the QD arm had abnormal clinically significant electrocardiogram findings during Cycle 23 Day 1 (study day 614). The participant's heart rate was 81 beats/minute with a QT interval of 394 msec, RR interval of 740.74 msec, and QTcF of 435.45 msec. The event was transient, and no treatment was required.

Clinical laboratory parameters:

Both participants in the QD arm reported laboratory values with CTCAE Grade ≥3. One participant reported increased gamma glutamyl transferase values on Day 1 of Cycles 4, 5, and 6. The same participant showed decreased lymphocyte count on Day 1 of Cycles 3 and 7.

The other participant reported a CTCAE Grade 4 decrease in potassium value on an unscheduled visit. None of these events were considered related to belumosudil.

Pharmacokinetic results:

Pharmacokinetic samples were collected for all 3 participants and were analyzed at predose, 3 hours postdose, and 5 hours postdose on C2D1 and C4D1. One participant in the QD arm had PK samples analyzed only for C2D1. The belumosudil plasma concentration across the 3 participants ranged from 73.9 ng/mL (predose) to 2940 ng/mL (projected Cmax at 3 hours).

One participant in the QD arm who completed the treatment with a sustained response showed a maximum concentration of belumosudil (2940 ng/mL) 3 hours postdose on C4D1. The other participant in the QD arm had a maximum concentration of belumosudil (2020 ng/mL) 3 hours postdose on C2D1. The participant in the BID arm had a maximum concentration of belumosudil (1020 ng/mL) 3 hours postdose on C2D1.

Belumosudil metabolites 1 and 2 were also analyzed for the same timepoints. The concentration of metabolite 1 was >10 ng/mL on C4D1 for the 3 hours and 5 hours postdose samples for one participant in the QD arm. Metabolite 1 was <10 ng/mL for all other timepoints. For the participant in the BID arm, the predose concentration of metabolite 2 was <10 ng/mL on C4D1. For all other timepoints, the concentration of metabolite 2 was >10 ng/mL.

Pharmacodynamic results:

Pharmacodynamic samples were not collected from the adolescent participants if the site had policies limiting the daily volume of blood permitted to be drawn for a clinical trial (less than the FDA guidelines).

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