Supplementary Appendix to Manuscript Entitled

Belumosudil for Chronic Graft-versus-Host Disease (cGVHD) After 2 or More Prior Lines of Therapy:
The ROCKstar Study

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

Protocol Number: KD025-213

Study Drug: KD025

IND Number: IND 125890

NCT Number: NCT03640481

Phase: 2

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Original Protocol: 25 June 2018

Amendment 1: 26 June 2019
| Study Title | A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects with Chronic Graft Versus Host Disease (cGVHD) After At Least 2 Prior Lines of Systemic Therapy |
|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical Phase | 2 |
| Study Background | Chronic graft-versus-host disease (cGVHD) remains a major complication of allogeneic hematopoietic cell transplantation (HCT) occurring in approximately 50% of transplant recipients and involving multiple organs. Patients with cGVHD require prolonged immunosuppressive treatment for an average of 2 to 3 years from the initial diagnosis, with 10% of those surviving for at least 7 years still requiring immunosuppressive treatment at that time and beyond. Glucocorticoids, with or without calcineurin inhibitors, remain the standard initial treatment, but are associated with significant side effects and unsatisfactory outcomes, particularly for patients with high-risk features of cGVHD. Recently, ibrutinib received Food and Drug Administration (FDA) approval for the treatment of adults with cGVHD after failure of one or more lines of systemic therapy. Despite this, there remains substantial unmet need for therapies with improved tolerability and effectiveness for adults and adolescents. KD025 is an orally available Rho-associated coiled-coil 2 (ROCK2) selective inhibitor. KD025 has been shown to downregulate pro-inflammatory T helper 17 cells and T follicular helper cells while upregulating anti-inflammatory regulatory T cells, which may potentially correct the immunological imbalance seen in cGVHD. Furthermore, KD025 has been shown to be active and well tolerated in cGVHD. Study KD025-208 enrolled subjects with active cGVHD who had previously received no more than 3 prior lines of treatment. Approximately two-thirds of patients with cGVHD treated with KD025 200 mg every day (QD) (Cohort 1) and 200 mg twice a day (BID) (Cohort 2) achieved clinical responses. |
| Study Objective(s)/Purpose | The objective of this study is to evaluate the efficacy and safety of KD025, at dose levels of 200 mg QD and 200 mg BID, in subjects with cGVHD who have previously been treated with at least 2 prior lines of systemic therapy. |
| Study Design | Phase 2, open-label, randomized, multicenter study in subjects aged ≥12 with cGVHD who have previously been treated with at least 2 prior lines of systemic therapy. Approximately 126 subjects with active cGVHD will be randomized (1:1) to receive treatment with one of two KD025 regimens:  
- Arm A: KD025 200 mg QD  
- Arm B: KD025 200 mg BID  
Randomized subjects withdrawn from the study before receiving any study drug will be replaced. Randomization will be stratified according to prior cGVHD treatment with ibrutinib (Yes/No) and severe cGVHD at baseline (Yes/No). |

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Subjects may receive treatment in 28-day treatment cycles until clinically significant progression of cGVHD. Subjects who have not achieved a response after 12 cycles of KD025 should be withdrawn if in the Investigator’s judgment there is no evidence of clinical benefit.

Subjects will undergo evaluations as outlined in the Study Assessments table (Appendix A).

The primary end point is the overall response rate (ORR), with responses as defined by the 2014 National Institutes of Health (NIH) Consensus Development Project on Clinical Trials in cGVHD.

Responses are assessed with respect to baseline.

| Eligibility criteria | Treat to clinically significant progression |
|----------------------|---------------------------------------------|
| • Aged ≥12 years     | OPEN LABEL                                  |
| • Underwent an HCT   | ARM A: Belumosudil 200 mg QD (n=86)         |
| • Has active cGVHD   | ARM B: Belumosudil 200 mg BID (n=66)        |
| • 2 to 5 prior lines of systemic therapy for cGVHD | PRIMARY END POINT |
| • Systemic therapy for cGVHD is indicated | ORR |

| Stratification factors |
|------------------------|
| • Prior ibrutinib (Y/N) |
| • Severe cGVHD (Y/N)   |

| Statistical considerations |
|----------------------------|
| • Interim analysis (IA) at 2 months (1-sided α=0.25%); primary analysis (PA) at 6 months |
| • At PA, in each arm, target ORR=55%, 1-sided α=2.25%, 90% power, 10% dropout rate |
| • Multiplicity adjustment - Hochberg procedure |
| • N=63 per arm |
| | – Target at least 10% per arm previously treated with ibrutinib |

| Number of Study Centers | Approximately 30 |
|-------------------------|------------------|
| Number of Subjects      | Approximately 126 |
| Approximate Duration of Subject Participation | Up to 2 weeks for screening, treatment until clinically significant progression of disease, and 4 weeks of follow-up. |

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| Study Treatment | KD025 will be provided as 200-mg tablets to be taken with food either QD (Arm A) or BID (Arm B). |
|-----------------|-----------------------------------------------------------------------------------------------|
| Criteria for Inclusion and Exclusion | **Inclusion Criteria**  
1. Male and female subjects at least 12 years of age who have had allogeneic HCT  
2. Previously received at least 2 and not more than 5 lines of systemic therapy for cGVHD  
3. Receiving glucocorticoid therapy with a stable dose over the 2 weeks prior to screening  
4. Have persistent cGVHD manifestations and systemic therapy is indicated  
5. Karnofsky (if aged ≥16 years)/Lansky (if aged <16 years) Performance Score of ≥ 60  

**Laboratory Parameters**  
6. Absolute neutrophil count ≥1.5 × 10⁹/L  
7. Platelet count ≥50 × 10⁹/L  
8. Alanine aminotransferase and aspartate aminotransferase ≤3 × upper limit of normal (ULN)  
9. Total bilirubin ≤1.5 × ULN  
10. Glomerular filtration rate (GFR) ≥30 mL/min/1.73 m² using the Modification of Diet in Renal Disease-4 variable formula  

**General Criteria**  
11. Female subjects of childbearing potential have a negative urine pregnancy test at screening. Females of childbearing potential are defined as sexually mature females without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, females who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression  
12. Sexually active females of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes:  
   • Intrauterine device plus one barrier method;  
   • Stable doses of hormonal contraception for at least 3 months (eg, oral, injectable, implant, transdermal) plus one barrier method;  
   • 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or  
   • A vasectomized partner  
13. For male subjects who are sexually active and who are partners of females of childbearing potential: agreement to use two forms of contraception as in criterion 12 above and to not donate sperm during the treatment period and for at least 3 months after the last dose of study drug  
14. Subject (or the subject’s legally authorized representative) is able to provide written informed consent/assent prior to the performance of any study-specific procedures  
15. Weight ≥40 kg  
16. It is in the best interest of the subject to participate in the study  

**Exclusion Criteria**  
1. Subject has not been on a stable dose/regimen of systemic cGVHD treatments for at least 2 weeks prior to screening. (Note: Concomitant corticosteroids, calcineurin inhibitors, sirolimus, mycophenolate mofetil, methotrexate, rituximab and CONFIDENTIALITY STATEMENT  
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extracorporeal photopheresis are acceptable. Systemic investigational GVHD treatments are not permitted.

2. Histological relapse of the underlying cancer or posttransplant lymphoproliferative disease at the time of screening.

3. Current treatment with ibrutinib. Prior treatment with ibrutinib is allowed with a washout of at least 28 days prior to randomization.

**General Criteria**

4. Female subject who is pregnant or breastfeeding.

5. History or other evidence of severe illness or any other conditions that would make the subject, in the opinion of the Investigator, unsuitable for the study (such as malabsorption syndromes, poorly controlled psychiatric disease or coronary artery disease).

6. Known active hepatitis B virus or hepatitis C virus or history of HIV.

7. Diagnosed with another malignancy (other than malignancy for which transplant was performed) within 3 years of enrollment, with the exception of:
   - Completely resected basal cell or squamous cell carcinoma of the skin.
   - Carcinoma in situ of the cervix.
   - Resected breast ductal carcinoma in situ.
   - Prostate cancer with Gleason score <6 and stable prostate-specific antigen over 12 months.

8. Has had previous exposure to KD025.

9. Known allergy/sensitivity to KD025 or any other ROCK2 inhibitor.

10. Subject has QTc(F) > 480 ms.

11. Subject has FEV1 ≤ 39% or has lung score of 3.

12. Subject considered unlikely to adhere to treatment and/or follow protocol in the opinion of the Investigator.

13. Treatment with any non-GVHD investigational agent, or any investigational device or procedure, within 28 days (or 5 half-lives, whichever is greater) of enrollment.

**Efficacy Variables**

**Primary End Point**

The primary efficacy end point is the ORR [including partial response (PR) and complete response (CR)]. Responses are as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD, and are assessed by Investigators.

**Secondary End Points**

- DOR
- Change in LSS score
- Response rate by organ system
- Time to response
- Time to next treatment
- Percentage of subjects who have a best response of PR and percentage of subjects who have a best response of CR
- Change in corticosteroid dose
- Change in calcineurin inhibitor dose
- FFS
- OS
- 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
| **Exploratory End Points** |  |
|---------------------------|---|
| • PROMIS Global Health subscores for physical and mental functioning |  |
| • ORR using sponsor assessments of overall response |  |
| • Pharmacodynamics - changes in the expression of relevant biomarkers after KD025 administration |  |

**Safety Variables**

Safety is a secondary end point. The primary safety outcome will be the percent of subjects in each arm experiencing adverse events (AEs).

Safety assessments include AEs, grade ≥3 AEs, serious adverse events (SAEs), physical examinations, vital sign measurements, clinical laboratory evaluations and echocardiograms (ECGs). Reasons for treatment discontinuation will be documented.

The AE reporting period for a subject enrolled in the study begins when the subject signs the informed consent and is continued through 28 days after their last dose study treatment.

**Pharmacokinetics**

Full pharmacokinetics (PK) profiles will be collected for approximately 12 subjects in each treatment arm at selected sites, and sparse PK sampling for the whole population.

**Pharmacodynamics**

Samples will be collected for exploratory pharmacodynamics analyses from all subjects at sites with appropriate capabilities prior to dosing with KD025 on day 1 of cycles 1, 2 and 7, and upon progression of cGVHD (or flare).

**Statistical Analysis**

**Sample Size:**

Sample size is based on the primary efficacy end point of ORR, with a target ORR of 55% and with one planned IA. With 63 subjects, and a 10% dropout rate, each treatment arm is estimated to have 90% power to yield a 95% confidence interval of ORR that excludes 30%. The Hochberg procedure will be applied for multiplicity adjustment for the primary efficacy end point of ORR.

**Analysis Population:**

The modified intent-to-treat (mITT) population is defined as all subjects who are randomized and receive at least one dose of study medication.

The mITT population is the primary population for the analysis of the primary efficacy end point.

**Data Presentations/Descriptive Statistics**

Three analyses are planned:

1. An IA will be conducted approximately 2 months after 126 subjects have been enrolled into the mITT population. A nominal 1-sided alpha of 0.0025 will be spent, but there will be no early study termination for efficacy.

2. The PA will be conducted approximately 6 months after 126 subjects have been enrolled into the mITT population, with 1-sided alpha 0.0225 (or 0.025 if the ORRs of both arms are significant at interim).

3. A follow-up analysis will be conducted approximately 12 months after 126 subjects have been enrolled into the mITT population.

Alpha will only be allocated to the primary end point, ORR. Demographics, subject disposition, and screening and baseline characteristics will be summarized for the ITT population.

AEs will be coded using the MedDRA dictionary (Version 20.1 or greater). The number and percentages of subjects experiencing treatment-emergent AEs will be tabulated by system-organ-class and preferred term and will be presented by treatment group. The number of events by preferred term will also be summarized. Tabulation by maximum severity and relationship...
to treatment will also be included by treatment group. Summary subject listing will be provided for SAEs, AEs resulting in study discontinuation, and deaths.

AEs, SAEs, related AEs, related SAEs, grade ≥3 AEs, related grade ≥3 AEs and AEs leading to withdrawal and treatment discontinuation will be summarized according to treatment group.

Laboratory results will be summarized by treatment group. Incidence of laboratory abnormalities will be summarized by treatment group. The worst on-study grade during the treatment period will be summarized. The incidence of grade ≥3 laboratory abnormalities under treatment and shifts in toxicity grading from baseline to highest grade post baseline will be displayed.

Vital sign measurements and ECGs will be summarized by treatment group at each scheduled time point using descriptive statistics and included in data listings.
**Supplemental Tables and Figures:**

**Table S1. Summary of ORR by dose and organ system**

| Organ system, n (%)                         | Belumosudil 200 mg QD (n=66) | Belumosudil 200 mg BID (n=66) | Total (N=132) |
|--------------------------------------------|--------------------------------|--------------------------------|---------------|
| Joints and fascia                          | 51 (77)                        | 49 (74)                        | 100 (76)      |
| CR                                         | 10 (20)                        | 10 (20)                        | 20 (20)       |
| PR                                         | 28 (55)                        | 23 (47)                        | 51 (51)       |
| ORR                                        | 38 (75)                        | 33 (67)                        | 71 (71)       |
| **Lower GI**                               | 6 (9)                          | 7 (11)                         | 13 (10)       |
| CR                                         | 4 (67)                         | 4 (57)                         | 8 (62)        |
| PR                                         | 0                              | 1 (14)                         | 1 (8)         |
| ORR                                        | 4 (67)                         | 5 (71)                         | 9 (69)        |
| **Mouth**                                  | 30 (45)                        | 42 (64)                        | 72 (55)       |
| CR                                         | 15 (50)                        | 17 (41)                        | 32 (44)       |
| PR                                         | 1 (3)                          | 7 (17)                         | 8 (11)        |
| ORR                                        | 16 (53)                        | 24 (57)                        | 40 (56)       |
| **Upper GI**                               | 13 (20)                        | 10 (15)                        | 23 (17)       |
| CR                                         | 7 (54)                         | 4 (40)                         | 11 (48)       |
| PR                                         | 1 (8)                          | 0                              | 1 (4)         |
| ORR                                        | 8 (62)                         | 4 (40)                         | 12 (52)       |
| **Esophagus**                              | 19 (29)                        | 12 (18)                        | 31 (23)       |
| CR                                         | 9 (47)                         | 5 (42)                         | 14 (45)       |
| PR                                         | 0                              | 0                              | 0             |
| ORR                                        | 9 (47)                         | 5 (42)                         | 14 (45)       |
| **Eyes**                                   | 48 (73)                        | 49 (74)                        | 97 (73)       |
| CR                                         | 8 (17)                         | 6 (12)                         | 14 (14)       |
| PR                                         | 8 (17)                         | 19 (39)                        | 27 (28)       |
| ORR                                        | 16 (33)                        | 25 (51)                        | 41 (42)       |
| **Liver**                                  | 9 (14)                         | 4 (6)                          | 13 (10)       |
| CR                                         | 2 (22)                         | 2 (50)                         | 4 (31)        |

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|       | PR   | ORR  | Skin  | CR   | ORR  | Lungs | CR   | ORR  | PR   | ORR  | PR   | ORR  |
|-------|------|------|-------|------|------|-------|------|------|------|------|------|------|
|       | 1 (11) | 0     | 55 (83) | 8 (15) | 10 (18) | 24 (36) | 4 (17) | 3 (13) | 7 (29) |       |      |      |
| BID, twice a day; CR, complete response; GI, gastrointestinal; ORR, overall response rate; PR, partial response; QD, every day.