Official Title：The Synopsis of BN101-201 Protocol

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CLINICAL STUDY PROTOCOL

A Phase 2, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of BN101/belumosudil in Subjects with Chronic Graft Versus Host Disease (cGVHD) After at Least 1 Prior Line of Systemic Therapy

Protocol Number：	**BN101-201**
Version：	**3.0**
Version Date：	**25 Feb 2022**
Sponsor：	**BK Pharmaceuticals Ltd.**
Agent：	**BioNova Pharmaceuticals (Shanghai) Ltd.**
Sponsor Contact：	**Yu Wang**
Sponsor Contact information：	**Telephone：186 2188 9377** **E-mail: yu.wang@bionovapharma.com**

Confidentiality Statement

The ownership of all information contained in this protocol is vested in the sponsor and its agents, and therefore, it is provided only for review by the investigator, co-investigators, ethics committees, and supervisory and regulatory authorities, and other relevant healthcare organizations. Without the written approval of the sponsor and its agents, it is strictly prohibited to communicate any information to third parties unrelated to this study, except for the necessary explanations when signing informed consent with potential subjects.

Protocol Signature Page

（Sponsor）

I agree：

- Conduct this trial in strict accordance with the protocol, the current International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), and the China National Medical Products Administration (NMPA) GCP Guidelines, as well as applicable regulations and guidelines.
- Responsible for initiating, applying for, organizing and funding this clinical trial, and conducting the audit of the clinical trial.

I have read the full text of this protocol and agree with all the provisions listed in the protocol.

Sponsor：BK Pharmaceuticals Ltd.

Agent：BioNova Pharmaceuticals (Shanghai) Ltd.

Project Lead of the Agent：Ye Hua, MD, MPH

Signature Date

Protocol Signature Page

（Study leading site）

I agree：

- Conduct this trial in strict accordance with the protocol, the current ICH GCP, and the China NMPA GCP Guidelines, as well as applicable regulations and guidelines.
- Keep all data information provided by the sponsor in accordance with confidentiality requirements, and when such data information is to be presented to the Ethics Committee (IEC), it must be marked as confidential.

I have read the full text of this protocol and agree with all the provisions listed in the protocol.

Study Leading Site：The First Affiliated Hospital of Soochow University

Principal Investigator：Depei Wu

Signature Date

Protocol Signature Page（Study site）

Protocol Number： BN101-201	**Protocol Version/Date：** 3.0/ 25 Feb 2022
Protocol Title： A Phase 2, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of BN101/belumosudil in Subjects with Chronic Graft Versus Host Disease (cGVHD) After at Least 1 Prior Line of Systemic Therapy	
Site Number：	**Investigator ：**
Study Site：	

I have fully read the clinical study protocol and understand its requirements. I agree to follow the protocol and timeline for the conduct of this clinical study. Modifications to the protocol that are not approved by the sponsor and/or contract research organization (CRO), and the IEC are considered to be contrary to the protocol.

I agree to conduct the trial in accordance with current ICH GCP and NMPA GCP guidelines and applicable regulations and guidelines, and to accept monitoring/auditing of the clinical trial by the sponsor and/or CRO, and verification/inspection by the drug regulatory authorities.

I agree to apply only the trial supplies including the study drug as specified in the protocol.

Signature of Principal Investigator

Name in block letters	**Signature**	**Date**

Sponsor and Agent

Sponsor	BK Pharmaceuticals Ltd.		
Agent	BioNova Pharmaceuticals (Shanghai) Ltd.		
Project Lead of the Agent：	Yu Wang, MD, MS		
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Protocol Synopsis

Protocol Number	BN101-201
Study Title	A Phase 2, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of BN101/belumosudil in Subjects with Chronic Graft Versus Host Disease (cGVHD) After at Least 1 Prior Line of Systemic Therapy
Version number/Date	3.0/ 25 Feb, 2022
Sponsor	BK Pharmaceuticals Ltd.
Agent	BioNova Pharmaceuticals (Shanghai) Ltd.
Phase	II
Indication	Subjects with Chronic Graft Versus Host Disease (cGVHD) After at Least 1 Prior Line of Systemic Therapy
Study Objectives	Primary Objective • To evaluate the efficacy and safety of BN101/belumosudil in subjects with cGVHD who had previously been treated with at least 1 prior line of systemic therapy. Secondary Objectives • To evaluate the PK profile of BN101/belumosudil in subjects with cGVHD who had previously been treated with at least 1 prior line of systemic therapy; • To evaluate other efficacy endpoints of BN101/belumosudil in subjects with cGVHD who had previously been treated with at least 1 prior line of systemic therapy. Exploratory Objective • To evaluate changes in the Patient-Reported Outcomes (PRO) Measurement Information System (PROMIS) Global Health sub-scores of physical and mental functioning
Study Design	This study is a multicenter, open, single-arm phase II clinical trial to enroll 30 patients with cGVHD who have undergone at least 1 but not more than 5 lines of systemic therapy, and to evaluate the efficacy, safety, and PK characteristics of BN101/belumosudil in Chinese patients with cGVHD. Eligible subjects after signing informed consent form will be enrolled to receive BN101/belumosudil (every 28-day cycle) until cGVHD progression, intolerable toxicity, initiation of a new cGVHD therapy, recurrence of hematological neoplasm, loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first. For subjects assessed as

	"Lack of Response - Mixed" and "Lack of Response - Progression"【Evaluated by the investigator based on the National Institutes of Health (NIH) Consensus Development Project on Criteria for Clinical Trials in cGVHD(2014) diagnosis and staging, and response criteria, hereinafter referred to as the NIH Consensus Criteria (2014)】, if the investigator believed that these subjects could continue to benefit from treatment with BN101/belumosudil, the treatment may be continued after a written application was submitted, and approval from the Sponsor's Medical Monitor as well as documentation of the subject's willingness to continue treatment was obtained. For subjects who did not achieve any response after 12 cycles of BN101/belumosudil treatment during the main study(the end of the main study is defined in section 3.5 of the main body), they should discontinue the investigational product treatment and withdraw from the study if they were judged by the investigator to have no clinical benefit (e.g., improvements in organ score, improvements in Lee symptom scores, reductions of corticosteroid/tacrolimus doses). The primary efficacy endpoint was the subject's overall response rate (ORR), which was assessed according to the NIH Consensus Criteria (2014) at each of the protocol-specified visit viewpoints, and then the ORR was calculated.
Number of Subjects	This study is an open, single-arm trial with the purpose of bridging Chinese cGVHD patients to the US registry study (KD025-213) to assess whether BN101/belumosudil treatment of Chinese versus Caucasian cGVHD patients is concordant in terms of efficacy, safety, and PK characteristics, the sample size of the trial is not determined by statistical assumptions. This study is planned to enroll 30 patients with cGVHD who have undergone at least 1 but not more than 5 lines of systemic therapy, and such a sample size is considered to be sufficient to meet the needs of assessment with the purpose of bridging.
Number of Study Centers	Approximately 6~9
Study duration	Approximately 2 years
Study Population	**Inclusion Criteria** Subjects who met **all** of the following conditions could be enrolled in the study: (1) Male or female subjects aged ≥ 18 years who have had allogeneic hematopoietic stem cell transplant (allo-HSCT). (2) Have persistent cGVHD manifestations and systemic therapy is indicated. (3) Previously received at least 1 and not more than 5 lines of systemic therapy for cGVHD. (4) Receiving glucocorticoid therapy with a stable dose over the 2 weeks prior to

screening; or 4 weeks of prednisone or equivalent doses of other corticosteroids at doses > 0.5 mg/kg/day with persistent manifestations of cGVHD and no improvement; or 2 attempts to reduce the hormone to a lower dose level fail and the prednisone dose still needs to be increased to > 0.25 mg/kg/day or an equivalent dose.

(5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score: 0 to 1.

(6) Life expectancy of more than 12 months.

General Criteria

(7) Female subjects of childbearing potential have a negative serum 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.

(8) 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:

- Intra-uterine contraceptive device plus 1 barrier method;
- Stable doses of hormonal contraception (e.g., oral, injectable, subcutaneously implanted, transdermal) for at least 3 months plus 1 barrier method;
- Two 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.

(9) For male subjects who are sexually active and who are partners of females of childbearing potential: must agree to use 2 recognized methods of contraception during the treatment period and for 3 months after the last dose of study drug (see criterion 8 above).

(10) Subject (or the subject's legally authorized representative) must be fully informed of the study contents and is able to provide written ICF prior to any study-specific procedures, and is willing to follow the treatment regimen and visit schedule.

Exclusion Criteria

Subjects who met **any** of the following conditions would be excluded from the study:

(1) Received a systemic investigational cGVHD treatment within 28 days of study entry, but prior treatment is allowed with a washout of at least 28 days or 5 half-lives.[Note: Corticosteroids, CNIs, sirolimus, mycophenolate mofetil (MMF), methotrexate, azathioprine, and *in vitro* photochemotherapy (ECP) are acceptable and subjects must have been on a stable dose/regimen of these for at least 2 weeks prior to screening].

(2) Recurrence of hematologic tumor (according to criteria for recurrence of the corresponding primary hematologic tumor) or post-transplant lymphoproliferative disease at screening.

(3) Current treatment with ibrutinib (except for ibrutinib with a washout of at least 28 days prior to the first dose of the investigational product).

Laboratory Tests

(4) Absolute neutrophil count (ANC) < 1.5×10^9/L.

(5) Platelet count < 50×10^9/L.

(6) Alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN), aspartate aminotransferase (AST) > 3 × ULN

(7) Total bilirubin (TBIL) > 1.5 × ULN.

(8) Creatinine clearance (CrCl) < 60 mL/min (Cockcroft-Gault formula).

General Criteria

(9) Pregnant or lactating women.

(10) History of severe illness, 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

- History of severe [New York Heart Association (NYHA) functional class III or IV] cardiovascular disorder, including but not limited to ventricular arrhythmias requiring clinical intervention, uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg); unstable angina pectoris, acute coronary syndrome, congestive cardiac failure, stroke, or other ≥ Grade 3 cardiac events within 6 months prior to enrollment; and NYHA functional class ≥ II or left ventricular ejection fraction (LVEF) < 50% by cardiac ultrasound at screening.
- Inability to take oral medications, severe (NCI CTCAE v5.0≥ Grade 3) chronic gastrointestinal dysfunction, malabsorption syndrome, or any other condition that affects gastrointestinal absorption.
- History of clear neurological or mental disorders (including epilepsy or

dementia), current mental disorders, or poor compliance that rendered the subject ineligible for participation in the study as judged by the investigator.

- History of other serious (NCI CTCAE v5.0≥ Grade 3) systemic disease that rendered the subject ineligible for participation in the clinical trial as judged by the investigator.

(11) Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or human immunodeficiency virus (HIV) infection. [Note: Active HBV infection is defined as positive for serum hepatitis B virus surface antigen (HBsAg) and/or hepatitis B virus e antigen (HBeAg), or HBV-DNA; subjects with positive hepatitis B virus core antibody (anti-HBc) should be confirmed for HBV-DNA, and subjects who are confirmed to be negative for HBV-DNA could be enrolled; active HCV infection is defined as positive for HCV-RNA, and subjects who are positive for hepatitis C virus antibody (HCV-Ab) could only be enrolled after confirmed to be negative for HCV-RNA. Positive is defined as ＞ the ULN].

(12) Diagnosed with another primary malignancy(other than malignancy for which allo-HSCT was performed) within 3 years of enrollment, with the exception of:

- Completely resected basal cell or squamous cell carcinoma of the skin;
- Surgically cured carcinoma in situ of the cervix;
- Resected breast ductal carcinoma in situ;
- Prostate cancer with Gleason score < 6 and stable prostate-specific antigen (PSA) over 12 months.

(13) Known allergy to the active ingredient or excipients of the investigational product, or any other selective ROCK2 inhibitors.

(14) Subjects requiring long-term proton pump inhibitors (e.g., rabeprazole, omeprazole) or CYP3A4 inducers (e.g., rifampin, phenobarbital).

(15) Prolongation of QT interval corrected by the Fridericia's formula (QTcF) of > 450 ms for males and > 470 ms for females at screening.

(16) Known alcohol or drug dependence.

(17) Forced expiratory volume in 1 second (FEV_1) ≤ 39% or pulmonary function score of 3 at screening.

(18) Treatment with any investigational agent, device, or procedure, within 28 days (or 5 half-lives, whichever is longer) prior to enrollment.

(19) Subjects considered unlikely to adhere to treatment and follow protocol in the opinion of the investigator.

	Criteria for completion of study drug therapy and early termination of study drug therapy: (1) Completion of study drug therapy - Completion of study drug therapy as defined by the protocol; or - cGVHD disease progression during treatment - Death of the subject (2) Early termination of study drug therapy Refers to the situation in which an enrolled subject becomes unfit to continue treatment with the study drug during the course of the study. Early termination of study drug treatment is defined as follows: - Recurrence of the subject's hematologic tumor during the course of the trial (according to the criteria for recurrence of the corresponding primary hematologic tumor). - The subject is discontinued due to an adverse event or serious adverse event that makes continuation of study drug treatment inappropriate; or the subject is discontinued due to an adverse event or serious adverse event for more than 14 days. - The investigator determines that the subject's continued treatment with the study drug may pose a potential risk greater than benefit to the subject, including: pregnancy; enrollment in the study and discovery that the subject does not meet the study protocol inclusion criteria and that continued treatment with the study drug poses a risk greater than benefit to the subject; failure to follow the protocol or doctor's orders, unauthorized use of other treatments, or failure to take the medication in a timely manner and at a dosage that would interfere with the assessment of efficacy and increase potential safety risks. - Subject withdraws informed consent/withdraws from the study. - Subject lost to follow-up. After discontinuation of study medication, subjects will undergo end-of-treatment visits and enter a safety follow-up period (including a 28-day follow-up after the last dose and a long-term safety follow-up).
Investigational Product	Investigational product: BN101/belumosudil Manufacturer: UPM Pharmaceuticals, Inc. Sponsor: BK Pharmaceuticals Ltd. Agent: BioNova Pharmaceuticals (Shanghai) Ltd. (The investigational drug was provided by the agent free of charge)

Ingredients: BN101/belumosudil, microcrystalline cellulose, hydroxypropylmethylcellulose, cross-linked sodium carboxymethylcellulose, anhydrous colloidal silicon dioxide, magnesium stearate, and Obadiol II (yellow 85F32410)

Specification: 200 mg (tablets equivalent to 200 mg BN101/belumosudil free base)

Storage conditions: Keep below 25°C

Expiry date: 24 months tentatively

Administration: Oral administration with or within 5 minutes after meals, once a day for 28 days

Dose adjustment: If adverse events occur during BN101/belumosudil treatment, the dose can be adjusted (see table below).

Toxicity*	Dose Adjustment
⩾ grade 3 hepatotoxicity (ALT/AST/TBIL)	Suspend BN101/belumosudil administration; Within 14 days§ Toxicity does not return to ≤ Grade 1 or baseline level, then discontinue BN101/belumosudil therapy; Within 14 days§ Toxicity returns to ≤ Grade 1 or Baseline level, resume BN101/belumosudil administration at a reduced dose level [e.g., 200 mg QD → 200 mg once every other day (QOD)]; If the reduced dose level is administered for one full treatment cycle tolerated by the subject without recurrence of Grade 1 or greater hepatic function abnormality, return the dose to the original level for the following treatment cycle; if this toxic reaction recurs after the reduced dose level, terminate BN101/belumosudil treatment.
Other ≥ grade 3 clinically significant toxicity associated with BN101/belumosudil	Suspend BN101/belumosudil administration; Within 14 days§ Toxicity does not return to ≤ Grade 1 or baseline level, then discontinue BN101/belumosudil therapy; Within 14 days§ Toxicity returns to ≤ Grade 1 or baseline level, then BN101/belumosudil administration is resumed at a reduced dose level [e.g., 200 mg QD → 200 mg QOD]; if the reduced dose level is administered for a full treatment cycle as tolerated by the subject, and there is no recurrence of Grade 1 or higher of this abnormality, then the next cycle of treatment the dose will be restored to the original level [e.g., 200 mg QOD → 200 mg QD]; If the toxic reaction recurs after administration at a

	<table><tr><td></td><td>reduced dose level, BN101/belumosudil treatment will be discontinued.</td></tr></table> *Severity of toxicity was determined according to NCI CTCAE v5.0. § The maximum time allowed for suspension of BN101/belumosudil administration due to toxicity was 14 days, and subjects who discontinued for more than 14 days were required to withdraw from the study. If a subject can tolerate 1 full cycle of treatment after a BN101/belumosudil dose reduction, the dose may be restored to the dose prior to the reduction for the next cycle.
Control drug	None
Research treatment and blood sampling	The study consisted of a screening period, a treatment period, and a safety follow-up period (including a 28-day follow-up after the last dose and a long-term safety follow-up). Subjects who sign informed consent form are screened and eligible subjects will receive BN101/belumosudil until cGVHD progression[according to NIH Consensus Criteria (2014)], intolerable toxicity, initiation of a new cGVHD therapy, recurrence of hematological neoplasm, loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first. Response assessments would be performed on Day 1 of Cycles 2 to 5 and every 2 cycles thereafter (i.e., Day 1 of Cycles 2, 3, 4, 5, 7, 9, 11, etc.). For subjects assessed as "Lack of Response - Mixed" and "Lack of Response - Progression"(see table 3 in the main body of the protocol), if the investigator believed that these subjects could continue to benefit from treatment with BN101/belumosudil, the treatment may be continued after a written application was submitted, and approval from the Sponsor's Medical Director as well as documentation of the subject's willingness to continue treatment was obtained until cGVHD progression, intolerable toxicity, initiation of a new cGVHD therapy, recurrence of hematological neoplasm, loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first. For subjects who did not achieve any response after 12 cycles of BN101/belumosudil treatment during the main study, they should discontinue the investigational product treatment and withdraw from the study if they were judged by the investigator to have no clinical benefit. Data lock and primary analysis will be performed 6 months after enrollment of the last subject. All subjects will continue to be followed up for an additional 6 months after the primary analysis as required by the protocol, i.e., the study will end 12 months after enrollment of the last subject, and a follow-up analysis will be performed at the end of the study. Subjects who have not yet experienced cGVHD progression at the end of the study, and in the judgment of the investigator, the benefits of continued dosing outweigh the risks, the sponsor will continue to provide BN101/belumosudil medication at no cost until cGVHD progression, intolerable toxicity, initiation of a new cGVHD therapy, recurrence of

	hematological neoplasm, loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first; or will need to be withdrawn from this study if, in the judgment of the investigator, there is no evidence of clinical benefit. Subjects who remain free of disease progression at the time of withdrawal from the study or who withdraw from the study for reasons other than adverse events should have the dose of BN101/belumosudil tapered every 2 weeks as required by the protocol (e.g., 200 mg QD → 200 mg QOD → discontinue treatment). Subjects who completed or prematurely terminated study drug therapy entered a follow-up period in which the study center contacted subjects by telephone approximately every 12 weeks to confirm their survival, any changes in cGVHD therapy, and any antitumor therapy until no more subjects were taking study drug. The safety assessment begins with the signing of informed consent form until 28 days after the last dose of study drug (unless otherwise indicated) and includes changes in physical examination, vital signs, laboratory tests, electrocardiograms, echocardiograms (if necessary), as well as adverse events, adverse events related to the study drug, and serious adverse events. In addition, the study will evaluate the PK profile of BN101/belumosudil and its metabolites, m1 and m2, in all subjects, and the first 12 subjects will require intensive collection of PK blood samples.See Appendix (PK Blood Sample Collection Schedule and PK Blood Sample Collection Time Window) for PK blood sample collection.
Concomitant medication and concomitant therapy	All comorbid medications or treatments will be documented during the study period. Initiation of new systemic cGVHD treatment will be considered as starting a new cGVHD treatment and will be considered a failure of BN101/belumosudil treatment. - Transient increases in corticosteroid dose (no more than 1 mg/kg/day of prednisone equivalent) for treatment of cGVHD episodes will be permitted during the study treatment period, provided that the dose is reduced to pre-enrollment levels within 6 weeks. If the dose remained elevated for more than 6 weeks, it was considered a BN101/belumosudil treatment failure. More than 2 episodes of cGVHD requiring an increase in the dose of corticosteroid therapy within the first 6 months of BN101/belumosudil treatment will also be considered a BN101/belumosudil treatment failure. - Continuation of treatment with calcineurin phosphatase inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, MMF, methotrexate, azathioprine, or extracorporeal photochemistry (ECP), which have been stabilized at baseline, is permitted during study treatment. - Local/organ-specific therapy for cGVHD is allowed during study treatment. - During study treatment, CYP3A4 inducers (e.g., rifampin, phenobarbital) are prohibited, proton pump inhibitors (e.g., rabeprazole, omeprazole) are permitted for short

	periods of time only (no more than 1 week), and CYP1A2 inhibitors/inducers, CYP3A4 inhibitors, drugs that prolong the QT/QTc interval should be used with caution (see Appendix for details of CYP3A4 and CYP1A2 inhibitors/inducers, and drugs that prolong the QT/QTc interval). - The use of other systemic therapies for cGVHD (including rituximab, ruxolitinib, ibrutinib, etc.) or other clinical trial medications is prohibited during study treatment. - Tobacco, alcohol, and caffeinated beverages or foods are prohibited on the day of PK sample collection.
Efficacy endpoints	The primary efficacy endpoint was the Overall Response Rate (ORR, including Complete Response [CR] and Partial Response [PR]), assessed according to the NIH consensus criteria (2014). Secondary efficacy endpoints included median Duration of Response (DOR), Change in Lee Symptom Scale Score, Response rate by organ system, Percentage of subjects with best efficacy as PR and percentage of subjects with best efficacy as CR, Change in corticosteroid dose, Change in CNI dose, Failure-Free Survival (FFS), Overall Survival (OS), Change in cGVHD severity based on the Physician-Reported Global cGVHD Activity Assessment, and Change in symptom activity based on cGVHD Activity Assessment Patient Self-Report.
Safety Endpoints	AEs, serious adverse events (SAEs), AEs related to the investigational product, Vital signs, Physical examination, Laboratory safety tests, 12-lead electrocardiograms (ECGs), etc.
PK Endpoints	PK parameters include C_{max}, time to peak (T_{max}), elimination half-life ($T_{1/2}$), area under the concentration-time curve from time 0 to the time of the last measurable concentration (AUC_{0-t}), area under the blood concentration-time curve from initiation of dosing to the extrapolated infinite time (AUC_{inf}), apparent clearance (CL_z/F), and apparent volume of distribution (V_z/F), clearance rate constant (K_{el}), steady-state trough concentration ($C_{min,ss}$), steady-state peak concentration ($C_{max,ss}$), steady-state mean blood concentration ($C_{av,ss}$), steady-state accumulation ratio expressed as AUC_{0-t} (R_{AUC1}), steady-state accumulation ratio expressed as AUCinf (R_{AUC2}), and steady-state accumulation ratio expressed as C_{max} (R_{Cmax}). If the metabolites m1 and m2 of BN101/belumosudil can be detected and characterized, the ratios of the molecular weight-adjusted metabolites (m1 and m2) to the prodrug (P) C_{max} and AUC (AUC_{0-t}, AUC_{inf}) also need to be calculated.
Exploratory Endpoints	Changes in PROMIS Physical and Mental Functioning Global Health Scores
End of study	Data lock and primary analysis will be performed 6 months after enrollment of the last subject. All subjects will continue to be followed up for an additional 6 months after the

	primary analysis as required by the protocol, i.e., the study will end 12 months after enrollment of the last subject, and a follow-up analysis will be performed at the end of the study. Subjects who have not yet experienced cGVHD progression at the end of the study, and in the judgment of the investigator, the benefits of continued dosing outweigh the risks, may submit a written request and, upon approval by the sponsor's Medical Director and documentation of the subject's willingness to continue the treatment, the sponsor will continue to provide BN101/belumosudil medication at no cost until cGVHD progression, intolerable toxicity, initiation of a new cGVHD therapy, recurrence of hematological neoplasm, loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first. Serious adverse events (SAEs), study drug use, and subject survival will continue to be collected for subjects who continue to be free of charge while the study drug, BN101/belumosudil, is administered at the end of the study. The study will end when all subjects stop taking the study drug.
Statistical Analysis	**Sample size:** Because this study is an open, single-arm trial with the purpose of bridging Chinese cGVHD patients to the US registry study (KD025-213) to assess whether BN101/belumosudil treatment of Chinese versus Caucasian cGVHD patients is consistent in terms of efficacy, safety, and PK characteristics, the sample size of this trial is not determined by statistical assumptions. This study is planned to enroll 30 patients with cGVHD who have undergone at least 1 but not more than 5 lines of systemic therapy. **Analysis Sets:** Modified Intent to Treat (mITT): All subjects who had used the study drug after signing the informed consent form for enrollment. Safety Set (SS): All subjects who had used the study drug after enrollment and had at least 1 safety assessment. Per Protocol Set (PPS): The PPS was a subset of the mITT, and included all subjects who have used the study drug after enrollment and have had at least 1 post-treatment efficacy assessment, as well as no major protocol deviations. The exact definition of a major protocol deviation and the inclusion criteria for the PPS were finally determined in the data review meeting. Pharmacokinetic analysis Set (PKS): all subjects who have used the study drug since enrollment and have post-administration PK data. Demographic and baseline characteristics of subjects were statistically analyzed based on mITT. mITT was the primary analysis population for the primary efficacy endpoint and PPS was the secondary analysis population. Safety analysis based on SS and PK analysis based on PKS.

Analysis Methods:

All statistical analyses were completed using SAS version 9.4 or higher. Specific statistical methods are described in the statistical analysis plan.

Continuous variables were described using mean, standard deviation, median, first quartile, third quartile, maximum, and minimum.

Categorical variables were described using frequencies and percentages. If required, 95% confidence intervals (95% CI) were calculated for frequencies and percentages.

Safety Analysis

Safety analysis was performed based on SS. Adverse events were coded in MedDRA (version 20.1 or above). Frequencies and percentages of subjects who experienced adverse events during treatment were summarized by system organ classification and preferred terminology and presented in tabular form. Adverse events of varying severity (according to NCI CTCAE v5.0) were summarized by frequency and tabulated by highest severity and correlation with study drug. Descriptively summarize adverse events, serious adverse events, adverse events of severity ≥ grade 3 (per NCI CTCAE v5.0), adverse events leading to withdrawal from the study, adverse events leading to discontinuation of study treatment, adverse events leading to dosage adjustments of the study medication, and adverse events/serious adverse events related to the study medication for each of the above categories. List subjects with each type of adverse event/serious adverse event and death.

Descriptive statistics of laboratory test abnormalities and changes in laboratory test results of severity ≥3 (according to NCI CTCAE v5.0) before and after treatment with study medications are presented in a cross-tabulation.

Descriptive statistics of vital signs, physical examination, and 12-lead electrocardiogram results are presented and listed.

Efficacy Analysis

Efficacy analyses based on mITT and PPS, with the results of the mITT analysis as the main focus.

Point estimates of ORR and their 95% CIs are calculated based on the binomial distribution exact probability method. multifactorial analysis using logistic regression models will also be performed if applicable.

Descriptive statistical analysis is provided for all secondary efficacy endpoints.

The following subgroups will be analyzed:

- Severe cGVHD (yes/no)
- Number of organs involved (<4 vs. ≥4)
- Number of treatment lines for prior systemic cGVHD (1 vs. ≥2)

	- Duration of cGVHD prior to enrollment (i.e., from time of cGVHD diagnosis to time of enrollment) - Lung involvement (yes/no) **Pharmacokinetic analysis** Mean (Mean±SD) drug-time curves for BN101/belumosudil (and its metabolites m1 and m2, if applicable) and individual drug-time curves for BN101/belumosudil (and its metabolites m1 and m2, if applicable) will be plotted for each subject. Descriptive statistics of PK parameters of BN101/belumosudil (and its metabolites m1 and m2, if applicable) in Chinese patients with cGVHD, and the statistics of each parameter included the number of samples, mean, standard deviation, coefficient of variation, geometric mean, geometric standard deviation, geometric coefficient of variation, median, first quartile, third quartile, minimum and maximum values.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
allo-HSCT	allogeneic-hematopoietic stem cell transplantation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the last measurable time point
AUC_{inf}	area under the blood concentration-time curve from initiation of dosing to imputed infinite time
BID	twice daily
BSC	best supportive care
$C_{av,ss}$	mean blood concentration of steady state
cGVHD	chronic graft versus host disease
C_{max}	maximum concentration observed
$C_{max,ss}$	maximum concentration observed of steady state
$C_{min,ss}$	minimal concentration observed of steady state
CNI	calcineurin inhibitor
CLz/F	apparent total plasma clearance
CR	complete response
CRO	contract research organization
CYP	cytochrome P450
DL_{CO}	diffusing capacity of carbon monoxide
DLT	dose-limiting toxicity
DoR	duration of response
EC	ethics committee
ECOG	eastern cooperative oncology group

Abbreviation	Definition
ECP	extracorporeal photopheresis
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
FDA	Food and Drug Administration
FEV1	forced expiratory volume (in the first second)
FFS	failure-free survival
FVC	forced vital capacity
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for/Conference on Harmonization
ICSR	Individual case safety reports
IRB	Institutional review board
LR	Lack of response
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMF	Mycophenolate Mofetil
NCI CTCAE v5.0	National Cancer Institute-Common Terminology Criteria for Adverse Events 5.0
NIH	National Institutes of Health
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PASI	Psoriasis Area and Severity Index

Abbreviation	Definition
PK	pharmacokinetic
PKS	Pharmacokinetic analysis Set
PPS	Per Protocol Set
PR	partial response
PROMIS	Patient-Reported Outcome Measurement Information System
PS	Performance Status
PTE	pre-treatment event
QA	quality assurance
QD	once daily
QOD	once every other day
QTcB	corrected QT interval using Bazetts's formula
QTcF	corrected QT interval using Fridericia's formula
ROCK	Rho-associated protein kinase
RV	residual volume
SAE	serious adverse event
SS	safety set
SUSAR	suspected unexpected serious adverse event
TBIL	total bilirubin
Tfh	T follicular helper
Th17	T-helper 17
TLC	total lung capacity
T_{max}	observed time to reach peak plasma concentration
Tregs	regulatory T cell
$T_{1/2}$	half-life
ULN	upper limit of normal
Vz/F	apparent volume of distribution
95%CI	95% confidence interval

1. STUDY BACKGROUND

1.1 Overview

Although gene therapy and cellular therapy (e.g., CAR-T) are increasingly being used to treat hematologic malignancies, the complications associated with these therapies and the long-term prognosis of most postoperative patients make allogeneic hematopoietic stem cell transplantation (allo-HSCT), a potentially curative treatment for hematologic neoplasms, one of the most desirable treatments for malignant hematologic neoplasms for today's patients and physicians, and with the widespread use of peripheral blood stem cell transplantation of human leukocyte antigen-incompatible (HLA)-identical siblings and unrelated donors in the clinic, the number of clinical cases of allo-HSCT is constantly on the rise[1].

Chronic graft versus host disease (cGVHD) remains a major complication of allo-HSCT involving multiple organs and occurring in up to 70% of transplant recipients depending upon donor and transplant characteristics[2]. Multicenter and registry data show a cumulative incidence of 30% to 50%[3,4]. 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[5],the disease has become a major cause of long-term survival and quality of life in post-transplant patients[1].

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[6].Therefore, the exploration of new systemic therapies for cGVHD is still a hot research topic.

Ibrutinib (IMBRUVICA) was approved by the FDA for the treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy based upon data from an open-label study (Study 1129; NCT02195869) of 42 subjects with cGVHD who had failed first line corticosteroid therapy and most patients with little organ involvement, the overall response rate (ORR) after treatment reached 67%, and based on the results of this study, the US FDA approved the indication of ibrutinib in August 2017 for the 2-line systemic treatment of cGVHD. Although ibrutinib has demonstrated good efficacy in cGVHD, 24% of subjects in this clinical study discontinued treatment due to adverse events (AEs) related to the study drug[7], and the incidence of AEs such as hemorrhage, infection, and atrial fibrillation caused by this class of BTK-inhibiting drugs is also high, which affects the long-term safety of patients taking.

In China, a second-line cGVHD indication for ibrutinib has not been approved. Currently, there is no approved standard second-line treatment for cGVHD, except for first-line corticosteroid

systemic therapy, which is the systemic standard of care for cGVHD. Thus, there is an unmet clinical need in this disease area.

1.2 Rho-Associated Protein Kinases

ROCKs are members of the serine/threonine kinase family, often studied for their role in cell morphology, motility, and shape through effects on the cytoskeleton[9,10]. Two ROCK isoforms have been identified, ROCK1 and ROCK2. While both are involved in Rho-mediated changes in the actin/myosin cytoskeletal network, ROCK1 and ROCK2 are not redundant signaling molecules and may serve different functions within cells[11,12,13]. Recent research has uncovered additional roles for ROCK signaling, in conditions including autoimmune disease[14] aggravated or caused by a Th17-polarized T cell response and pulmonary fibrosis[15]. Rho guanosine triphosphate (GTP)ase-mediated signaling pathways play a central role in coordinating and balancing T cell mediated immune responses, including T cell receptor-mediated signaling, cytoskeletal reorganization, and the acquisition of the appropriate T cell effector program[16].

Studies have demonstrated that aberrant activation of ROCK2 leads to induction of interleukin (IL)-17 and IL-21 via interferon regulatory factor 4 (IRF4)-dependent mechanism [17]. In addition, ROCK activity was found to be up-regulated in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus[18], and inhibition of ROCK2 effectively decreased IL-17 production in vivo and demonstrated efficacy in arthritis and lupus mouse models. Autoimmunity also involves alterations to regulatory T cells that suppress activation of the immune system and play a critical role in maintaining immunological tolerance to self-antigens and inhibiting autoimmune responses [19]. ROCK2 inhibition may increase the suppressive function of regulatory T cells. Therefore, specific inhibition of ROCK2 is used in the treatment of autoimmune diseases.

1.3 BN101/belumosudil Non-clinical study

Kadmon Corpration, LLC. (hereinafter referred to as Kadmon) has now completed a non-clinical evaluation of BN101/belumosudil(i.e., KD025[1]), summarized as follows.

Non-clinical pharmacological studies suggest that BN101/belumosudil may be of therapeutic benefit in a variety of indications, particularly for autoimmune and fibrotic diseases. In vitro, BN101/belumosudil has demonstrated an impact on the T-helper 17 (Th17) as well as on the actin/myosin cytoskeletal network and collagen formation. In vivo, BN101/belumosudil has demonstrated efficacy in a variety of clinically relevant animal models of disease including

[1] The former code for BN101 was KD025, and since the code used for the overseas clinical trial was KD025, the use of the former code KD025 has been retained for parts of this protocol.

cGVHD, diffuse cutaneous systemic sclerosis (dcSSc), idiopathic pulmonary fibrosis (IPF), and other autoimmune diseases.

BN101/belumosudil plasma exposures in nonclinical animal species generally increased with dose, were dose proportional or greater than dose proportional, and showed some accumulation. The elimination half-life of belumosudil was variable in nonclinical studies with values of approximately 2 hours in mouse, 1-7 hours in rat and rabbit, and 1-3 hours in dog. BN101/belumosudil undergoes first pass metabolism in all evaluated species after oral administration to form a ROCK2 active metabolite, BN101/belumosudil m1(minor human metabolite), and a metabolite that is relatively less active against ROCK2, BN101/belumosudil m2(major human metabolite).

Distribution studies demonstrated BN101/belumosudil distribution primarily into tissues associated with elimination (GI, liver, kidney, urinary bladder), adrenal gland, and exocrine glandular tissue. BN101/belumosudil has some affinity for melanin. BN101/belumosudil excretion was via the faecal route (~90%). BN101/belumosudil and BN101/belumosudil m1 are > 99% bound to human, dog and rat plasma proteins; BN101/belumosudil m2 is > 99% bound to human plasma protein.

Based on in-vitro assessment, CYP3A4 and CYP1A2 were the predominant CYP isoforms responsible for the metabolism of BN101/belumosudil.

GLP-compliant rat and dog general toxicology/toxicokinetic studies of acute, subchronic (1 and 3 month), and chronic (6-month rat and 9-month dog) duration have been completed. The primary nonclinical toxicology finding at/near clinically relevant exposures were limited to changes in the cardiovascular (BP lowering), hepatic (transaminitis, hypertrophy/increased organ weight, and cholestasis/inflammation), renal (increased BUN, tubular changes, pigmentation, intracellular protein droplets in the epithelium), GI (decreased appetite), and hematopoietic/immunologic (anemia with regeneration and thymic/splenic lymphoid depletion) systems. Safety pharmacology studies [including human ether-à-go go related gene (hERG) (in vitro), central nervous system (rat), respiratory system (rat), and cardiovascular system (dog)] demonstrated a low likelihood of adverse and/or non-monitorable central nervous system, respiratory, or cardiovascular system effects associated with BN101/belumosudil at clinically relevant exposure levels. Embryo-fetal toxicology (rats and rabbits) and fertility (rats) studies showed that BN101/belumosudil demonstrated embryo-fetal toxicity/teratogenicity as well as reduced male fertility (reduced fertility index/sperm concentration/motility and increased abnormal sperm percentage; testes/epididymis (decreased organ weights and degenerative histopathology). Male fertility findings were generally at higher then clinically relevant exposures. In addition, there was no evidence of genotoxicity in the in vitro Bacterial Reverse Mutation Assay, the in vitro Mammalian Chromosome Aberration Test, or the in vivo

Mammalian Erythrocyte Micronucleus Test mutagenicity assay.

For more information about the BN101/belumosudil nonclinical study see the Investigator's Brochure.

1.4 Overseas clinical studies of BN101/belumosudil

The former code for BN101 was KD025, and since the code used for the overseas clinical trial was KD025, the use of the former code KD025 has been retained for parts of this protocol.

To date, 11 clinical studies of BN101/belumosudil have been completed in foreign countries:

- 8 Phase 1 studies (SLx-2119-09-01、KD025-101、KD025-102、KD025-103、KD025-105、KD025-106、KD025-107and KD025-108) designed to determine the safety, tolerability, and PK of escalating single- and multiple-oral doses of BN101/belumosudil in healthy male and/or post-menopausal female subjects, the potential for drug-drug interactions, and Bioavailability and metabolites of BN101/belumosudil.
- 3 Phase 2 studies in subjects with psoriasis vulgaris(KD025-205、KD025-206 and KD025-211).

In addition, there are 2 phase I studies and 4 ongoing Phase II clinical studies abroad:

- phase 1 PK study of normal liver function and varying degrees of hepatic impairment (KD025-109).
- Phase 1 study to investigate the effects of BN101/belumosudil on QTc interval (KD025-110)
- Phase 2 Idiopathic pulmonary fibrosis (KD025-207).
- Phase 2 Diffuse cutaneous systemic sclerosis (KD025-209).
- Phase 2 Chronic graft versus host disease (KD025-208 and KD025-213).

1.4.1 Pharmacokinetics

Final PK data are presented for all eight completed Phase 1 studies in healthy volunteers (Studies SLx-2119-09-01、KD025-101、KD025-102、KD025-103、KD025-105、KD025-106、KD025-107 and KD025-108) and the Phase 2 studies in patients with psoriasis vulgaris (KD025-205、KD025-206).

A total of 215 healthy volunteers (210 male and 5 female) were exposed to a single- or multiple-doses of BN101/belumosudil for a duration up to 28 days, with doses ranging from 20 mg QD to 1000 mg QD to 500 mg BID. The study drug administered in these studies consisted of capsules or tablets.

BN101/belumosudil was the main analyte detected in all clinical studies, time to peak plasma concentration (T_{max}) is 1-6 hours. C_{max} and AUC increases slightly greater than dose proportionate over the 20 to 500 mg QD range, and less than dose proportionate for doses > 500 mg. After a single

oral dose of 200 mg BN101/belumosudil tablets, the absolute bioavailability of BN101/belumosudil [AUC based on the AUC from initiation of administration to the imputed infinite time (AUC_{inf})] is 64%, it is distributed to the tissues, with an elimination half-life ($T_{1/2}$) of ~7 hours, and the major routes of elimination are the bile and/or the intestine. Little accumulation of BN101/belumosudil has been observed after multiple dosing.

Two metabolites, BN101/belumosudil m1 and BN101/belumosudil m2, rapidly appeared in plasma and were readily eliminated. A major metabolite, BN101/belumosudil m2, was detected at C_{max} levels ~20% that of parent and AUC ~15% that of parent. A minor metabolite, BN101/belumosudil m1, was detected at C_{max} levels < 5% of parent and AUC ~2% parent. C_{max} of and exposure to both metabolites increased with dose. Little to no accumulation of BN101/belumosudil m2 or BN101/belumosudil m1 was observed after multiple doses of BN101/belumosudil.

Plasma systemic exposure (C_{max} and AUC) of BN101/belumosudil was approximately 2-3–fold higher under the fed state compared with the fasted state. As such, it was determined that BN101/belumosudil should be taken with food or within 5 minutes of eating.

The results of the drug interaction study (KD025-107) suggest that CYP3A4 is likely to play a major role in the metabolism of BN101/belumosudil to its metabolites BN101/belumosudil m2 and BN101/belumosudil m1. While no meaningful effect of itraconazole on the PK of belumosudil was noted, a decrease in exposure in both metabolites was observed. Co-administration with rifampicin resulted in decreased exposure of belumosudil and BN101/belumosudil m2 (belumosudil C_{max} and AUC geometric mean ratio [GMR] of 0.28 and 0.45), but an increase in exposure of BN101/belumosudil m1 (C_{max} and AUC GMR of 2.3 and 2.5, respectively). Geometric mean t½ values decreased from 7.89 to 2.17 hours for belumosudil alone and co-administered with rifampicin, respectively.

A delay in absorption was observed when belumosudil was co-administered with a moderate or strong PPI. Exposure of both the parent and associated metabolites decreased significantly when administered with either PPI (Geometric mean ratios of C_{max} and AUC ranged from 0.27 to 0.69 in combination with omeprazole [coadministered with omeprazole: BN101/belumosudil monotherapy] and from 0.06 to 0.18 in combination with rabeprazole [coadministered with rabeprazole: BN101/belumosudil monotherapy]).The above results suggest a continued focus on the use of CYP3A4 inducers and proton pump inhibitors and their clinical relevance in clinical studies of BN101/belumosudil.

1.4.2 Efficacy

BN101/belumosudil is currently in clinical development in the United States in multiple immune

disease areas, as described in Section 1.4, for indications including cGVHD, psoriasis, idiopathic pulmonary fibrosis and diffuse cutaneous systemic sclerosis.Clinical trials of BN101/belumosudil for the treatment of chronic graft-versus-host disease have been implemented primarily in the United States, with a total of two clinical trials (KD025-208 and KD025-213).

KD025-208 is an Phase 2a, dose-escalation, open-label study to evaluate the safety, tolerability, and activity of BN101/belumosudil in subjects with cGVHD who have already received 1-3 prior lines of therapy. Of these subjects, 50% had cGVHD involving at least 4 organs and 67% had received ⩾2 lines of prior systemic therapy.Kadmon and the U.S. FDA held a Type B meeting in May 2018, and based on the preliminary clinical data from study KD025-208 and the current status of treatment for cGVHD, the U.S. FDA agreed to Kadmon's Phase II, open, randomized, multicenter study KD025-213 as a registrational clinical trial and file an NDA after combining the data from other completed clinical studies in aggregate. And subsequently granted Breakthrough Therapy Designation status to BN101/belumosudil for cGVHD in October 2018.On July 16, 2021, the U.S. FDA approved the marketing of BN101/belumosudil for the treatment of pediatric patients with chronic graft-versus-host disease (cGVHD) who have failed prior treatment with at least 2 systemic therapies (age⩾12 years) and adult patients.

BN101/belumosudil in study KD025-208 showed encouraging efficacy, with ORRs of 65%, 69%, and 62% as of February 19, 2020 from Cohort 1 (200 mg QD, N = 17), Cohort 2 (200 mg BID, N = 16), and Cohort 3 (400 mg QD, N = 21), respectively, with complete response (CR) was observed in all organs and overall severity (GSR), except in the lungs, where only partial response (PR) was observed. Also, efficacy was durable, with a Kaplan-Meier estimated median duration of response (DOR) of 35 weeks (8 months) and a median failure-free survival (FFS) of 10.7 months in the mITT response subject population. 65% of the subjects had achieved dose reductions in corticosteroid use, with 17% of them completely discontinuing systemic corticosteroid therapy while receiving BN101/belumosudil. Improvement in Lee Symptom Scale scores was reported in 53%, 44%, and 52% of subjects in these 3 cohorts, respectively.

KD025-213 is a registrational clinical trial with subjects still in follow-up, a Phase II, open, randomized, multicenter study designed to evaluate the efficacy and safety of BN101/belumosudil in subjects with cGVHD who have undergone at least 2 lines of prior systemic therapy. Subjects were randomly assigned to two different BN101/belumosudil dose groups, Group A: BN101/belumosudil 200 mg QD and Group B: BN101/belumosudil 200 mg BID, with either group meeting the endpoints established by the study considered a positive result. The study assumed an expected target ORR of 55%, with more than 90% certainty that the lower limit of the 95% confidence interval (CI) for the

ORR would be greater than 30%, and that approximately 63 patients would be required in each group, and that the actual subjects enrolled in the trial would be 66 in each group. As of February 19, 2020 (6 months after enrollment of the last subject), the ORR in the 200 mg QD group was 72.7% (95% CI: 60.4, 83.0), CR was 4.5%, and PR was 68.2%; in the 200 mg BID group, the ORR was 74.2% (95% CI: 62.0, 84.2), CR was 1.5%, and PR was 72.7%; ORR for all subjects was 73.5% (95% CI: 65.1, 80.8), CR was 3.0%, and PR was 70.5%. The median duration of response in the 200 mg QD group was 21.1 weeks (95% CI: 9.4, NA).The median time to first response in the 200 mg QD group was 4.4 weeks (95% CI: 3.7, 40.6). Response was observed in all key subgroups.

1.4.3 Safety

As of 19 February 2020, more than 600 individuals have been dosed with BN101/belumosudil as participants of Phase 1 and 2 Kadmon sponsored studies, includes healthy volunteers and patients with immune or fibrotic diseases taking BN101/belumosudil in doses ranging from 20 to 1000 mg QD and 500 mg BID.

Phase I studies completed in 8 healthy volunteers showed that BN101/belumosudil was well tolerated and showed an acceptable safety profile across the 20mg-1000mg QD dose range. Very few SAEs occurred and none were associated with BN101/belumosudil. One case was an ankle fracture, while the two SAEs were caused by moderate hepatic injury from the subjects' underlying disease. Elevated liver function tests were reported, but all were mild to moderate and recovered upon discontinuation of study drug. Some infectious events, including upper respiratory tract infections, were also reported.

Analysis of Phase 2 safety data from subjects with cGVHD, IPF, and psoriasis suggests an acceptable, manageable safety profile for belumosudil. Overall, treatment-emergent AEs (TEAEs) have generally been consistent with those expected in the populations enrolled in each of the studies, the summarized TEAEs are shown in Table 1.

Refer to the Investigator's Brochure for details of the BN101/belumosudil clinical PK, efficacy and safety summary.

Table 1 Treatment Emergent Adverse Events Occurring in ⩾5% of Subjects at Any Dose Level in Studies of cGVHD (KD025-208 and KD025-213), IPF (KD025-207) or Psoriasis (KD025-205, KD025-206, and KD025-211) by System Organ Class and Preferred Term (Safety Population)

Note: In view of small sample sizes, data across all doses of belumosudil in psoriasis studies is pooled.

	Number (%) of Subjects							
	cGVHD				IPF		Psoriasis	
System Organ Class Preferred Term	Total N = 186	200 mg QD N = 83	200 mg BID N = 82	400 mg QD N = 21	400 mg QD N = 68	BSC N = 24	BN101/belumosudil N = 148	Placebo N = 18
Subjects with at least one TEAE	183 (98.4%)	82 (98.8%)	81 (98.8%)	20 (95.2%)	67 (98.5%)	18 (75.0%)	97 (65.5%)	9 (50.0%)
Gastrointestinal disorders	126 (67.7%)	56 (67.5%)	54 (65.9%)	16 (76.2%)	31 (45.6%)	5 (20.8%)	29 (19.6%)	0
Diarrhoea	57 (30.6%)	27 (32.5%)	23 (28.0%)	7 (33.3%)	17 (25.0%)	0	7 (4.7%)	0
Nausea	52 (28.0%)	23 (27.7%)	21 (25.6%)	8 (38.1%)	7 (10.3%)	3 (12.5%)	11 (7.4%)	0
Vomiting	33 (17.7%)	18 (21.7%)	11 (13.4%)	4 (19.0%)	3 (4.4%)	0	8 (5.4%)	0
Abdominal pain	22 (11.8%)	10 (12.0%)	8 (9.8%)	4 (19.0%)	2 (2.9%)	0	0	0
Dysphagia	18 (9.7%)	12 (14.5%)	4 (4.9%)	2 (9.5%)	1 (1.5%)	1 (4.2%)	0	0
Constipation	17 (9.1%)	8 (9.6%)	6 (7.3%)	3 (14.3%)	4 (5.9%)	0	2 (1.4%)	0
Dry mouth	13 (7.0%)	8 (9.6%)	5 (6.1%)	0	1 (1.5%)	0	1 (0.7%)	0
Infections and infestations	116 (62.4%)	53 (63.9%)	48 (58.5%)	15 (71.4%)	34 (50.0%)	9 (37.5%)	37 (25.0%)	2 (11.1%)
Upper respiratory tract infection	56 (30.1%)	24 (28.9%)	25 (30.5%)	7 (33.3%)	7 (10.3%)	4 (16.7%)	5 (3.4%)	1 (5.6%)
Pneumonia	17 (9.1%)	9 (10.8%)	8 (9.8%)	0	7 (10.3%)	0	1 (0.7%)	0
Influenza	11 (5.9%)	3 (3.6%)	7 (8.5%)	1 (4.8%)	3 (4.4%)	0	4 (2.7%)	0
Respiratory, thoracic and mediastinal disorders	109 (58.6%)	49 (59.0%)	46 (56.1%)	14 (66.7%)	45 (66.2%)	13 (54.2%)	9 (6.1%)	1 (5.6%)
Dyspnea	46 (24.7%)	22 (26.5%)	17 (20.7%)	7 (33.3%)	19 (27.9%)	4 (16.7%)	0	0
Cough	44 (23.7%)	20 (24.1%)	17 (20.7%)	7 (33.3%)	13 (19.1%)	8 (33.3%)	1 (0.7%)	0
Productive cough	19 (10.2%)	9 (10.8%)	9 (11.0%)	1 (4.8%)	3 (4.4%)	2 (8.3%)	0	0
Nasal congestion	18 (9.7%)	10 (12.0%)	7 (8.5%)	1 (4.8%)	1 (1.5%)	0	0	0
Hypoxia	12 (6.5%)	5 (6.0%)	3 (3.7%)	4 (19.0%)	1 (1.5%)	0	0	0
General disorders and administration site conditions	105 (56.5%)	49 (59.0%)	41 (50.0%)	15 (71.4%)	24 (35.3%)	3 (12.5%)	7 (4.7%)	0
Fatigue	61 (32.8%)	32 (38.6%)	20 (24.4%)	9 (42.9%)	11 (16.2%)	1 (4.2%)	3 (2.0%)	0
Oedema peripheral	41 (22.0%)	20 (24.1%)	15 (18.3%)	6 (28.6%)	6 (8.8%)	0	1 (0.7%)	0
Pyrexia	25 (13.4%)	14 (16.9%)	8 (9.8%)	3 (14.3%)	1 (1.5%)	0	2 (1.4%)	0
Musculoskeletal and connective tissue disorders	93 (50.0%)	42 (50.6%)	38 (46.3%)	13 (61.9%)	24 (35.3%)	5 (20.8%)	12 (8.1%)	0
Muscle spasms	30 (16.1%)	13 (15.7%)	11 (13.4%)	6 (28.6%)	5 (7.4%)	2 (8.3%)	0	0

System Organ Class Preferred Term	Number (%) of Subjects							
	cGVHD				IPF		Psoriasis	
	Total N = 186	200 mg QD N = 83	200 mg BID N = 82	400 mg QD N = 21	400 mg QD N = 68	BSC N = 24	BN101/belumosudil N = 148	Placebo N = 18
Arthralgia	24 (12.9%)	11 (13.3%)	8 (9.8%)	5 (23.8%)	4 (5.9%)	0	4 (2.7%)	0
Pain in extremity	19 (10.2%)	8 (9.6%)	7 (8.5%)	4 (19.0%)	2 (2.9%)	0	0	0
Back pain	13 (7.0%)	6 (7.2%)	7 (8.5%)	0	7 (10.3%)	2 (8.3%)	3 (2.0%)	0
Muscular weakness	12 (6.5%)	7 (8.4%)	3 (3.7%)	2 (9.5%)	3 (4.4%)	0	0	0
Myalgia	11 (5.9%)	5 (6.0%)	3 (3.7%)	3 (14.3%)	1 (1.5%)	0	0	0
Investigations	89 (47.8%)	39 (47.0%)	38 (46.3%)	12 (57.1%)	26 (38.2%)	3 (12.5%)	33 (22.3%)	3 (16.7%)
Gamma-glutamyltransferase increased	22 (11.8%)	9 (10.8%)	13 (15.9%)	0	6 (8.8%)	1 (4.2%)	0	1 (5.6%)
Alanine aminotransferase increased	21 (11.3%)	10 (12.0%)	9 (11.0%)	2 (9.5%)	10 (14.7%)	1 (4.2%)	11 (7.4%)	1 (5.6%)
Aspartate aminotransferase increased	20 (10.8%)	10 (12.0%)	9 (11.0%)	1 (4.8%)	8 (11.8%)	0	7 (4.7%)	1 (5.6%)
Blood alkaline phosphatase increased	14 (7.5%)	8 (9.6%)	6 (7.3%)	0	1 (1.5%)	0	0	0
Blood creatinine increased	14 (7.5%)	4 (4.8%)	8 (9.8%)	2 (9.5%)	3 (4.4%)	1 (4.2%)	1 (0.7%)	0
Weight decreased	11 (5.9%)	5 (6.0%)	4 (4.9%)	2 (9.5%)	2 (2.9%)	0	0	0
Metabolism and nutrition disorders	77 (41.4%)	37 (44.6%)	29 (35.4%)	11 (52.4%)	13 (19.1%)	2 (8.3%)	8 (5.4%)	2 (11.1%)
Hyperglycaemia	26 (14.0%)	11 (13.3%)	12 (14.6%)	3 (14.3%)	3 (4.4%)	0	1 (0.7%)	0
Decreased appetite	20 (10.8%)	12 (14.5%)	4 (4.9%)	4 (19.0%)	5 (7.4%)	0	0	0
Dehydration	12 (6.5%)	6 (7.2%)	4 (4.9%)	2 (9.5%)	2 (2.9%)	0	1 (0.7%)	0
Hyperkalaemia	12 (6.5%)	5 (6.0%)	4 (4.9%)	3 (14.3%)	0	0	0	0
Hypokalaemia	11 (5.9%)	6 (7.2%)	5 (6.1%)	0	0	0	1 (0.7%)	0
Hypophosphataemia	10 (5.4%)	5 (6.0%)	4 (4.9%)	1 (4.8%)	0	0	0	0
Nervous system disorders	74 (39.8%)	30 (36.1%)	35 (42.7%)	9 (42.9%)	24 (35.3%)	4 (16.7%)	16 (10.8%)	0
Headache	40 (21.5%)	15 (18.1%)	19 (23.2%)	6 (28.6%)	3 (4.4%)	1 (4.2%)	9 (6.1%)	0
Dizziness	12 (6.5%)	3 (3.6%)	7 (8.5%)	2 (9.5%)	7 (10.3%)	1 (4.2%)	3 (2.0%)	0
Neuropathy peripheral	10 (5.4%)	4 (4.8%)	5 (6.1%)	1 (4.8%)	0	0	0	0
Skin and subcutaneous tissue disorders	72 (38.7%)	31 (37.3%)	33 (40.2%)	8 (38.1%)	10 (14.7%)	3 (12.5%)	12 (8.1%)	2 (11.1%)
Pruritus	16 (8.6%)	6 (7.2%)	10 (12.2%)	0	3 (4.4%)	0	6 (4.1%)	1 (5.6%)
Injury, poisoning and procedural complications	58 (31.2%)	30 (36.1%)	22 (26.8%)	6 (28.6%)	16 (23.5%)	3 (12.5%)	21 (14.2%)	1 (5.6%)
Contusion	18 (9.7%)	10 (12.0%)	5 (6.1%)	3 (14.3%)	1 (1.5%)	0	2 (1.4%)	0
Fall	18 (9.7%)	8 (9.6%)	9 (11.0%)	1 (4.8%)	4 (5.9%)	1 (4.2%)	2 (1.4%)	0

System Organ Class Preferred Term	Number (%) of Subjects							
	cGVHD				IPF		Psoriasis	
	Total N = 186	200 mg QD N = 83	200 mg BID N = 82	400 mg QD N = 21	400 mg QD N = 68	BSC N = 24	BN101/belumosudil N = 148	Placebo N = 18
Vascular disorders	56 (30.1%)	25 (30.1%)	26 (31.7%)	5 (23.8%)	7 (10.3%)	2 (8.3%)	4 (2.7%)	0
Hypertension	31 (16.7%)	15 (18.1%)	12 (14.6%)	4 (19.0%)	2 (2.9%)	0	3 (2.0%)	0
Psychiatric disorders	34 (18.3%)	13 (15.7%)	15 (18.3%)	6 (28.6%)	12 (17.6%)	1 (4.2%)	9 (6.1%)	0
Depression	12 (6.5%)	2 (2.4%)	7 (8.5%)	3 (14.3%)	3 (4.4%)	0	3 (2.0%)	0
Anxiety	11 (5.9%)	4 (4.8%)	5 (6.1%)	2 (9.5%)	7 (10.3%)	0	1 (0.7%)	0
Insomnia	10 (5.4%)	6 (7.2%)	2 (2.4%)	2 (9.5%)	5 (7.4%)	0	2 (1.4%)	0
Renal and urinary disorders	34 (18.3%)	15 (18.1%)	15 (18.3%)	4 (19.0%)	6 (8.8%)	1 (4.2%)	4 (2.7%)	0
Acute kidney injury	11 (5.9%)	3 (3.6%)	7 (8.5%)	1 (4.8%)	0	0	0	0
Blood and lymphatic system disorders	30 (16.1%)	13 (15.7%)	13 (15.9%)	4 (19.0%)	7 (10.3%)	1 (4.2%)	1 (0.7%)	0
Anaemia	21 (11.3%)	10 (12.0%)	11 (13.4%)	0	2 (2.9%)	1 (4.2%)	0	0

Abbreviations: BID=twice daily; BSC=best supportive care; cGVHD=chronic graft versus host disease; IPF=Idiopathic pulmonary fibrosis; QD=once daily.

1.5 BN101-101 Study

BN101-101 is a randomized, double-blind phase I clinical study conducted in Chinese healthy volunteers to evaluate the tolerability, safety and pharmacokinetic (PK) profile of different dose levels of BN101/belumosudil administered as a single dose in healthy volunteers. A total of 2 study cohorts were enrolled: cohort 1 (BN101/belumosudil or placebo 200 mg single oral dose) and cohort 2 (BN101/belumosudil or placebo 400 mg single oral dose). A total of 85 subjects were screened for this study; 24 subjects were enrolled in the study and underwent randomization, 23 received study drug administration, 23 completed the study, and 1 subject withdrew early due to an adverse event prior to drug administration. Eleven subjects in cohort 1 received study medication and completed the study, of which 8 received BN101 and 3 received placebo; 12 subjects in cohort 2 received study medication and completed the study, of which 9 received BN101 and 3 received placebo.

The 23 subjects included in the modified intention to treat analysis set (mITT) had a mean (range) age of 31.7 (20-43) years, 73.9% were male and 26.1% were female, a mean (range) body weight of 62.76 (49.4-78.5) kg, and a mean (range) BMI of 22.13 (19.5-23.9) kg/m^2.

A total of 4 (17.4%, 4/23) subjects reported 4 TEAEs during the study period; PTs reported by subjects receiving BN101 included: decreased body mass index, positive urine leukocytes, and elevated blood triglycerides (1 subject each, 5.9%); PTs reported by subjects receiving placebo included: abnormal electrocardiogram T waves (1 subject, 16.7%). All TEAEs were grade 1, and no subject had a grade 2 or higher TEAE.

No serious adverse events or deaths were reported during the study period, and no subjects withdrew early from the study due to AE. No clinically significant laboratory test abnormalities were noted during the study period, with the exception of positive urine leukocytes and elevated blood triglycerides (1 subject each receiving BN101, 5.9%). No subject was found to have a QTcF interval value of $\geqslant$450 ms or a QT interval of $\geqslant$480 ms, and no subject had a change in QTcF interval from baseline of $\geqslant$30 ms after dosing. Overall, BN101 was well tolerated as a single dose at 200 mg and 400 mg, and no unintended safety events were observed. Overall, BN101 has a favorable safety profile in healthy Chinese subjects.

The PK parameters of plasma BN101 in the subjects are shown in Table 2. BN101 was rapidly absorbed after a single oral dose, peaking at a median of 1.5 hours (range: 0.5-2.0 hours); the elimination half-life was highly variable, with a median elimination half-life of 10.35 hours and 8.92 hours at the 200 mg dose and 400 mg dose, respectively. Overall, the AUC_{0-24} of BN101 increased slightly with dose, but was lower than dose proportionality, with a mean AUC_{0-24} of 9040.44 ng*h/mL at the 200 mg dose and 9984.00 ng*h/mL at the 400 mg dose, respectively.The C_{max} was similar in the

2 dose cohorts, with a mean C_{max} of 2355.02 ng*h/mL at the 200 mg dose and 2355.02 ng*h/mL at the 400 mg dose, respectively.

Table 2 Plasma BN101/belumosudil pharmacokinetic parameters-PK analysis set

Treatment group	Statistic	PK Parameters				
		AUC_{0-24} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	C_{max} (ng/mL)	$T_{1/2}$ (h)	T_{max} (h)
BN101 200mg (N=8)	Median	6883.41	7635.11	2204.59	10.35	1.50
	Minimum	4057.36	4490.96	976.96	2.13	0.5
	Maximum	18074.16	19561.24	4265.25	48.01	2.0
	Arithmetic mean	9040.44	10055.32	2355.02	14.28	/
	Coefficient of variation	58.64	59.39	45.53	103.52	/
BN101 400mg (N=9)	Median	8120.87	10264.37	2181.44	8.92	1.50
	Minimum	4426.67	4837.27	941.48	3.85	0.5
	Maximum	19691.89	20375.86	3939.14	28.69	2.0
	Arithmetic mean	9984.00	10981.49	2315.84	11.80	/
	Coefficient of variation	56.21	51.12	48.25	69.22	/

N is the number of subjects entering the analysis set in each group.

1.6 Rationale for the design of this study

As BN101/belumosudil has completed clinical development for cGVHD in the U.S., the registration study (KD025-213) met clinical endpoints and supported the conclusion that benefits outweighed risks. A rolling submission NDA for the cGVHD indication based on this study was also completed at the end of November 2020 and was fully approved by the FDA on July 16, 2021 in the United States. Given the global development status of BN101/belumosudil in the cGVHD indication, and based on the recommendation of the NMPA, we first conducted a PK bridging clinical trial in healthy volunteers to initially assess the safety, drug exposure and metabolites of BN101/belumosudil in healthy individuals to determine the BN101/ belumosudil starting dose and PK profile. Given that the PK bridging clinical trial in healthy volunteers has been substantially completed and met the bridging objective, the Sponsor currently plans to conduct a bridging study to evaluate the efficacy, safety and PK characteristics of BN101/belumosudil for the treatment of Chinese patients with cGVHD. This bridging study is an open, single-arm trial in Chinese patients with cGVHD, and because it is designed for bridging purposes, the sample size is not determined by statistical assumptions.

This study is planned to enroll 30 patients with cGVHD who have undergone at least 1 but not more than 5 lines of systemic therapy. Considering that the recommended dose of both cGVHD clinical trials in Western populations was 200 mg QD and the highest administered dose of BN101/belumosudil in the phase I dose-escalation study reached 1000 mg QD/500 mg BID and

was well tolerated, combined with the pharmacokinetic profile of 200 mg orally in the phase I study in Chinese healthy volunteers was consistent with the results in the overseas study, without any TEAE associated with the investigational drug, the starting dose of this cGVHD bridging clinical trial was also set at 200 mg QD.

2. STUDY OBJECTIVES/PRUPOSE

Primary Objective：

- To evaluate the efficacy and safety of BN101/belumosudil in subjects with cGVHD who had previously been treated with at least 1 prior line of systemic therapy.

Secondary Objectives

- To evaluate the PK profile of BN101/belumosudil in subjects with cGVHD who had previously been treated with at least 1 prior line of systemic therapy;
- To evaluate other efficacy endpoints of BN101/belumosudil in subjects with cGVHD who had previously been treated with at least 1 prior line of systemic therapy.

Exploratory Objective

- To evaluate changes in the Patient-Reported Outcomes (PRO) Measurement Information System (PROMIS) Global Health sub-scores of physical and mental functioning.

3. STUDY POPULATION

3.1 Inclusion Criteria

Subjects who met all of the following conditions could be enrolled in the study:

(1) Male or female subjects aged ≥ 18 years who have had allogeneic hematopoietic stem cell transplant (allo-HSCT).

(2) Have persistent cGVHD manifestations and systemic therapy is indicated.

(3) Previously received at least 1 and not more than 5 lines of systemic therapy for cGVHD[2].

(4) Receiving glucocorticoid therapy with a stable dose over the 2 weeks prior to screening; or 4 weeks of prednisone or equivalent doses of other corticosteroids at doses > 0.5 mg/kg/day with persistent manifestations of cGVHD and no improvement; or 2 attempts to reduce the hormone to a lower

[2] The following approach should be used when documenting prior cGVHD treatment：

- The initiation of one or more new systemic therapies for cGVHD will be considered the initiation of a new first-line treatment
  - If multiple medications are intended to be initiated at the same time, the dates of initiation of treatment with different medications may be spaced up to 4 weeks apart due to schedule delays or medication availability
- Topical medications are not considered a line of therapy

dose level fail and the prednisone dose still needs to be increased to > 0.25 mg/kg/day or an equivalent dose.

(5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score: 0 to 1.

(6) Life expectancy of more than 12 months.

General Criteria

(7) Female subjects of childbearing potential have a negative serum 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.

(8) 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：

- Intra-uterine contraceptive device plus 1 barrier method；
- Stable doses of hormonal contraception (e.g., oral, injectable, subcutaneously implanted, transdermal) for at least 3 months plus 1 barrier method；
- Two 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.

(9) For male subjects who are sexually active and who are partners of females of childbearing potential: must agree to use 2 recognized methods of contraception during the treatment period and for 3 months after the last dose of study drug (see criterion 8 above).

(10) Subject (or the subject's legally authorized representative) must be fully informed of the study contents and is able to provide written ICF prior to any study-specific procedures, and is willing to follow the treatment regimen and visit schedule.

3.2 Exclusion Criteria

Subjects who met **any** of the following conditions would be excluded from the study：

(1) Received a systemic investigational cGVHD treatment within 28 days of study entry, but prior treatment is allowed with a washout of at least 28 days or 5 half-lives.[Note: Corticosteroids, CNIs, sirolimus, mycophenolate mofetil (MMF), methotrexate, azathioprine, and *in vitro* photochemotherapy (ECP) are acceptable and subjects must have been on a stable dose/regimen of these for at least 2 weeks prior to screening].

(2) Recurrence of hematologic tumor (according to criteria for recurrence of the corresponding primary hematologic tumor) or post-transplant lymphoproliferative disease at screening.

(3) Current treatment with ibrutinib (except for ibrutinib with a washout of at least 28 days prior to the first dose of the investigational product).

Laboratory Tests

(4) Absolute neutrophil count (ANC) < 1.5×10^9/L.

(5) Platelet count < 50×10^9/L.

(6) Alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN), aspartate aminotransferase (AST) > 3 × ULN

(7) Total bilirubin (TBIL) > 1.5 × ULN.

(8) Creatinine clearance (CrCl) < 60 mL/min (Cockcroft-Gault formula).

General Criteria

(9) Pregnant or lactating women.

(10) History of severe illness, 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

- History of severe [New York Heart Association (NYHA) functional class III or IV] cardiovascular disorder, including but not limited to ventricular arrhythmias requiring clinical intervention, uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg); unstable angina pectoris, acute coronary syndrome, congestive cardiac failure, stroke, or other ≥ Grade 3 cardiac events within 6 months prior to enrollment; and NYHA functional class ≥ II or left ventricular ejection fraction (LVEF) < 50% by cardiac ultrasound at screening.
- Inability to take oral medications, severe (NCI CTCAE v5.0≥ Grade 3) chronic gastrointestinal dysfunction, malabsorption syndrome, or any other condition that affects gastrointestinal absorption.
- History of clear neurological or mental disorders (including epilepsy or dementia), current mental disorders, or poor compliance that rendered the subject ineligible for participation in the study as judged by the investigator.
- History of other serious (NCI CTCAE v5.0≥ Grade 3) systemic disease that rendered the subject ineligible for participation in the clinical trial as judged by the investigator.

(11) Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or human immunodeficiency virus (HIV) infection. [Note: Active HBV infection is defined as positive for serum hepatitis B virus surface antigen (HBsAg) and/or hepatitis B virus e antigen (HBeAg), or HBV-DNA; subjects with positive hepatitis B virus core antibody (anti-HBc)

should be confirmed for HBV-DNA, and subjects who are confirmed to be negative for HBV-DNA could be enrolled; active HCV infection is defined as positive for HCV-RNA, and subjects who are positive for hepatitis C virus antibody (HCV-Ab) could only be enrolled after confirmed to be negative for HCV-RNA. Positive is defined as ＞ the ULN].

(12) Diagnosed with another primary malignancy(other than malignancy for which allo-HSCT was performed) within 3 years of enrollment, with the exception of:

- Completely resected basal cell or squamous cell carcinoma of the skin;
- Surgically cured carcinoma in situ of the cervix;
- Resected breast ductal carcinoma in situ;
- Prostate cancer with Gleason score < 6 and stable prostate-specific antigen (PSA) over 12 months.

(13) Known allergy to the active ingredient or excipients of the investigational product, or any other selective ROCK2 inhibitors.

(14) Subjects requiring long-term proton pump inhibitors (e.g., rabeprazole, omeprazole) or CYP3A4 inducers (e.g., rifampin, phenobarbital).

(15) Prolongation of QT interval corrected by the Fridericia's formula (QTcF) of > 450 ms for males and > 470 ms for females at screening.

(16) Known alcohol or drug dependence.

(17) Forced expiratory volume in 1 second (FEV_1) ≤ 39% or pulmonary function score of 3 at screening.

(18) Treatment with any investigational agent, device, or procedure, within 28 days (or 5 half-lives, whichever is longer) prior to enrollment.

(19) Subjects considered unlikely to adhere to treatment and follow protocol in the opinion of the investigator.

3.3 Criteria for completion of study drug therapy and early termination of study drug therapy

Eligible subjects will be enrolled to receive BN101/belumosudil (every 28-day cycle) until cGVHD progression【Evaluated by the investigator based on the National Institutes of Health (NIH) Consensus Development Project on Criteria for Clinical Trials in cGVHD(2014) diagnosis and staging, and response criteria, hereinafter referred to as the NIH Consensus Criteria (2014)】, intolerable toxicity, initiation of a new cGVHD therapy, recurrence of hematological neoplasm (according to the recurrence criteria of the corresponding primary hematologic tumor), loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first.

For subjects assessed as "Lack of Response - Mixed" and "Lack of Response - Progression" (See

section 7.1.1, table 4) , if the investigator believed that these subjects could continue to benefit from treatment with BN101/belumosudil, the treatment may be continued after a written application was submitted, and approval from the Sponsor's Medical Director as well as documentation of the subject's willingness to continue treatment was obtained. In such cases, the rationale for continuing treatment must be clearly documented. In addition, "Lack of Response - Mixed" will be considered a progression event in the analysis of outcomes.

For subjects who did not achieve any response after 12 cycles of BN101/belumosudil treatment during the main study(the end of the main study is defined in section 3.5 of the main body), they should discontinue the investigational product treatment and withdraw from the study if they were judged by the investigator to have no clinical benefit (e.g., improvements in organ score, improvements in Lee symptom scores, reductions of corticosteroid/tacrolimus doses).

(1) Completion of study drug therapy

- Completion of study drug therapy as defined by the protocol;
- cGVHD disease progression during treatment;
- Death of the subject.

(2) Early termination of study drug therapy

Refers to the situation in which an enrolled subject becomes unfit to continue treatment with the study drug during the course of the study. Early termination of study drug treatment is defined as follows:

- Recurrence of the subject's hematologic tumor during the course of the trial (according to the criteria for recurrence of the corresponding primary hematologic tumor).
- The subject is discontinued due to an adverse event or serious adverse event that makes continuation of study drug treatment inappropriate; or the subject is discontinued due to an adverse event or serious adverse event for more than 14 days.
- The investigator determines that the subject's continued treatment with the study drug may pose a potential risk greater than benefit to the subject, including: pregnancy; enrollment in the study and discovery that the subject does not meet the study protocol inclusion criteria and that continued treatment with the study drug poses a risk greater than benefit to the subject; failure to follow the protocol or doctor's orders, unauthorized use of other treatments, or failure to take the medication in a timely manner and at a dosage that would interfere with the assessment of efficacy and increase potential safety risks.
- Subject withdraws informed consent/withdraws from the study.
- Subject lost to follow-up.

After discontinuation of study medication, subjects will undergo end-of-treatment visits and enter

a safety follow-up period (including a 28-day follow-up after the last dose and a long-term safety follow-up).

Subjects have the right to withdraw from the study at any stage of the study under the terms of informed consent, or to be "withdrawn" (or "dropped") from the study even if they do not explicitly withdraw from the study but no longer accept the study medication or the study evaluations. The reasons for withdrawal should be understood and documented to the extent possible, e.g., perceived intolerance of certain AEs associated with the study drug, other reasons for not being able to continue in the clinical study, or unexplained loss of visits.

(3) Treatment of withdrawn subjects

The investigator must complete the reason for the subject's withdrawal from the study on the electronic case report form (eCRF) and contact the subject to complete the evaluation program for the end-of-treatment visit (EOT) and safety follow-up (28 ± 7 days after the last dose of study drug or prior to initiation of a new treatment for systemic cGVHD) whenever possible, and keep records, documenting, whenever possible, the time of the subject's last dose of study drug. The eCRF should be retained for subjects who withdraw from the trial for whatever reason.

During the main study, after a subject terminates study treatment, the investigator must follow up on all pre-existing AEs and SAEs that occurred during the Safety Follow-Up Period [28 ± 7 days after the last dose of study drug or prior to initiation of new treatment for systemic cGVHD, whichever occurs first], report on new AEs and SAEs (whether or not related to the study drug) occurring during this period, with SAEs and AEs related to the study drug to be followed up until resolution of the AE and SAE, and until, in the investigator's opinion, the event is stabilized or irreversible. Any SAE is required to follow the SAE Reporting Procedures (see Section 8.6.2.2) and contact the sponsor in a timely manner.

3.4 Early Termination of the Study/Closure of the Research Center

The Sponsor has the right to terminate the Study at any time and the Sponsor and the Investigator have the right to close the Research Center at any time. This, of course, can only be carried out after mutual agreement. Termination of the study must be reported to the Institutional Review Board (IRB) and the Ethics Committee (EC). Upon early termination of the study or early closure of the research center, all study materials (except for documents that must be retained at the research center) must be returned to the sponsor. The investigator must retain other documents until notified of their destruction by the sponsor. Reasons for early termination of a trial or closure of a research center include, but are not limited to, the following reasons:

- New information leads to unfavorable risk/benefit judgments about the study drug, e.g., due to:

- lack of efficacy of the study drug, either in this or other studies; or
- other unfavorable safety findings, including clinical examination and non-clinical manifestations;

- In the opinion of the sponsor, continuation of the study is not justified for medical, ethical, or commercial reasons;
- It is unlikely that the study will be completed within an acceptable timeframe due to difficulties in enrolling subjects;
- Suspension or termination due to requirements of health/regulatory authorities.

3.5 End of study

Data lock and primary analysis will be performed 6 months after enrollment of the last subject. All subjects will continue to be followed up for an additional 6 months after the primary analysis as required by the protocol, i.e., the study will end 12 months after enrollment of the last subject, and a follow-up analysis will be performed at the end of the study. Subjects who have not yet experienced cGVHD progression at the end of the study, and in the judgment of the investigator, the benefits of continued dosing outweigh the risks, may submit a written request and, upon approval by the sponsor's Medical Director and documentation of the subject's willingness to continue the treatment, the sponsor will continue to provide BN101/belumosudil medication at no cost until cGVHD progression, intolerable toxicity, initiation of a new cGVHD therapy, recurrence of hematological neoplasm, loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first. If, in the judgment of the investigator, there is no evidence of clinical benefit, withdrawal from the study is required. Subjects who remain free of disease progression at the time of withdrawal from the study or who withdraw from the study for reasons other than adverse events should have the dose of BN101/belumosudil tapered every 2 weeks as required by the protocol (e.g., 200 mg QD → 200 mg QOD → discontinue treatment).

Serious adverse events (SAEs), study drug use, and subject survival will continue to be collected for subjects who continue to be free of charge while the study drug, BN101/belumosudil, is administered at the end of the study.

The study will end when all subjects stop taking the study drug (Unless terminated earlier for the reasons set forth in Section 3.4).

4. STUDY DESIGN

4.1 Type of study and design rationale

Trial Design：

This study is a multicenter, open, single-arm phase II clinical trial to enroll 30 patients with

cGVHD who have undergone at least 1 but not more than 5 lines of systemic therapy, to evaluate the efficacy, safety, and PK characteristics of BN101/belumosudil in Chinese patients with cGVHD.

Subjects who sign an EC-approved ICF with confirmed screening eligibility will be enrolled to receive BN101/belumosudil (every 28-day cycle). Concomitant use of other cGVHD treatments (e.g., corticosteroids, CNI, MMF, sirolimus, and ECP) that had been stabilized in dose/regimen prior to screening was permitted during the study period, but initiation of new systemic cGVHD treatments was not permitted. Efficacy assessments were performed on Day 1 of Cycles 2 to 5 and every 2 cycles thereafter (i.e., Day 1 of Cycles 2, 3, 4, 5, 7, 9, 11, etc.). For subjects assessed as "Lack of Response - Mixed" and "Lack of Response - Progression" (See section 7.1.1, table 4) , if the investigator believed that these subjects could continue to benefit from treatment with BN101/belumosudil, the treatment may be continued after a written application was submitted, and approval from the Sponsor's Medical Director as well as documentation of the subject's willingness to continue treatment was obtained. For subjects who did not achieve any response after 12 cycles of BN101/belumosudil treatment during the main study(the end of the main study is defined in section 3.5 of the main body), they should discontinue the investigational product treatment and withdraw from the study if they were judged by the investigator to have no clinical benefit (e.g., improvements in organ score, improvements in Lee symptom scores, reductions of corticosteroid/tacrolimus doses). Subjects who remain free of disease progression at the time of withdrawal from the study or who withdraw from the study for reasons other than adverse events should have the dose of BN101/belumosudil tapered every 2 weeks as required by the protocol (e.g., 200 mg QD → 200 mg QOD → discontinue treatment).

Data lock and primary analysis will be performed 6 months after enrollment of the last subject. All subjects will continue to be followed up for an additional 6 months after the primary analysis as required by the protocol, i.e., the study will end 12 months after enrollment of the last subject, and a follow-up analysis will be performed at the end of the study. Subjects who have not yet experienced cGVHD progression at the end of the study, and in the judgment of the investigator, the benefits of continued dosing outweigh the risks, the sponsor will continue to provide BN101/belumosudil medication at no cost until cGVHD progression, intolerable toxicity, initiation of a new cGVHD therapy, recurrence of hematological neoplasm, loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first.

Serious adverse events (SAEs), study drug use, and subject survival will continue to be collected for subjects who continue to be free of charge while the study drug, BN101/belumosudil, is administered at the end of the study.

Subjects who have not terminated BN101/belumosudil treatment at the end of the main study will

have a uniform end-of-treatment visit at the end of the main study.

AEs that remain at the end-of-treatment visit will be subject to continued follow-up, and all SAEs and AEs related to study treatment will be subject to follow-up until the event is resolved and the investigator considers the event to be stabilized or irreversible.

Twelve subjects at the designated centers will receive dense PK blood collection and the remaining subjects will receive sparse PK blood collection.

The primary efficacy endpoint of the study was ORR, defined as the proportion of subjects evaluated as CR or PR according to the NIH Consensus Criteria (2014) at any one post-baseline assessment. Secondary efficacy endpoints included median Duration of Response (DOR), Change in Lee Symptom Scale Score, Response rate by organ system, Percentage of subjects with best efficacy as PR and percentage of subjects with best efficacy as CR, Change in corticosteroid dose, Change in CNI dose, Failure-Free Survival (FFS), Overall Survival (OS), Change in cGVHD severity based on the Physician-Reported Global cGVHD Activity Assessment, and Change in symptom activity based on cGVHD Activity Assessment Patient Self-Report.

Changes in the PROMIS Physical Psychological Functioning Global Health Score will be analyzed as an exploratory endpoint of this study.

If a subject withdraws early from the study, the withdrawn subject will not need to be replaced and will not be able to re-enter this trial.

4.2 Randomization and blinding

This study is a non-randomized, open-label design that does not require randomization or blinding, and will use subject numbers to differentiate between subjects.

Patients who have signed the ICF will be assigned a subject number for screening evaluation in the format of "XX-XXX", where the first two digits of "XX" are the study center number and the last three digits of "XXX" are the subject number in the format of "XX-1XX" for the first screening and "XX-2XX" for the second screening. If the subject number of the first screening for the first subject in Center 01 is 01-101, the subject number of the third screening for the first time in Center 02 is 02-103, and if the subject needs to undergo the second screening, the subject number of the second screening is 02-203, and so on.

Subject numbers will be assigned in strict order in this trial, and in the event of a subject who withdraws early from the study, that subject's number will no longer be used.

4.3 Experimental Procedures and Phases

The study procedures are described in Appendix 1. In addition to the assessment items described in this protocol, with the consent of the subject, the investigator may take a series of photographs to

further document changes in cGVHD (e.g., skin, joint range of motion).

4.3.1 Screening/baseline period (-14 days ~ -1 day)

The screening period begins with the signing of the ICF. The ICF must be signed before any study-required or study-related operation, procedure, or assessment is performed. Patients must be given sufficient time to ask questions and make voluntary decisions before signing the ICF.

Data on screening failures also need to be recorded in the electronic data capture (EDC) system.

Unless otherwise specified, the Screening Period Assessment Program was to be completed within 14 days prior to the first administration of study drug. Subjects who meet all inclusion criteria while not meeting any of the exclusion criteria may be enrolled in the study. Subjects' eligibility for enrollment must be confirmed by the sponsor's Medical Director or Contract Research Organization (CRO) medical monitor prior to administration of study drug. Subjects who fail screening are permitted to be rescreened 1 time with the approval of the Medical Monitor; however, candidate subjects who fail screening because of abnormal laboratory indicators may not be rescreened after medical intervention. Subjects undergoing rescreening must sign a new ICF and be given a new screening number, and are permitted to receive the test(s) for which they passed the previous screening if they passed the previous screening test and are within the time window for this screening.

The procedures and assessments for the specific screening period are as follows:

1) Obtain written informed consent;
2) Demographic information (including gender, age/date of birth, ethnicity);
3) Past medical history;
4) History of transplantation (including indications for transplantation and type of transplantation);
5) History of GVHD (acute and chronic);
6) History of cGVHD treatment (including previous lines of therapy for cGVHD);
7) cGVHD severity assessment (-7 days to -1 day);
8) Full physical examination (including height);
9) Vital signs (including temperature, respiratory rate, sitting blood pressure and pulse);
10) weight and body mass index (calculated from height and weight: BMI = weight (kg)/height^2 (m^2));
11) ECOG PS score;
12) blood routine, urinalysis, blood biochemistry (-7 days to -1 day);
13) Virology;
14) 12-lead ECG (supine position);
15) Echocardiogram [left ventricular ejection fraction (LVEF)];
16) Serum pregnancy test (-7 days to -1 day, for women of childbearing age only);

17) Co-administered medications/treatments (including doses of corticosteroids and other cGVHD treatments);
18) Pre-treatment events (PTE);
19) Physician cGVHD activity assessment (-7 days to -1 day);
20) Complete pulmonary function tests [-7 days to -1 day, including FEV1, FVC, carbon monoxide diffusion (DLCO, corrected for Hb), total lung capacity (TLC), and residual air volume (RV)];
21) Patient-reported cGVHD activity assessment (-7 days to -1 day);
22) Lee Symptom Scale score (-7 days to -1 day);
23) PROMIS Physical Psychological Functioning Global Health Score (-7 days to -1 day);
24) Review of inclusion/exclusion criteria.

4.3.2 Cycle 1

4.3.2.1 Cycle 1, Day 1 (C1D1)

Prior to dosing

1) Co-administered medications/treatments (including doses of corticosteroids and other cGVHD treatments);
2) PTE；
3) Symptom-directed physical examination;
4) Vital signs (including temperature, respiratory rate, sitting blood pressure and pulse);
5) body weight;
6) ECOG PS score;
7) Blood routine*、urinalysis*、blood biochemistry*；
8) 12-lead electrocardiogram [3 consecutive measurements within 60 minutes prior to drug administration, each 1-2 minutes apart];
9) chocardiogram (LVEF) #;
10) Urine pregnancy test (for women of childbearing age only, positive results to be confirmed by serologic testing)§；
11) PK blood collection (within 60 minutes prior to dosing, only for subjects receiving intensive PK blood collection);

* If a subject has had these tests performed within 3 days prior to the administration of this study drug, the above tests do not need to be performed again on the day of study drug administration.

It is up to the investigator to decide whether or not to perform this test based on the subject's condition.

§ If a subject has had a serum pregnancy test within 7 days prior to the administration of this study drug, the test does not have to be repeated on the day of study drug administration.

Drug administration and post administration

1) Administration of study drug;
2) Issue study drug and subject logs;
3) 12-lead electrocardiogram [1.5 hours (±20 minutes) after drug administration, with 3 consecutive measurements taken at 1- to 2-minute intervals];
4) PK blood collection [only for subjects undergoing intensive PK blood collection: 1 hour (± 10 minutes), 1.5 hours (± 10 minutes), 2 hours (± 10 minutes), 3 hours (± 10 minutes), 4 hours (± 15 minutes), 6 hours (± 15 minutes), 8 hours (± 15 minutes), 12 hours (± 60 minutes), and 24 hours (± 60 minutes, which was before administration on Day 2)];
5) Combined medications/treatments (including doses of corticosteroids and other cGVHD treatments);
6) AE.

4.3.2.2 Cycle 1, days 8 and 15 (C1D8, C1D15, time window for targeting the appropriate examination: ±3 days)

1) Symptom-directed physical examination;
2) Vital signs (including temperature, respiratory rate, sitting blood pressure and pulse);
3) Body weight;
4) Blood routine and blood biochemistry;
5) Echocardiogram (LVEF)[#];
6) PK blood collection (within 60 minutes prior to drug administration, day 15 only);
7) Study drug administration;
8) Issuance/retrieval of subject logs;
9) Combined medications/treatments (including doses of corticosteroids and other cGVHD treatments);
10) AE.

It is up to the investigator to decide whether or not to perform this test based on the subject's condition.

4.3.3 Day 1 of Cycle 2 ~ Cycle N (C2D1 ~ CxD1, time window for the corresponding examination: ±3 days):

Prior to dosing

1) Co-medication/treatment (including doses of corticosteroids and other cGVHD treatments);
2) AE
3) Symptom-directed physical examination;
4) Vital signs (including temperature, respiratory rate, sitting blood pressure and pulse);

5) Body weight;
6) ECOG PS score;
7) Blood routine, urine, and blood biochemistry;
8) 12-lead electrocardiogram (3 consecutive measurements taken within 60 minutes prior to dosing on Day 1 of Cycle 2 and Cycle 4, each 1 to 2 minutes apart);
9) Echocardiogram (LVEF)[#];
10) Urine pregnancy test (for females of childbearing age only, positive results to be confirmed by serologic testing);
11) PK blood collection (within 60 minutes prior to dosing on Cycle 2, Cycle 3 and Cycle 4 Day 1);
12) Physician cGVHD activity assessment[†];
13) cGVHD response assessment[†];
14) Pulmonary function tests† [may also be assessed post-dose; where a complete pulmonary function test including FEV1, FVC, DLCO (corrected for Hb), TLC, and RV is required on Day 1 of Cycle 4, Cycle 7, and every 6 cycles thereafter (e.g., Cycle 13, Cycle 19, as applicable), and on other cycles (e.g., Cycle 2, Cycle 3, Cycle 5, and Cycle 6, etc.), a spirometer test only (including FEV1 and FVC testing) is required];
15) Patient-reported cGVHD activity assessment[†];
16) Lee Symptom Scale score[†];
17) PROMIS Physical-Psychological Functioning Global Health Score[†].

The decision to perform this test was made by the investigator on a subject-by-subject basis.

[†] ssessments were performed on day 1 of cycles 2 to 5 and on day 1 of every 2 cycles thereafter (i.e., day 1 of cycles 2, 3, 4, 5, 7, 9, 11, etc.).

Drug administration and post administration

1) Administration of study drug;
2) Dispensing/recovery of study drug and subject logs;
3) Combined medications/treatments (including doses of corticosteroids and other cGVHD treatments);
4) AE;
5) 12-lead electrocardiogram [3 consecutive measurements 1.5 hours (± 20 minutes) after dosing on Day 1 of Cycle 2 and Cycle 4 at 1-2 minute intervals; single measurement 1.5 hours (± 20 minutes) after dosing on Cycle 7 and subsequent visits];
6) PK blood collection [For subjects receiving intensive PK blood collection: 1 hour (± 10 minutes), 1.5 hours (± 10 minutes), 2 hours (± 10 minutes), 3 hours (± 10 minutes), 4 hours (± 15 minutes), 6 hours (± 15 minutes), 8 hours (± 15 minutes), 12 hours (± 60 minutes), 24 hours (± 60 minutes,

i.e., before Day 2 administration), 1.5 hours (± 10 minutes), and 4 hours (± 10 minutes) after Day 1 administration in Cycle 4; for subjects undergoing sparse PK blood collection: 1.5 hours (± 10 minutes), and 4 hours (± 10 minutes) after Day 1 administration in Cycle 2 and Cycle 4].

4.3.4 End-of-treatment visit (within 7 days after the last dose or at the end of the main study)

If a subject terminates study drug treatment for any reason (other than loss of visit, death), an end-of-treatment visit needs to be completed within 7 days of the last dose of study drug. If the subject voluntarily requests to withdraw from the study, every effort should also be made to convince the subject to accept the end-of-treatment visit. If the subject has not terminated study drug treatment at the end of the main study, an end-of-treatment visit is also required at the end of the main study. This visit is assessed as follows:

1) Combined medications/treatments (including doses of corticosteroids and other cGVHD treatments);
2) AE;
3) Symptom-directed physical examination;
4) Vital signs (including temperature, respiratory rate, sitting blood pressure and pulse);
5) Body weight;
6) ECOG PS score;
7) Blood routine, urine, and blood biochemistry;
8) 12-lead electrocardiogram;
9) Echocardiogram (LVEF)#;
10) Urine pregnancy test (for females of childbearing age only, positive results to be confirmed by serologic testing);
11) Recovery of study drug and subject logs;
12) Physician cGVHD activity assessment;
13) cGVHD response assessment;
14) Complete Pulmonary Function Test [If a complete pulmonary function test was performed within one month prior to this visit, only spirometry (including FEV1 and FVC) is required this time];
15) Patient-reported cGVHD activity assessment;
16) Lee Symptom Scale score;
17) PROMIS Physical-Psychological Functioning Global Health Score.

The decision to perform this test was made by the investigator on a subject-by-subject basis.

4.3.5 Follow-up 28 days after last dose (±7 days)

1) Combined medications/treatments (including doses of corticosteroids and other cGVHD treatments);
2) AE;
3) Symptom-directed physical examination;
4) Vital signs (including temperature, respiratory rate, sitting blood pressure and pulse);
5) Body weight;
6) ECOG PS score;
7) Blood routine, urine, and blood biochemistry;
8) 12-lead electrocardiogram;
9) Echocardiogram (LVEF)#;
10) Urine pregnancy test (for females of childbearing age only, positive results to be confirmed by serologic testing).

The decision to perform this test was made by the investigator on a subject-by-subject basis.

4.3.6 Long-Term Safety Follow-Up

Subjects who terminate study treatment early before the end of the main study will be contacted by telephone by the study center approximately every 12 weeks to confirm their survival, any changes in cGVHD treatment, and any antitumor therapy until the end of the main study (see Section 3.5).

Subjects who have not yet experienced cGVHD progression at the end of the study, and in the judgment of the investigator, the benefits of continued dosing outweigh the risks, may submit a written request and, upon approval by the sponsor's Medical Director and documentation of the subject's willingness to continue the treatment, the sponsor will continue to provide BN101/belumosudil medication at no cost until cGVHD progression, intolerable toxicity, initiation of a new cGVHD therapy, recurrence of hematological neoplasm, loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first. During this period, subjects will return to the study center in accordance with their clinical practice, and the study will continue to collect SAEs, study drug use, and survival (or can be contacted by phone). In addition, SAEs for this group of subjects will need to be collected up to 28 days (±7) after the last dose or the initiation of new cGVHD therapy.

4.3.7 Unscheduled visits

During the study period, the investigator may decide whether to add unscheduled visits based on clinical needs (e.g., clinically significant laboratory test abnormalities, AEs, etc.). During unscheduled visits, the corresponding tests and AEs, etc. should be recorded in the original data and eCRF. If the same test is performed multiple times on the same day, only one set of test values (e.g., the earliest test result of the day) should be recorded in the eCRF, but all abnormal values of repeated tests should be

recorded in the eCRF.

4.4 Pharmacokinetic Sample Collection, Handling, Transportation, and Testing

4.4.1 Pharmacokinetic Sample Collection

The first 12 subjects from the designated centers will be enrolled in the intensive PK blood collection program and the remaining subjects will be enrolled in the sparse PK blood collection program.

The time points and allowed time windows for intensive PK blood collection and sparse PK blood collection are shown in Appendix 2 and Appendix 3, respectively.

Subjects will be informed in advance that they will be required to take their study medication at the study center on the day of PK blood collection. The investigator will be required to keep a true record of the actual time of blood collection and sample number, and a protocol deviation report will be required for any blood samples collected outside of the allowed time window.

4.4.2 Pharmacokinetic Sample Handling, Storage and Transportation

PK samples will be processed in accordance with the requirements of the Standard Operating Procedures of the Biological Sample Testing Unit or the laboratory manual provided by it. Each sample tube should be identified with a sample number and the subject number, initials, sample number, date and time of blood collection, and date and time of centrifugation should be detailed on the Pharmacokinetic Blood Sample Collection and Centrifugation Form. Note: Blood samples should be collected to avoid hemolysis as much as possible.

Processed samples are stored frozen in accordance with the standard operating procedures of the biospecimen testing unit or the laboratory manual provided by the unit until they are shipped to the biospecimen testing unit. Transportation of samples is handled by a specialized cold-chain transportation company, which provides temperature data reports for the entirety of the sample shipment.

Specific PK sample collection, handling, storage and transportation requirements are described in the SOPs of the biospecimen testing unit or in the laboratory manual provided by the unit.

4.4.3 Pharmacokinetic Sample Assays

PK blood samples collected for the analysis of blood concentrations of BN101/belumosudil and its metabolites m1 and m2 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Methodology establishment, validation, and sample analysis will be performed by the biological sample testing unit. An analytical method validation plan will be developed, following the Guidelines for Validation of Methods for Quantitative Analysis of Biological Samples[20]and the relevant standard operating procedures of the testing unit. Methodological validation includes: selectivity, lower limit of

quantification and range of correction (standard curve performance), accuracy, precision, matrix effects, and stability of analytes in the biological matrix as well as in solution throughout storage and handling. Biological sample analysis will be performed according to the sample analysis plan and after completion of analytical method validation, PK blood samples will be pre-treated and assayed using validated LC-MS/MS methods. Biological sample reanalysis (Incurred sample reanalysis, ISR) will be performed in accordance with the appropriate guidelines and testing unit standard operating procedures.

The establishment and validation of specific biological sample analysis methods are described in the Biological Sample Analysis Program.

5. STUDY TREATMENT

5.1 Name of drug, physical and chemical properties, character, specification, composition, usage, packaging, storage

5.1.1 Investigational product

Chinese name:	BN101/belumosudil tablets
Chinese Pinyin:	BN101/belumosudil Pian
Trade name:	To be decided
Dosage form:	Tablet
Manufacturer:	UPM Pharmaceuticals, Inc.
Sponsor:	BK Pharmaceuticals Ltd.
Agent:	BioNova Pharmaceuticals (Shanghai) Ltd.
Ingredients:	BN101/belumosudil-, microcrystalline cellulose, hydroxypropylmethylcellulose, crosslinked sodium carboxymethylcellulose, anhydrous colloidal silicon dioxide, magnesium stearate, and Obadiol II (yellow 85F32410)
Specification:	200 mg (tablets equivalent to 200 mg BN101/belumosudil free base)
Storage conditions:	Store below 25°C
Expiry date:	24 months tentatively

5.1.2 Control drug

There is no control drug in this trial.

5.2 Method of administration

Take orally with meals or within 5 minutes after meals, once daily for 28 days.

5.3 Drug packaging

Labels are designed and drug packaging and labeling are performed by the sponsor and CRO for all study drugs in accordance with the Good Clinical Practice (GCP) and applicable national regulations. Subject number and visit number are also included in the labeling to facilitate drug

distribution, recall and statistics. Spare medications should be prepared and used only when the original medication to be used is not suitable for re-use (e.g., lost, soiled, etc.).

5.4 Drug labeling

Drug labeling includes at least the following:

- Drug for clinical trials only
- Manufacturer, sponsor and agent
- Protocol number
- Subject number
- Storage conditions
- Expiry date
- Dosage
- Product batch number

A sample label is shown below:

Packaging specification 30 tablets/bottle Packaging label

Name: BN101/belumosudil Tablets, 200 mg	Subject ID：
Protocol Number： BN101-201	Direction for Use: Oral, _Day, _Tablets Each Time
Batch No.：	For Clinical Trial Use Only
Package： 30 Tablets/Bottle	Strength： 200 mg
Product Date：	Keep Away from Children
Storage Condition： Store below 25°C	Expired Date：
Sponsor： BK Pharmaceuticals Ltd.	Agent： BioNova Pharmaceuticals (Shanghai) Ltd.

5.5 Drug Distribution, Recording and Recovery

The study drugs used in this trial will be provided free of charge by the agent [BioNova Pharmaceuticals (Shanghai) Ltd.] and will be distributed to each research center according to the plan, and each clinical research center will assign a person to be responsible for receiving, storing, distributing, recovering the study drugs and the corresponding records. The drug administrator or investigator of each research center is required to store sufficient study drugs according to the sponsor's recommendation and distribute them according to the requirements of the protocol.

The management of investigational drugs at each clinical research center should meet the following requirements:

1) A dedicated person (e.g., pharmacist) is responsible for receiving investigational drugs and supplies provided by the agent;
2) complete records are required for the receipt, distribution, and use of investigational drugs and supplies;

3) The study drugs and supplies should be stored in a reasonable and safe manner;
4) The investigational drug should only be prescribed by the Principal Investigator or a research physician authorized by the Principal Investigator;
5) The investigational drug should only be distributed to eligible subjects in accordance with the protocol;
6) Investigators should keep empty packages of used medications and unused medications for monitoring and retrieval by the monitor.
7) After counting the medication at the visit, the loss of medication needs to be recorded in detail. Overdose of medication, misuse of medication, omission of administration of medication, and loss of medication need to be recorded in the original medical record.

During the study period, the investigator should follow up on the subjects' medication intake to ensure that the subjects are taking the study medication correctly; and remind the subjects of the expiration date of the medication to ensure that the subjects are taking the medication within the expiration date. The investigator should keep a detailed record of the number of medications used by the subject and determine the subject's adherence to the medication.

Used drugs, empty packages, etc. are counted by the supervisors and may be disposed of by the research centers as medical waste or destroyed according to the standard operating procedures in effect at each research center. Unused and expired medications are collected by the sponsor.

At the end of the trial, the record of study drug shipments must be consistent with the quantities used and destroyed/returned, and any discrepancies need to be documented with the reason for the discrepancy.

6. Treatment of subjects

6.1 Dose Adjustment

Subjects who experience any clinically significant toxicity during treatment will need to be considered for suspension or termination of study drug therapy. Subjects who experience an AE related to study treatment may be dosed according to Table 3.

Table 3 BN101/belumosudil dose adjustment

Toxicity *	Dose Adjustment
⩾ grade 3 hepatotoxicity （ALT/AST/TBIL）	• Suspend BN101/belumosudil administration; • Within 14 days§toxicity does not return to ≤ Grade 1 or baseline level, then discontinue BN101/belumosudil therapy; • Within 14 days§toxicity returns to ≤ Grade 1 or Baseline level, resume BN101/belumosudil administration at a reduced dose level [e.g., 200 mg QD → 200 mg once every other day (QOD)]; If the reduced dose level is administered for one full treatment cycle tolerated by the subject without recurrence of Grade 1 or greater hepatic function abnormality, return the dose to the original level for the following treatment cycle[e.g., 200 mg QOD → 200 mg QD]； • If this toxic reaction recurs after the reduced dose level, terminate BN101/belumosudil treatment.
Other ≥ grade 3 clinically significant toxicity associated with BN101/belumosudil	• Suspend BN101/belumosudil administration; • Within 14 days§toxicity does not return to ≤ Grade 1 or baseline level, then discontinue BN101/belumosudil therapy; • Within 14 days§toxicity returns to ≤ Grade 1 or baseline level, then BN101/belumosudil administration is resumed at a reduced dose level [e.g., 200 mg QD → 200 mg QOD]; if the reduced dose level is administered for a full treatment cycle as tolerated by the subject, and there is no recurrence of Grade 1 or higher of this abnormality, then the next cycle of treatment the dose will be restored to the original level [e.g., 200 mg QOD → 200 mg QD]; • If the toxic reaction recurs after administration at a reduced dose level, BN101/belumosudil treatment will be discontinued.
* Severity of toxicity was determined according to NCI CTCAE v5.0. §The maximum time allowed for suspension of BN101/belumosudil administration due to toxicity was 14 days, and subjects who discontinued for more than 14 days were required to withdraw from the study.If a subject can tolerate 1 full cycle of treatment after a BN101/belumosudil dose reduction, the dose may be restored to the dose prior to the reduction for the next cycle.	

6.2 Management of Missed Doses

Subjects should endeavor to take the study drug at the same time each day as prescribed by the protocol.

If vomiting occurs after taking BN101/belumosudil and an insufficient dose of study drug is administered, no make-up dose is required. It is sufficient to continue to take the prescribed dose the following day.

Subjects who noticed a missed dose of study medication were allowed to take one make-up dose of the current dose if it was more than 12 hours before the next dose and still take the prescribed dose on the following day; if it was less than 12 hours before the next dose, there was no make-up dose of the current medication, and the dose was still taken on the following day.

6.3 Management of Overdose

An overdose dose of BN101/belumosudil has not been established. In clinical studies of BN101/belumosudil, a 500 mg BID dose of BN101/belumosudil given to healthy volunteers for 28 consecutive days was well tolerated, suggesting that the drug has a wide safety window and that overdose is unlikely. There is no known antidote for BN101/belumosudil and no specific treatment recommendations in case of suspected overdose. Investigators should exercise comprehensive judgment in the management of subjects with suspected overdose based on their clinical condition.

The reporting and management of overdose is detailed in Section 8.9.

6.4 Combinations of medications and treatments

All comorbid medications and treatments during the study period are to be documented. If a new systemic cGVHD treatment is initiated during the study period it will be considered as initiation of a new cGVHD treatment and will be considered as a failure of BN101/belumosudil treatment.

6.4.1 Corticosteroids

Therapeutic doses of corticosteroids are to be collected throughout the study. After≥2 weeks of BN101/belumosudil use, the dose of corticosteroids may be reduced at the discretion of the investigator.

A transient increase in corticosteroid dose (no more than 1 mg/kg/day prednisone equivalent) is permitted during cGVHD episodes, but this dose must be adjusted to the pre-enrollment dose level within 6 weeks. If the dose remains elevated for more than 6 weeks, it will be considered a BN101/belumosudil treatment failure. The occurrence of more than 2 episodes of cGVHD requiring an increase in corticosteroid dose during the first 6 months of BN101/belumosudil treatment will also be considered a BN101/belumosudil treatment failure.

If the planned response assessment falls during a cGVHD episode of treatment, this response assessment will still be performed as planned, but the assessment will not be included in the primary efficacy analysis.

6.4.2 Systemic cGVHD Therapies

Per the eligibility criteria, subjects receiving standard of care systemic cGVHD therapies such as calcineurin inhibitors (tacrolimus, cyclosporine), sirolimus, MMF, methotrexate, rituximab or ECP, may be enrolled if they have been on a stable dose/schedule. During the study treatment period, it is permissible to continue cGVHD treatment as described above at doses/regimens that have stabilized prior to enrollment, but it is not permissible to increase the dosage of these medications unless the increase in dosage is used only to maintain the current therapeutic level of the medication (e.g., to maintain the current blood concentration).Doses and schedules of these therapies will be collected throughout the study and changes will be documented.

6.4.3 Topical / Organ Specific Therapies for cGVHD

Use of topical / organ specific therapies for cGVHD is permitted and must be documented (Includes name of drug, dose administered, site of administration, reason for administration, etc.)

6.4.4 Proton Pump Inhibitors

The use of proton pump inhibitors (e.g., rabeprazole, omeprazole) is permitted only for short periods (no more than 1 week) during study treatment.

6.4.5 CYP 3A4 Inhibitors / Inducers

CYP3A4 inducers (e.g., rifampicin, phenobarbital) are prohibited during study treatment, and CYP3A4 inhibitors should be used with caution. A list of CYP3A4 inducers/inhibitors is detailed in Appendix 12.

6.4.6 CYP1A2 Inhibitors / Inducers

CYP1A2 inhibitors / inducers should be used with caution. A list of CYP1A2 inducers/inhibitors is detailed in Appendix 13.

6.4.7 Drugs Prolonging the QTc Interval

Drugs that prolong QT/QTc should be used with caution. A list of drugs that prolong the QT/QTc interval is detailed in Appendix 14.

6.4.8 Other Prohibited Combination Medications

The use of systemic immunosuppressive drugs against cGVHD (including rituximab, ruxolitinib, ibrutinib, etc.) or other clinical trial medications is prohibited during study treatment.

Tobacco, alcohol, and caffeinated beverages or foods are prohibited on the day of PK sample collection.

6.5 Treatment Compliance

The investigator shall emphasize adherence to the subject during the informed consent conversation. During the course of the trial, if subjects' compliance is poor, the investigator should find out the reasons and actively take appropriate measures (e.g., emphasize the importance of protocol compliance to the subjects), and keep a complete record of the non-compliance, the reasons, and the appropriate measures taken.

The investigator or other study personnel authorized by the investigator shall keep timely and accurate records of the quantity of study medication dispensed/recovered to/from each subject, the date, and the actual amount taken to ensure that subjects are taking the medication as prescribed by the protocol. The actual amount taken should be consistent with the dose required by the protocol. Subjects will be required to accurately complete a medication diary card.

Subjects' medication adherence will be calculated for this study based on the number of medications dispensed/recalled:

$$\text{Compliance} = \frac{\text{Actual amount of medication taken by the subject}}{\text{amount of medication to be taken by the subject}} \times 100\%$$

7. Study endpoints/indicators

7.1 Efficacy endpoints/indicators

7.1.1 Primary efficacy endpoints/indicators

The primary efficacy endpoint is the overall response rate (ORR). Responders include subjects that achieve a [PR+CR]. Responses are defined by the 2014 National Institutes of Health (NIH) Consensus Development Project on Clinical Trials in cGVHD.

Assessment of cGVHD response will be performed on Day 1 of Cycles 2 to 5 and on Day 1 of every 2 cycles thereafter (i.e., Day 1 of Cycles 2, 3, 4, 5, 7, 9, 11, etc.). As far as possible, the same investigator performed the response assessment on the subjects.

Overall response will be assessed using a total score of 10 systems (including skin, eye, mouth, esophagus, upper gastrointestinal tract, lower gastrointestinal tract, liver, lungs, joints and fascia, and overall severity score). Overall response at each assessment time point will be categorized as CR, PR, or Lack of response (LR), where LR includes unchanged (LR-U), mixed (LR-M), or progressive (LR-P) (see Table 4). The above assessments were based on NIH consensus criteria (2014).

Table 4 cGVHD Response Definitions

Response	Definition
Complete Response (CR)	Resolution of all manifestations of cGVHD in each organ or site
Partial Response (PR)	Improvement in at least one organ or site without progression in any other organ or site
Lack of Response (LR)	
Mixed (LR-M)	Complete or partial response in at least one organ accompanied by progression in another organ*
Unchanged (LR-U)	Outcomes that do not meet the criteria for complete response, partial response, progression or mixed response
Progression (LR-P)	Progression in at least one organ or site without a response in any other organ or site
* Considered progression for purposes of analysis	

Pulmonary function testing is required (FEV_1) for this assessment. The same equipment and tester should be used during the course of the study to the extent possible. Pulmonary function tests should be conducted in accordance with study guidelines and the American Thoracic Society/European Respiratory Society standardization[21]of lung function testing. The normal expected value and the lower limit of the normal expected value of spirometry (including FEV_1 and FVC) are recommended to refer to our normal expected value and the lower limit of the normal expected value of spirometry based on 7115 cases of people aged 4-80 years in 6 administrative regions of China for judgment [22,23] .

7.1.2 Secondary efficacy endpoints/indicators

Secondary efficacy endpoints included median Duration of Response (DOR), Change in Lee

Symptom Scale Score, Response rate by organ system, Percentage of subjects with best efficacy as PR and percentage of subjects with best efficacy as CR, Change in corticosteroid dose, Change in CNI dose, Failure-Free Survival (FFS), Overall Survival (OS), Change in cGVHD severity based on the Physician-Reported Global cGVHD Activity Assessment, and Change in symptom activity based on cGVHD Activity Assessment Patient Self-Report.

Lee Symptom Scale Score

Changes in symptom burden/bother will be explored using the Lee cGVHD Symptom Scale (Appendix 7). Symptom burden will be assessed on Screening/Day 1 of each cycle starting on Cycle 1 Day 1, as well as at the EOT visit. The questionnaire asks subjects to indicate the degree of bother that they experienced due to symptoms in seven domains potentially affected by chronic GVHD (skin, eyes, mouth, breathing, eating and digestion, energy, and emotional distress). The degree to which subjects report that they are bothered by a symptom represents a global assessment incorporating not only the intensity of the symptom and its frequency, but also the degree to which it causes emotional disturbance or interferes with functioning.

cGVHD Activity Assessment – Patient Self Report (Appendix 9)

Changes in the cGVHD Activity Assessment – Patient Self Report will be evaluated.

Change in Corticosteroid Dose

The change in systemic corticosteroid dose over time will be determined. If subjects are not using prednisone as the corticosteroid therapy, then the prednisone dose equivalent will be determined. See Appendix 15 for specific corticosteroid equivalent dose conversions.

Failure Free Survival (FFS)

FFS is defined as the absence of cGVHD treatment change, non-relapse mortality and recurrent malignancy.

7.1.3 Exploratory Endpoints

The PROMIS Physical Psychological Functioning Global Health Score (Appendix 8) will be evaluated as an exploratory efficacy endpoint for this study.

7.2 Safety Endpoints/indicators

Safety endpoints included change from baseline in vital signs, physical examination, laboratory tests (including blood routine, blood biochemistry, and urinalysis), 12-lead electrocardiogram [including Bazetts' formula-corrected QT interval (QTcB) and QTcF means and maxima], as well as AEs, including SAEs, and AEs related to study drug.

AEs (including SAEs) as well as abnormal laboratory findings will be categorized for severity according to NCI CTCAE v5.0.

Safety assessments are conducted throughout the study and, unless otherwise indicated, safety assessments begin with the signing of the ICF and continue until the end of safety follow-up after discontinuation of study drug [i.e., during the main study period, 28 ± 7 days after the final study drug administration or prior to initiation of a new treatment for systemic cGVHD, whichever occurs first].

For subjects who continue to receive study medication after the end of the subject's study, SAEs occurring during this period will continue to be collected from the subject [until 28 ± 7 days after the final study medication is administered or before starting new treatment for systemic cGVHD, whichever occurs first].

7.3 PK Endpoints/indicators

PK parameters include C_{max}, time to peak (T_{max}), elimination half-life ($T_{1/2}$), area under the concentration-time curve from time 0 to the time of the last measurable concentration (AUC_{0-t}), area under the blood concentration-time curve from initiation of dosing to the extrapolated infinite time (AUC_{inf}), apparent clearance (CL_z/F), and apparent volume of distribution (V_z/F), clearance rate constant (K_{el}), steady-state trough concentration ($C_{min,ss}$), steady-state peak concentration ($C_{max,ss}$), steady-state mean blood concentration ($C_{av,ss}$), steady-state accumulation ratio expressed as AUC_{0-t} (R_{AUC1}), steady-state accumulation ratio expressed as AUCinf (R_{AUC2}), and steady-state accumulation ratio expressed as C_{max} (R_{Cmax}). If the metabolites m1 and m2 of BN101/belumosudil can be detected and characterized, the ratios of the molecular weight-adjusted metabolites (m1 and m2) to the prodrug (P) C_{max} and AUC (AUC_{0-t}, AUC_{inf}) also need to be calculated.

8. Safety assessment

Assess the safety of the subject from the time of signing the ICF to 28 days after the last dose of study drug according to NCI CTCAE v5.0. The following data need to be recorded for drug safety assessment:

- AE/SAE、AE related to study drug
- Laboratory Data
- Physical examination
- Vital signs
- 12-lead electrocardiogram

8.1 Vital Signs

Seated pulse rate and blood pressure measurements will be performed as outlined in the schedule of assessments (Appendix 1). Measurements will be taken with the subject sitting, having rested in this position for at least 5 minutes. Vital signs should be taken before ECGs and other scheduled assessments. Respiratory rate and temperature will also be measured.

8.2 Physical examination

Physical examination was performed according to the study assessment schedule (Appendix 1), assessing by organ and system, with a comprehensive physical examination including: height, general condition, head and neck, lymph nodes, skin, chest, abdomen, musculoskeletal system (including limbs and spine), and nervous system.

8.3 Twelve-lead ECG

Twelve-lead ECGs will be performed as outlined in the schedule of assessments (Appendix 1). ECGs will be recorded after the subject has rested in the supine positon for at least 5 minutes. ECGs should be performed prior to any blood sample collections. When triplicate measurements are required, they should be taken at 1-2 minute intervals. Abnormalities in the ECG that lead to a change in subject management (e.g., dose delay, need for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded in the AE eCRF. If ECG abnormalities meet criteria defining them as serious, they must be reported as an SAE (See specifically Section 8.6.2.2).

8.4 Clinical Laboratory Parameters

Clinical laboratory tests will be performed as outlined in the schedule of assessments (Appendix 1). Samples should be taken predose. Specific inspections are listed in the table below.

Table 5 Clinical Laboratory Tests

Name of Test	Content of Test
Blood routine	Hemoglobin (Hb), Erythrocyte Compaction (HCT), Red Blood Cell Count (RBC), White Blood Cell Count (WBC), Leukocyte Sorting Count (including Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils), Platelets (PLT)
Urine routine	pH, urinary protein (U-PRO), urinary white blood cells (U-WBC), urinary red blood cells (U-RBC), urinary glucose (U-GLU), urinary occult blood, urinary chologen, urinary bilirubin, urinary nitrites, and urinary ketone bodies (U-KET)
Blood biochemistry	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyltransferase (gamma-GGT), total bilirubin (TBIL), direct bilirubin (DBIL), albumin (ALB), total protein (TP); creatinine (sCr), urea (Urea) or urea nitrogen (BUN), uric acid (UA), potassium (K), sodium (Na), chlorine (Cl), calcium (Ca), phosphorus (P), magnesium (Mg), blood glucose (GLU)
Virology	Hepatitis B Surface Antigen (HBsAg), Hepatitis B Surface Antibody (HBsAb), Hepatitis B Core Antibody (HBcAb), Hepatitis B e Antigen (HBeAg), Hepatitis B e Antibody (HBeAb), Hepatitis C Antibody (HCV-Ab), Human Immunodeficiency Virus (HIV) Antibody, Hepatitis B Virus DNA (HBV-DNA) (if applicable), Hepatitis C Virus RNA (HCV-RNA) (if applicable)

Abnormalities in clinical laboratory tests that lead to a change in subject management (eg, dose delay, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF page. Laboratory results will be classified using the CTCAE v5.0. If laboratory values constitute part of an event that meets criteria

defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 8.6.2.2).

8.5 Pregnancy Testing

Pregnancy testing is performed only on women of childbearing age. Urine pregnancy testing is optional except during the screening period when serum pregnancy testing is mandatory, but a positive urine pregnancy test result needs to be confirmed by serum pregnancy testing.

8.6 Adverse Event

8.6.1 Definition

8.6.1.1 Adverse Event

An adverse event (AE) is any adverse medical event that occurs in a subject following the use of an investigational drug, whether or not causally related to the study drug or study procedure. Thus, an AE can be any adverse or undesired sign, symptom, or disease, including AEs related to the study drug, significant laboratory outliers, new diseases that develop during the study period, and exacerbations of pre-existing diseases or symptoms prior to the trial (excluding the disease for which the test drug is intended to treat).

In this study, any event that is clearly caused by progression of the disease (any degree or exacerbation of symptoms expected from the proposed treatment of the disease) is not reported as an AE, with the exception of deaths due to disease progression. Deterioration of the studied disease condition at a rate greater than expected should be reported as an AE.

The investigator is responsible for assessing the relationship between all AEs and the study drug. However, the Principal Investigator may delegate judgment to other qualified clinicians who are participating in this study but remain responsible for it. The investigator must provide a list of those who are appropriately qualified and accept the delegation.

Pre-Treatment Event

A pre-treatment event (PTE) is any adverse medical event that occurs after a clinical study subject signs an ICF and before the first study drug is administered; the event is not necessarily causally related to participation in the study.

Other points to consider for pre-treatment events and adverse events

An unfavorable outcome may usually be:

- Indicate a new diagnosis or an unintended worsening of a preexisting condition (intermittent events due to a preexisting underlying condition should not be considered a PTE or AE).
- necessitate therapeutic intervention.
- Invasive diagnostic procedures are required.
- The need to discontinue or change the dose of the study drug or concomitant medication.

- The investigator considers it an unfavorable outcome for any reason.
- PTE/AEs resulting from study procedures (e.g., bruising after blood collection) should be recorded as PTE/AEs.

Diagnostic Comparison Signs and Symptoms:

Each event should be recorded as a single diagnosis and accompanying signs or symptoms should not be recorded as a separate AE. If the diagnosis is unknown, the signs or symptoms may be recorded as a PTE or AE accordingly.

In general, AEs that are secondary to other events (e.g., caused by other events or clinical sequelae) should be documented as their primary event unless the secondary event is of severe magnitude or is an SAE. however, clinically significant secondary events that occur at a different time than the primary event should be documented as separate AEs in the eCRF. if the correlation between the events is unclear, they should be separately Recording.

Laboratory test values, vital signs, and ECG results:

Abnormal laboratory tests, vital signs, and electrocardiogram results that meet one of the following criteria will be documented as AE:

- Progression from baseline indicators with clinical symptoms;
- Resulting in a change in study medication (e.g., dose adjustment, temporary or permanent discontinuation, etc.);
- Requires medical intervention or change in combination therapy;
- Clinically significant in the judgment of the investigator.

If clinically significant abnormal laboratory tests, vital signs, or electrocardiogram results are symptomatic of a disease or syndrome (e.g., cholecystitis resulting in elevations of alkaline phosphatase and bilirubin greater than 5 times the upper limit of normal), record the diagnosis (i.e., cholecystitis) on the AE form of the eCRF only. Instead, record an abnormal laboratory test or abnormal vital sign on the AE form of the eCRF and indicate whether the test value is above or below the normal range (e.g., record "elevated potassium" rather than "abnormal potassium"). If a laboratory test abnormality or vital sign abnormality has a standardized clinical term, the clinical term should be recorded in the eCRF (e.g., an elevated potassium level of 7.0 mmol/L should be recorded as "hyperkalemia"). If the same clinically significant laboratory test abnormality or vital sign abnormality is observed over multiple follow-up visits, it should be documented in the eCRF on a case-by-case basis according to a graded change in the severity of the abnormality or a change in the etiology of the abnormality.

Pre-existing diseases：

- Pre-existing diseases (present at the time of signing the ICF) are considered concomitant conditions and should not be recorded as PTE or AE. Baseline evaluations (e.g., laboratory tests, electrocardiograms, echocardiograms, etc.) should not be recorded as a PTE unless they are related to study operations; however, if a subject has a worsening of such concomitant condition or develops a complication, the worsening or complication should be recorded accordingly as either a PTE (the worsening or complication occurs prior to the initiation of the administration of the study drug) or an AE (the worsening or complication occurs after the initiation of the study drug). The investigator should ensure that the terminology of the recorded event reflects the change in the condition (e.g., "worsening of ...").
- If the subject has a pre-existing intermittent condition (e.g., asthma), the episode should be recorded as a PTE/AE only if the episodes become more frequent, severe, or exacerbated, i.e., the investigator should ensure that the terminology of the recorded AE describes the change in the condition relative to baseline (e.g., "...the worsening").
- If the subject has a degenerative concomitant condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should be recorded as a PTE/AE only if the condition worsens more than expected. In addition, the investigator should ensure that the recorded AE terminology describes the change in the condition (e.g., "...the worsening").

persistent or recurrent AE:

- A persistent AE is an AE that persists in the subject without remission between evaluation time points. This AE is recorded only once on the eCRF. The initial severity of the event should be recorded and updated as the event worsens to record the worst severity of the event.
- Recurrent AE is defined as an AE that has resolved between the two evaluation time points but then occurs again. the occurrence of the event should be documented separately in the eCRF.

Pre-planned surgery or operation:

- Pre-planned operations (surgical or therapeutic) scheduled prior to the signing of the ICF are not considered PTEs or AEs; however, if a pre-planned operation is performed earlier due to a worsening of a pre-existing condition (e.g., as an emergency), the worsening of the condition should be documented accordingly as a PTE or an AE.Complications resulting from any planned operation should be reported as an AE.
- Elective Surgery or Operations: Elective surgery or operations performed in the absence of a change in the subject's condition should not be reported as a PTE or AE but should be documented in the subject's original data. Complications resulting from elective surgery should be reported as an AE.

8.6.1.2 Significant Adverse Events

A significant adverse event is defined as any occurrence of an AE and apparent abnormality in hematology or other laboratory tests, other than SAEs, that results in the use of targeted medical measures (e.g., discontinuation of medication, dose reduction, and symptomatic treatment).

8.6.1.3 Adverse Events Associated with Investigational Drugs

A new drug or a new use of a drug that produces a harmful or undesired, causally related reaction to the application of the drug at any dose during pre-approval clinical investigational dosing, especially during a period when therapeutic doses have not yet been established, should be considered an Investigational Drug-Related AE. In determining that an AE is an investigational drug-related AE, there must be at least a reasonable likelihood that there is a correlation between the AE and the investigational drug, i.e., the AE needs to be considered to be an investigational drug-related AE in all cases where the possibility of a correlation cannot be ruled out.Refer to section 8.6.1.5 below for the criteria for determining causality between an AE and an investigational drug.

8.6.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that occurs during any phase of the study (i.e., Screening, Treatment, Follow-Up), at any dose of study drug, and that meets one or more of the following criteria:

- Leading to Death[a]
- Life-threatening adverse event[b]
- Inpatient hospitalization or prolongation of existing hospitalization[c]
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions[d]
- Congenital anomaly/birth defect[e]
- Important medical event[f]

For example, significant medical events that are not immediately life-threatening, or fatal, or that require hospitalization, but that jeopardize the subject, or that require medical intervention to prevent the above outcomes, require immediate scientific medical judgment and a decision on whether to report them expeditiously. These should also be considered SAEs.

SAEs are further explained below:

a AE resulted in the death of the subject.

b The occurrence of an AE that immediately poses a risk of death to the subject. Excludes those AEs that may result in death after severe progression, e.g., drug-induced hepatitis without liver failure.

c Any AE that results in hospital admission and prolonged hospitalization. excluding

conditions such as elective surgery or admission for tests decided prior to the trial and for which the course of treatment was not altered during the course of the study.

d Any AE that results in injury, impairment, or disruption of the subject's functioning and/or physiological structure, physical activity, or quality of life.

e Suspicion that exposure of either parent to the study drug will result in adverse outcomes in offspring.

f A significant medical event that, although not immediately life-threatening, resulting in death or hospitalization, may, in the medical judgment of the subject, expose the subject to injury or require medical intervention to prevent the occurrence of the conditions listed above, which includes, but is not limited to, a medical event that does not result in hospitalization, but that requires intensive treatment for anaphylactic bronchospasm, malignant hemorrhagic disease, or convulsions, either in the emergency room or at home.

In this study, any serious event (other than death) that is clearly due to progression of disease (any degree or exacerbation of symptoms expected from the disease to be treated) is not recorded and reported as an SAE.

8.6.1.5 Relationship to Study Drug

The causal relationship of an AE to the study drug is categorized as definitely related, probably related, probably unrelated, definitely unrelated, and undeterminable. Of these, definitely related, possibly related, and undeterminable are considered to be related to the study drug.

Table 6 Determination of causal relationship between adverse events and study drugs

definitely related	The time sequence between drug use and the onset of the AE is reasonable; the AE stops, or rapidly decreases or improves, after discontinuation of the drug; with reuse, the AE recurs and may be markedly worse (i.e., a positive re-excitation test); the event is consistent with the type of AE known to be associated with the investigational drug for the drug under suspicion; and the influence of other confounding factors, such as the original disease, has been ruled out.
probably related	The timing of the reaction is consistent with the chronological order of administration of the drug, the reaction is consistent with the type of reaction known to occur with the study drug, and the subject's clinical status or other therapeutic modalities are likely to produce the reaction.
probably unrelated	The timing of the reaction does not correspond to the chronology of the administration of the drug, the reaction is not quite consistent with the type of reaction known to occur with the investigational drug, and the subject's clinical status or other therapeutic modalities may have produced the reaction. Possibilities related to medication administration cannot be ruled out.
definitely unrelated	The timing of the reaction does not correspond to the chronological order of administration of the drug, the reaction has a type of reaction consistent with that known for non-study drugs, the subject's clinical status or other treatment modalities may also produce the reaction, the reaction is eliminated by improvement in disease status or cessation of other treatment modalities, the reaction occurs with repeated use of other treatments, and there is a strong correlation with other risk factors.
undeterminable	The timing of the reaction is not clearly related to the chronological order in which the

	medication was administered, the reaction is similar to the type of reaction known to occur with the study medication, and other medications used at the same time may cause the same reaction without an adequate basis for judgment.
AE：Adverse Events	

8.6.1.6 Criteria for Severity of Adverse Events

The severity of an AE shall be documented in accordance with NCI CTCAE v5.0.The severity of an AE that is not identified in NCI CTCAE may be assessed according to the following scale:

Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;

Grade 2: Moderate; minimal, localized or non-invasive interventions; age-related limitations in instrumental activities of daily living (ADLs) (instrumental ADLs are defined as cooking, grocery or clothing shopping, using the phone, money management, etc.);

Grade 3: Severe or medically significant, but not immediately life-threatening; hospitalization or prolonged hospitalization; disability; limitations in self-ADLs (self-ADLs refer to bathing, dressing and undressing, eating, toileting, and taking medications, rather than being bedridden);

Grade 4: life-threatening consequences; urgent intervention indicated;

Grade 5: death related to AE.

All AEs or other signs and symptoms that occur during the course of the study should be recorded on the AE page of the eCRF, regardless of whether it is related to the clinical trial. A record should be given for any AE in all subjects who are in the study period.

8.6.1.7 Measures Related to Investigational Drugs

- Discontinuation – The study drug is permanently discontinued because of a specific AE.
- Dose Unchanged – No discontinuation of study drug is required for a specific AE.
- Unknown – Used only when the measure taken cannot be determined.
- Not Applicable – Discontinuation of the study drug for reasons other than the specific AE, e.g., the study was terminated, the subject died, the study drug was discontinued before the AE occurred.
- Dose Reduction – Dose reduction due to a specific AE.
- Dose Interruption – Temporary interruption (suspension) (including subject-initiated interruption of dosing) of an investigational drug because of a specific AE and subsequent resumption of dosing.

8.6.1.8 Outcome of Adverse Events

The outcomes of AE can be described as follows:

- Recovered/Resolved: the "(S)AE termination date" should be noted.
- Recovering/ Resolving: the event is still not fully resolved, but the subject is in the recovery phase. Follow-up visits are required.
- Not Recovered/Unresolved: the incident is ongoing.
- Recovered/Resolved with Sequelae: Only if the subject will have sequelae that will last for a long period of time or for life, e.g., blindness due to diabetes mellitus, hemiplegia due to stroke. The "(S)AE termination date" should be indicated.
- Fatal: "(S)AE termination date" should be noted. Time of death needs to be recorded when AE is fatal.
- Unknown: the AE was not known to the investigator, e.g., the subject was lost to follow-up.

If the AE outcome is rated as "Recovering/Resolving", or "Not Recovered/Unresolved", or "Unknown", the AE termination date may be temporarily withheld.

The date of termination of the AE must be recorded if the AE outcome is rated as "recovered/resolved" or "recovered/resolved with sequelae."

All AEs must be followed to determine the final outcome until the event is resolved and the investigator considers the event to be stable or irreversible.

When the subject completes the clinical study, the investigator should follow the outcome of the AE related to the study drug until the event is resolved and, in the opinion of the investigator, stabilized or irreversible.

8.6.2 Collection and reporting procedures

8.6.2.1 Adverse Event Collection and Reporting

PTE and AE collection period

Collection of PTE will begin when the subject signs informed consent and continue until the subject first receives study drug or until screening failure. For subjects who withdraw from the study prior to study drug administration, PTE will be collected until the subject withdraws from the study.

Collection of AEs will begin when the subject first receives study drug and continue until 28 ± 7 days after the last dose of study drug or until initiation of new treatment for systemic cGVHD, whichever occurs first, whether or not related to study drug, and must be collected and recorded by the investigator. Only AEs/SAEs related to study treatment were collected and recorded 28±7 days after the last dose of study drug or after initiation of new systemic cGVHD treatment and were required to be followed until the event was resolved and the investigator considered the event to be stabilized or irreversible.

The end date of the PTE/AE was the date when the event was resolved and deemed stable or

irreversible by the investigator.

PTE and AE Reporting

At each study visit, the investigator will assess whether a subjective AE has occurred.A neutral question may be asked, such as "How have you felt since your last visit?" . Subjects may report AEs that occur at any other time during the study.

All PTEs occurring in subjects must be monitored until symptoms subside or until any clinically relevant changes in laboratory tests have returned to baseline, or until a satisfactory explanation for the change has been provided. Non-severe PTEs related or unrelated to study operations are not required to be followed up for study protocol purposes.

All subjects experiencing AEs, whether or not related to study drug use, must be monitored until symptoms have subsided and any clinically relevant changes in laboratory test values have returned to baseline, or until a satisfactory explanation for the observed changes has been provided.

All clinically significant laboratory test abnormalities confirmed by laboratory retesting will be followed until these abnormalities have returned to acceptable levels or have been satisfactorily explained.

All PTEs and AEs that occur within the collection timeframe specified in this protocol must be fully documented on the PTE/AE page of the eCRF. The documentation must be supported by primary sources and should provide a detailed description of each incident, including the information listed below:

- Event terminology
- Start and end dates
- Severity
- Investigator's judgment of causal relationship (relevant or irrelevant) between the event and study drug administration (not required for PTE)
- Investigator's judgment of causal relationship between the event and study procedures, including details of suspected procedures
- Relevant measures taken with respect to the study drug (not applicable for PTEs)
- Event outcome

Subject diaries and questionnaires will not be used as the primary means of collecting AEs. However, if the investigator identifies a potential AE through the information collected in these documents, the subject should be followed up appropriately for medical evaluation. Through this follow-up, if it is determined that a previously unreported AE has been identified, it should be reported following normal reporting requirements.

8.6.2.2 Serious Adverse Event Collection and Reporting

For all any SAE that occurs within the collection timeframe specified in this protocol, the investigator must complete the Serious Adverse Event (SAE) Report Form provided by the sponsor or its representative, sign and date it, and report it to the sponsor and its representative by mail or fax immediately within 24 hours of being informed.

Contact Information - The fax number and e-mail address of the sponsor or his/her representative will be kept in the investigator's folder at the research center. Questions regarding drug safety and pharmacovigilance can be contacted in the above manner.

Table 7 Serious Adverse Event Reporting Units and Contact Information

Reporting unit	Fax/telephone/email
Sponsor	E-mail: yu.wang@bionovapharma.com; Tel: 18621889377
Representative of the sponsor	E-mail: Bionova_PV@ppccro.com

SAEs should detail the description of symptoms, severity, time of onset, time of management, measures taken, time and mode of follow-up and regression. All SAEs should also be completed on the eCRF form at the same time, and it needs to be ensured that the information provided on the SAE reporting form is consistent with the data recorded in the eCRF about the event.

The investigator must provide an assessment of the causal relationship of the event to the study drug at the time the SAE is reported. If the investigator is unsure whether the AE is an SAE, then it needs to be conservatively assessed as an SAE until its nature can be demonstrated.

For all SAEs, the investigator needs to follow up until there are clear results to ensure that all problems are resolved. Administer necessary treatments and therapeutic measures during follow-up to ensure that subject harm is minimized and subject safety is adequately ensured. Detailed follow-up information is recorded (e.g., at the end of the study, whether special treatment is needed, whether hospitalization is required, etc.).

The investigator is to submit a follow-up report to the sponsor until the SAE is resolved, the investigator believes the event has stabilized (returned to baseline levels, proven unresolvable/permanent), or is irreversible (death of the subject). In the case of permanent impairment, follow-up is to continue until the SAE is considered to have stabilized.

8.7 Death

8.7.1 Recording of Deaths

All deaths occurring throughout the study period (including within 28 days of the last dose of study drug, and during the survival follow-up period), including deaths resulting from disease progression, must be recorded in the appropriate module of the eCRF.

If the death of the subject occurs, the event is to be reported as an AE [if the death was due to

disease progression and the death cannot be attributed to any of the NCI CTCAE v5.0 Level 5 AEs, report the AE by disease progression with a severity level of Level 5, or, if the death of the subject was due to an AE (e.g., cardiac disease: cardiac arrest), report the death as a Level 5 for that AE], and Record the cause of death in the appropriate place on the eCRF. The investigator must determine the primary cause of death and appropriately categorize the reason for the subject's withdrawal from the trial. If the cause of death is unknown at the time of reporting, it should be recorded as "unexplained death" on the eCRF AE form and the exact cause of death should be further investigated.

8.7.2 Reporting of death

The report of death should include information such as disease progression and primary or secondary cause of death, if any. An autopsy may be helpful in the assessment of the cause of death, and if an autopsy is performed, the report should include the results of the autopsy.

Deaths must be reported as SAEs to the sponsor or its representative within 24 hours of notification by completing the Serious Adverse Event (SAE) Reporting Form and, in accordance with GCP requirements, the investigator should provide the sponsor and the Ethics Committee with other required information such as autopsy reports and final medical reports. Deaths to be reported include the following two:

- Deaths, whether or not related to the study drug, that occurred from the time the subject signed informed consent until 28 days after the last dose of study drug;
- Deaths that are definitely related or possibly related to the study drug after 28 days after the last dose of study drug (excluding deaths that are not related to the study drug).

8.8 Hospitalization

In general, hospitalization is defined as remaining in an inpatient or emergency ward for observation or treatment (for more than 24 hours). An AE requiring hospitalization is considered a SAE. hospitalization or extended hospitalization for non-medical reasons/convenience, etc. or purely for the purpose of a clinical trial that does not meet the criteria for a medical event cannot be treated as a SAE.

The following hospitalizations are not considered SAEs:

- Staying in an emergency room or other hospital department for no more than 24 hours that does not result in hospitalization (unless considered a medically significant or life-threatening event);
- Hospitalization resulting from elective surgery that was planned prior to the signing of the ICF;
- Hospitalization resulting from a clinical trial protocol requirement;

- Hospitalization resulting from a requirement for a health physical examination (e.g., routine colonoscopy);
- Hospitalization that is not for the purpose of disease treatment and was planned prior to enrollment and needs to be documented;
- Hospitalization not related to a health condition and not requiring medical/surgical intervention (e.g., lack of housing, financial hardship, need for patient care, family reasons);
- Hospitalization for Medicare reimbursement reasons.

Hospitalization for elective surgery, routine clinical procedures, physical examination, admission for observation, or as required by the protocol, but not for AE, is not considered an AE, but is documented in the medical record. If an unanticipated event occurs during this process, it is reported as a "serious" or "non-serious" AE according to routine criteria.

8.9 Pregnancy

Pregnancy in Female Subjects

If a female subject becomes pregnant during the study (from the time of signing informed consent to 28 days after the last dose of study drug), a Pregnancy Report Form should be completed in the same timeframe as the SAE report, reported promptly to the Sponsor, and documented in the eCRF for follow-up of outcomes.

Any occurrence during pregnancy of: spontaneous or induced abortion, birth defects or congenital malformations in the newborn, malformations and anomalies in stillbirths, and serious complications in the mother and newborn should be documented and reported as an SAE.

During the study period, female subjects should discontinue the study drug as soon as they become pregnant and notify the investigator. The investigator should advise the subject and discuss the risks of continuing the pregnancy and possible effects on the fetus, and the subject must withdraw from the study. The investigator should continue to follow subjects until delivery and 30 days after delivery; subjects who fail to deliver will be followed until the end of the pregnancy.

Pregnancy in the Spouse of a Male Subject

If the spouse of a male subject becomes pregnant during the study period (from the time the male subject signs the informed consent to 28 days after the last dose of study drug), a Pregnancy Report Form should be completed in the same timeframe as the SAE report, reported promptly to the Sponsor, and documented in the eCRF for follow-up of the outcome.

Any occurrence during pregnancy of: spontaneous or induced abortion, birth defects or congenital malformations in the newborn, malformations and anomalies in stillbirths, and serious complications in the mother and newborn should be documented and reported as SAEs.

Spouses of male subjects should notify the investigator as soon as they become pregnant during

the study period. The investigator should advise the subject and his/her spouse to discuss the risks of continuing the pregnancy and the possible effects on the fetus; male subjects do not have to withdraw from the study, but the investigator should continue to follow the subject's spouse until delivery and for 30 days after delivery, and in the case of those who fail to deliver, follow up until the end of the pregnancy is required.

8.10 Overdose

An overdose dose of BN101/belumosudil has not been determined. Overdose in this study is defined as the intentional or unintentional ingestion of more than the dose to which each subject was assigned according to the study protocol. For the purposes of this study, drug overdoses without clinical signs or symptoms will not be considered AEs. drug overdose-induced AEs will be documented on the AE page of the eCRF in accordance with Section 8.6.2.1 (Collection and Reporting of AEs). SAEs due to drug overdose will be reported according to the procedures described in Section 8.6.2.2 (Collection and Reporting of SAEs).

There are no known specific antidotes for study drug overdose. If an overdose is suspected, supportive therapy should be given based on the subject's clinical condition.

8.11 Rapid Reporting of Suspected Unexpected Serious Adverse Reaction by the Sponsor

Sponsors are required to report Suspected Unexpected Serious Adverse Reactions (SUSARs) to the appropriate authorities on an expedited basis as an Individual Case Safety Report (ICSR) in accordance with the latest applicable regulations. The investigator should sign and read the relevant safety information of the clinical trial provided by the sponsor in a timely manner upon receipt and consider the subject's treatment, whether to adjust it accordingly, communicate with the subject as early as possible if necessary, and should report suspected unexpected serious adverse reactions provided by the sponsor to the ethics committee.

The content of the ICSR should be reported in accordance with the requirements of the ICH《E2B(R3): Management of Clinical Safety Data: Data Elements for the Transmission of ICSR》. The terminology should be coded using ICH《M1: MedDRA》.SUSAR is defined as all unanticipated and serious adverse reactions occurring during a clinical trial that are definitely related to or suspected to be related to the test drug.

An unexpected adverse reaction is an adverse reaction whose nature, severity, consequences, or frequency are different from the expected risks described in current information about the test drug (e.g., documents such as the investigator's brochure). The investigator's brochure serves as the primary document that provides the safety reference information used to determine whether an adverse reaction is expected or unexpected. Refer to Section 8.6 of this protocol for the determination of whether it is a

SAE and the determination of causality. For SUSAR, expedited reporting should also be performed when the sponsor and investigator cannot agree on the AE and drug causality determination, and either party determines that a relationship to the test drug cannot be ruled out.

SAEs occurring at the end of the clinical trial or after the end of follow-up until the conclusion of the review and approval is obtained should be reported by the investigator to the sponsor, and should also be subject to expedited reporting if they are unexpected serious adverse reactions. Other situations where rapid reporting is required are:

1) For known, serious adverse reactions with an increased incidence judged to be clinically important;
2) where there is a clear hazard to the exposed population, e.g. where the drug is ineffective in the treatment of a life-threatening condition;
3) Significant safety findings (e.g., carcinogenicity) in newly completed animal testing;
4) information obtained by the sponsor from other sources about unexpected serious adverse reactions and other potentially serious safety risks associated with the investigational drug;
5) When the sponsor and investigator cannot agree in the determination of causality between the AE and the drug, and in the judgment of either one of them, a correlation with the study drug cannot be ruled out.

The following conditions are generally excluded from expedited reporting:

1) Non-SAE;
2) SAE not related to the test drug;
3) Serious but expected adverse reactions;

Please refer to the Standards and Procedures for Rapid Reporting of Safety Data During Drug Clinical Trials for specific reporting procedures.

SUSAR Rapid Reporting Timeframe:

1) For fatal or life-threatening SUSARs, sponsors should report as soon as possible, but no later than 7 days after first notification, and report, and complete follow-up information within the next 8 days. [Note: The day the sponsor is first notified is Day 0.]
2) For non-fatal or life-threatening SUSARs, the sponsor shall report as soon as possible, but not more than 15 days, after initial notification.

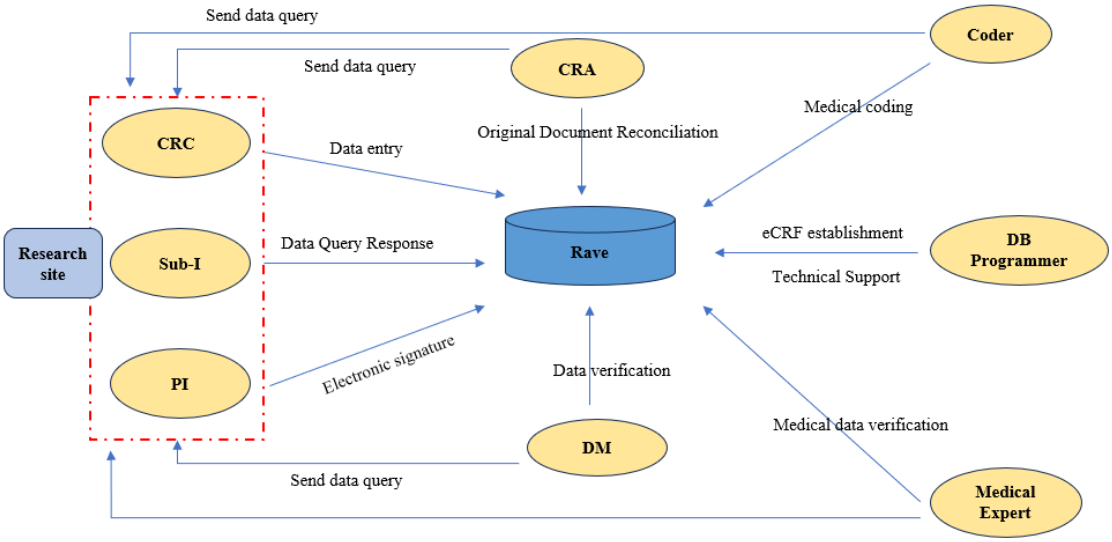
After the initial report, the sponsor should continue to follow up and report new information or changes to the previous report, etc., in a timely manner in the form of a follow-up report, with a reporting time limit of 15 days from the date the new information is obtained.

9. Data Managment

9.1 Data Management workflow

The study data management is the responsibility of the CRO Data Department to ensure the authenticity, integrity, privacy and traceability of clinical trial data.

9.1.1 Workflow



9.1.2 Role and Responsibility

EDC Role	Responsibility
Clinical Research Coordinator (CRC)	1) Data Entry
	2) Add comments
	3) Answer Query
Sub Investigator (Sub-I)	1) Data Entry
	2) Add comments
	3) Answer query
	4) Electronic signature
Principal Investigator (PI)	1) Data Entry
	2) Add comments
	3) Answer query
	4) Electronic signature
Clinical Research Associate (CRA)	1) Source data consistency check
	2) Send query
Medical Monitor (MM)	1) Send query
Data Management (DM)	1) Send query
	2) Answer query
	3) Freeze and Unfreeze data

EDC Role	Responsibility
Read-only	1) Read-only
Safty	1）Send query
Coder	1) Send query

9.2 Database design and creation

Construction of the eCRF database in the Medidata Rave system by the CRO Data Department shall comply with FDA 21 CFR Part 11. Data traces such as system entry, data entry, modification, or deletion should be managed in the database, and the establishment of the database should adopt the Clinical Data Exchange Standards Association (CDISC) standard.

9.3 Data Entry

Information shall be entered into the EDC database by the Investigator or the site staff authorized by the Investigator as soon as possible after the completion of the visit, and the data entry shall be carried out in strict accordance with the principle of "what you see is what you record". After the original data is entered, any changes made to the eCRF are automatically recorded in the system.

9.4 Data verification

Based on the finalized data verification plan, the data manager will set up a data logic verification process in the EDC system.

Once the data are entered into the EDC system, if there is any illogical data, the system verification will kick in and trigger a query. These queries will need to be reviewed and answered by the investigator or site staff authorized by the investigator. When updated data make logical checks no longer valid, the data query is immediately closed; if the clinical center confirms the data and provides a response, the data manager is required to review the response information. When justified, the data query is closed; when the data issue is not resolved, the data administrator can continue to communicate with the clinical center by adding data queries until they are finally resolved.

Subject data lists/reports are programmed to be generated to support manual data verification throughout the study. Manual challenges can be added to the EDC system when data arises that requires clarification/verification/confirmation by the investigator. Before locking the database, the data manager confirms that all queries have been resolved and the investigator completes an electronic signature in the EDC system to ensure the integrity and accuracy of the subject data in the EDC system.

9.5 Medical coding

The Data Manager of the CRO Data Department is responsible for the medical coding of this study. Coding will include past medical history, concomitant medication and AE.

Medical history and AE will be coded according to the MedDRA dictionary (version 20.1 or above), and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD), and the dictionaries used will be the versions confirmed by the sponsor.

During the coding process, any data issues that could not be coded due to inappropriate, inaccurate, or ambiguous provision of medical terminology would be requested by the data manager to be verified and confirmed by the investigator in the form of a data query.

Prior to database lock, the data manager sends a medical coding report to the sponsor and is required to be reviewed by the sponsor.

10. Statistical Considerations

10.1 General Principles

A statistical analysis plan will be developed by the biostatistician and principal investigator based on the study protocol, refined and documented prior to the first database lock. Detailed statistical analysis methods will also be specified in the statistical analysis plan.

All statistical analyses will be completed using SAS version 9.4 or above.

Continuous variables will be described by calculating the total number of cases, missing values, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum values.

Categorical variables are described using frequencies and percentages for each category. If required, 95% confidence intervals (95% CI) for frequencies and percentages are calculated.

10.2 Sample size determination

This study is an open, single-arm trial with the purpose of bridging Chinese cGVHD patients to the US registry study (KD025-213) to assess whether BN101/belumosudil treatment of Chinese versus Caucasian cGVHD patients is concordant in terms of efficacy, safety, and PK characteristics, the sample size of the trial is not determined by statistical assumptions.

This study is planned to enroll 30 patients with cGVHD who have undergone at least 1 but not more than 5 lines of systemic therapy, and such a sample size is considered to be sufficient to meet the needs of assessment with the purpose of bridging.

10.3 Statistical Analysis Population

Modified Intent to Treat (mITT): all subjects enrolled and having used at least one dose of study drug.

Per Protocol Set (PPS): The PPS was a subset of the mITT, and included all subjects who have used the study drug after enrollment and have had at least 1 post-treatment efficacy assessment, as well as no major protocol deviations. The exact definition of a major protocol deviation and the inclusion criteria for the PPS were finally determined in the data review meeting.

Safety Set (SS): All subjects who had used the study drug after enrollment and had at least 1 safety assessment.

Pharmacokinetic analysis Set (PKS): all subjects who have used the study drug since enrollment and have post-administration PK data.

Demographic and baseline characteristics of subjects were statistically analyzed based on mITT. mITT was the primary analysis population for the primary efficacy endpoint and PPS was the secondary analysis population. Safety analysis based on SS and PK analysis based on PKS.

10.4 Subgroup Analyses

Subgroup analyses will be conducted for the following subgroups:

- Severe cGVHD (Yes / No)
- Number of organs involved (<4 / ⩾4)
- Number of prior lines of therapy (1 vs. ≥2)
- Duration of cGVHD before enrolment (i.e., from time of cGVHD diagnosis to time of enrolment)
- Lung involvement (Yes / No)
- Prior ruxolitinib (Yes / No)
- Prior ibrutinib (Yes / No)

10.5 Data Analysis

Database lock and primary analyses are planned to occur approximately 2 to 3 months after the last subject is enrolled to complete 6 cycles of study medication. All subjects will continue to be followed up for an additional 6 months after the primary analysis as required by the protocol, i.e., the study will end 12 months after enrollment of the last subject, and a follow-up analysis will be performed at the end of the study.

10.6 Statistical Analysis Methods

10.6.1 Distribution of subjects and baseline characterization

Information on subjects who failed screening was tabulated, with the list including screening number and screening failure reason. Screening failure subjects were summarized, including the number of screening cases, the number of screening failures, and the percentage of various screening failure reasons.

Demographic information and baseline metrics will be analyzed based on mITT. Descriptive statistics will be performed for all demographic information and baseline characteristics (e.g., gender, age, ethnicity, height, weight, past medical history, transplantation history, history of GVHD, history of treatment for cGVHD, cGVHD severity, etc.)

10.6.2 Efficacy Analyses

10.6.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the ORR, defined as the proportion of subjects evaluated as CR or PR according to the NIH Consensus Criteria (2014) at any one post-baseline assessment. Point estimates and 95% CIs for ORR will be calculated. The 95% CI for ORR is calculated based on the binomial distribution exact probability method.

ORR is calculated based on mITT and PPS, with mITT as the primary analytic outcome.

10.6.2.2 Secondary Efficacy Endpoints

Secondary endpoints are as follows:

- DoR, defined as the time from the first evaluation of CR or PR to the confirmed occurrence of cGVHD progression. For subjects who had not experienced cGVHD progression at the end of the study, the date of their last objective evaluation was used as the DoR censoring date.
- Changes in the Lee Symptom Scale Score: Analyses will include:
  - Number of subjects with a ⩾7 point reduction
  - Number of subjects with a ⩾7 point reduction on 2 consecutive assessments
  - Duration of a ⩾7 point reduction
- Response by organ system: The response assessment for the nine individual organs (Skin, Eyes, Mouth, Esophagus, Upper GI, Lower GI, Liver, Lungs, and Joints and fascia).
- Number and percentage of subjects who have a best response of PR and number and percentage of subjects who have a best response of CR.
- Change in corticosteroid dose
  - The prednisone equivalent dose of corticosteroids (mg/kg/day) during the study will be analyzed.
- Change in calcineurin inhibitor dose.
- FFS, FFS is defined as the absence of cGVHD treatment change, non-relapse mortality and recurrent malignancy. Median FFS (from first dose of BN101/Belumosudil) and landmark FFS at 1 year(if applicable) will be analyzed.
- OS, defined as time from first dose of BN101/belumosudil to the date of death due to any cause.
- Changes in cGVHD global severity rating using the Clinician-Reported Global cGVHD Activity Assessment
- Changes in symptom activity using the cGVHD Activity Assessment Patient Self-Report

Descriptive statistics will be provided for all secondary endpoints.

For DoR (only for subjects determined to have CR and/or PR), FFS, and OS, the median, first quartile, third quartile, and their two-sided 95% CIs were calculated using the Kaplan-Meier method, and survival curves were plotted.

10.6.2.3 Exploratory efficacy endpoints

Descriptive statistics of changes in PROMIS Physical Mental Functioning Global Health Score.

10.6.3 Safety Analyses

Treatment exposure will be summarized.

For vital signs (including temperature, respiratory rate, sitting blood pressure, and pulse), and physical examination, describe post-treatment changes relative to baseline.

Descriptive statistics of laboratory test abnormalities will be indexed and presented in a cross-tabular format to show the change in laboratory test results of severity $\geqslant$3 (per NCI CTCAE v5.0) pre- and post-treatment with study medications.

For 12-lead ECGs, changes in mean and maximum QTcB and QTcF values relative to baseline will be calculated.

Each type of AE occurring during the study was coded using MedDRA (version 20.1 or above), frequency summarized according to system organ classification, preferred terminology, and frequency summarized and tabulated for AEs of different severity according to the highest level of severity (grades 1-5 according to NCI CTCAE v5.0) and relevance to the study drug. Count the number of subjects who experienced each type of AE, regardless of the number of AEs reported per subject.Descriptively summarize AEs, SAEs, AEs of severity $\geqslant$ grade 3 (according to NCI CTCAE v5.0), AEs leading to withdrawal from the study, AEs leading to discontinuation of study treatment, AEs leading to dose adjustments of the study medication, and correlation with the study medication for each of the above types of AEs/SAEs. List of subjects with each type of AE/SAE and death.

10.6.4 Pharmacokinetic Analyses

Individual drug-time profiles of BN101/belumosudil and its metabolites (m1 and m2) were plotted for each subject, and average drug-time profiles of BN101/belumosudil and its metabolites (m1 and m2) were plotted.

PK parameters of BN101/belumosudil and its metabolites (m1 and m2) were analyzed.PK parameters included, but were not limited to C_{max}, T_{max}, $T_{1/2}$, AUC_{0-t}, AUC_{inf}, CLz/F, Vz/F, K_{el}, $C_{min,ss}$, $C_{max,ss}$, $C_{av,ss}$, R_{AUC1}, R_{AUC2}, R_{Cmax}. If metabolites m1 and m2 of BN101/belumosudil can be detected and identified, the ratios of molecular weight-adjusted metabolites (m1 and m2) to the prodrug (P) C_{max} and AUC (AUC_{0-t}, AUC_{inf}) will also need to be calculated. The statistics for PK parameters

include, but are not limited to, number of cases, arithmetic mean, standard deviation, coefficient of variation, median, first quartile, third quartile, minimum and maximum values.

PK analysis methods will be presented in a separate PK analysis plan.

10.7 Interim Analysis

No interim analysis is planned for this study.

11. Clinical Trial Management

11.1 Statement

This clinical trial will be conducted in accordance with the sponsor's and CRO's standard operating procedures, which are designed to ensure that the trial adheres to the Declaration of Helsinki (2013 version), Guidelines for Good Clinical Practice issued by the ICH[24], Guidelines for Good Clinical Practice issued by the NMPA[25] and the requirements of drug clinical trial regulations were implemented.

By signing the protocol, the investigator agrees to follow the instructions and procedures set forth in the protocol and to follow the principles of GCP to which this protocol conforms, as well as all local regulations and principles of medical research used.

11.2 Ethical Aspects

The study was designed and prepared on the basis of the Declaration of Helsinki of the World Medical Association, taking into account the rights and welfare of patients. Patients who voluntarily agree to participate in a clinical trial and sign the ICF will only become subjects if the clinical trial principal investigator or investigator explains the purpose of the trial and all potential possibilities to the patient.

Clinical trial investigators and investigators participating in the trial should properly understand and be familiar with the study plan and be able to take preparatory measures in advance, such as countermeasures in the event of unanticipated adverse events, required reports, and adequate training. Clinical investigators must comply with the Declaration of Helsinki (2013 version), Guidelines for Good Clinical Practice[24] issued by the ICH, and Good Clinical Practice (GCP) [25]issued by the NMPA, as well as relevant regulations, when conducting clinical trial studies.

The principal investigator and the personnel involved in the study should comply with the contents specified on the trial protocol and scientifically conduct the trial with the currently recognized level of technology.

In accordance with national policies and regulations, the investigator is required to provide the EC with trial-related documentation.

A copy of the EC approval and a list of the documents reviewed must be submitted to the sponsor

before the drug is shipped to the investigator.The EC approval document must be accompanied by a list of all committee members involved in the discussion of the approval document and their respective responsibilities.

When the EC approves this study protocol, the sponsor is required to register on the Drug Clinical Trial Registration and Information Publication Platform.

Before the clinical trial starts, it must be approved by the EC and the pharmacovigilance administration.

Modifications to the study protocol need to be submitted to the EC for approval and communicated to the health authorities according to local requirements.

During the course of the clinical study, the investigator must inform the EC of any SAE related to the safety of the clinical study that may affect the safety of the subjects and the conduct of the trial.

The EC should be informed of the end of the study.

11.3 Original Data Verification

The investigator must handle all data obtained in the course of the clinical study appropriately to ensure the rights and privacy of the subjects participating in the clinical study. The investigator must consent to the access and review of clinical study data by the monitor/auditor/inspector as required to verify the accuracy of the original data and to understand the progress of the study. If validation of the original records is not possible, the investigator should agree to assist the Supervisor/Auditor/Inspection in further validation of the quality control of the data.

11.4 Quality Assurance and Audit

All drugs and materials applied in all clinical studies must be subject to quality control. The sponsor and its authorized personnel or the relevant healthcare governing body have the right to audit the clinical study, the purpose of which is to ensure the authenticity of the data recorded in the clinical study as well as to comply with the provisions of the clinical study protocol.

The study will be organized, conducted and reported in accordance with the standard operating procedures of the protocol, the sponsor and the CRO. Quality Assurance (QA) is defined in ICH E6 as "a planned systematic action to ensure that the conduct of a trial and the generation, recording, and reporting of data are in accordance with GCP and applicable regulatory requirements". Sponsor QA will be performed in accordance with the provisions of the Study Audit Plan.ICH E6 Section 5.19.3(b) states that the development of the Audit Plan and the Trial Audit Process should be guided by the significance of the trial in the filing with the competent authority, the number of subjects in the trial, the type and complexity of the trial, the level of risk posed to the trial subjects, and any identified issues.QA Work can be outsourced to a CRO or independent consultant. The investigator is required to support the audit by attending the audit as requested by the auditor and allowing the auditor to have

direct access to the raw data/documentation, including all medical records, study-related documents and correspondence, and informed consent documents for the clinical trial. Subjects in clinical studies will be informed of the process of clinical study review, but subject privacy and data information will be strictly protected.

11.5 Informed Consent Form

It is the responsibility of the investigator to explain to each subject the purpose, methodology, benefits and potential risks of this clinical trial, alternative treatments available, and the rights and obligations of the subject in accordance with the Declaration of Helsinki; subjects should be made aware that they have the right to withdraw from this trial at any time and that their personal interests will not be jeopardized. An ICF signed by the subject must be obtained prior to any operational procedure related to the clinical trial.

A verbal explanation must be given when giving written informed consent to the subject. Informed consent must be dated and signed by each subject or his/her legal guardian or representative. One copy of the signed ICF (including the information page) will be kept by the subject and the other copy will be retained by the clinical center for retention in the study file.

The ICF must be agreed to and signed by the subject before any study-related process begins. Prior to obtaining informed consent, the investigator or his/her designee should provide the subject with sufficient time and opportunity to inquire about the details of the trial and to decide whether to participate in the trial. The informed consent process needs to be documented in the medical record on the day of the screening visit.

The investigator is responsible for the informed consent process. If any information is obtained during the trial that is relevant to the subject's willingness to continue participation in this trial, the ICF must be updated and given to the subject to confirm the subject's willingness to continue participation. The revised ICF requires ethical approval before it is given to the subject.

By signing the informed consent, the subject/patient must also agree to allow the sponsor's authorized clinical trial monitor, drug regulatory authority, to access the raw data obtained about the clinical study, and the accessor must abide by the confidentiality statement.

11.6 Protocol Amendment

If there are any major changes in the implementation of the protocol after approval by the EC, the principal investigator of the responsible unit shall write and sign a "Statement of Protocol Amendment". At the same time, it must be reported to the EC for approval before implementation.

For non-substantial modifications, the principal investigator of the clinical center， the statistician, and the sponsor should discuss and decide on the modifications together and inform the

other participating centers. The investigator shall not implement any protocol deviation or change without the consent of the sponsor and prior review and written approval by the EC (ICH E6 4.5.2).

Any changes to the protocol, whether significant or non-significant, are required to be in writing. Substantial protocol revisions that clearly affect the safety of subjects, the scope of the study, or the scientific quality of this study require approval from all study clinical center ECs. In order to protect the safety of all subjects in the study, the above requirements shall not prevent the investigator or sponsor from taking any emergency measures. If the investigator believes that immediate protocol changes are necessary for safety reasons, the investigator must promptly notify the sponsor's Designated Authority and notify the Clinical Center EC in accordance with the policies established by the EC approving the study, and with local regulations and policies. Changes affecting only aspects of the administration of the study do not require substantive protocol revisions or EC approval; however, the EC must be notified of these changes.

11.7 Protocol deviation

The investigator is required to perform this clinical trial in accordance with the EC approved clinical trial protocol and in compliance with GCP regulations. The protocol has been developed to enable the investigator to follow the provisions of ICH E6 Section 4. During the course of the trial, the investigator should not deviate from the protocol unless emergency measures are taken to eliminate immediate harm to subjects. When other unintended circumstances occur that require deviation from the procedures specified in the protocol, the investigator should consult with the Medical Monitor (and IRB or EC, as necessary) to determine the appropriate measures to take.

The clinical center shall document all protocol deviations in the subject's original data, including, but not limited to, the time of occurrence of the protocol deviation, the time of discovery, a description of the event, and the measures taken. In the event of a serious protocol deviation, the clinical center shall promptly notify the medical monitor, clinical monitor, IRB and EC.

11.8 Case Report Form

The CRO database programmer will create an eCRF in the EDC system. eCRFs identify different subjects on the eCRF only by appropriate identification codes (e.g., study clinical center number and subject number) and initials. eCRFs are used to record clinical study information about subjects and are an integral part of the study and related research reports, so data entry must be accurate and complete. eCRFs are entered in the EDC system by the investigator or a staff member authorized by Investigator (to be noted on the Study Authorization Form) to make entries in the EDC system. All data entry must be ensured to be completed and stored. The investigator must declare, through an electronic signature, that all information in the eCRF is true.

In clinical studies, completion of the eCRF is usually required as soon as possible after each visit

to document the subject's condition.

Medical history records and other records related to the subject's disease progression during the course of the study are maintained by the investigator. These records should contain the following: original or copies of laboratory data and results of other medical tests (e.g., electrocardiograms, etc.), which must be kept at the clinical center along with the subject's medical history.

11.9 Monitor

The sponsor commissions the CRO to conduct the monitoring work.

Prior to the selection of a clinical center to participate in the study, a center selection visit will be conducted to confirm that the center, instrumentation, and staff meet the protocol requirements and GCP.

During the course of the study, the CRO conducts on-site inspections of the clinical centers according to the inspection plan and completes an inspection report for each inspection.

The activities of the monitor for study monitoring include:

- Clinical center study initiation visit to collect and distribute necessary pre-study required documents; give guidance instructions to the investigator and his/her clinical staff regarding the protocol, study process, and expectations; obtain assurances that the investigator will conduct the trial in accordance with the study requirements and the GCP, and present the study materials to the investigator and the appropriate study staff.
- Monitor Visit: In accordance with GCP requirements, the monitor involved in the current study is fully aware of the issues related to confidentiality and compares the data in the eCRF with the data in the hospital or clinical records (source material). Prior to the start of the study, the monitor should discuss with the investigator the specific items required as source material, determine the nature and location of all source material to ensure that the sponsor or investigator is aware of the source of the raw data used to complete the eCRF, and that the sponsor authorizes the monitor's authority for checking and verifying; all observations and findings made during the monitoring process must be verifiable. If the electronic records are kept at the clinical center, the method of checking must be discussed with the study member.

The original information must be available at a minimum to confirm:

- Subject identity, eligibility and participation in the trial;
- Proper informed consent procedures;
- The date of the visit;
- Documentation of safety and efficacy parameters;
- AE adequate reporting and visits;

- Treatment of concomitant medications;
- Records of receipt/dispensing/return of medications;
- Study drug administration information;
- Subject completion of treatment, termination of treatment, or withdrawal from the study, and appropriate reasons;
- Data are true, accurate, and complete;
- Subject safety and rights are protected;
- The investigator conducts compliance with the currently approved protocol, GCP and all relevant regulatory requirements.

The objectives that need to be achieved by surveillance include:

- Checking and evaluating the progress of the study;
- Reviewing the clinical data collected;
- Implement a source document verification process;
- Identify any problems and develop solutions.

During the course of the study, the monitor will need to have direct access to all relevant documents with the consent of the investigator, who will ensure that he or she and relevant clinical staffs meet with the monitor on a regular basis to discuss the findings of the visit and any relevant issues.

11.10 Intellectual Property

All information obtained from the sponsor is the intellectual property of the company, and as such must be kept strictly confidential by the clinical trial investigator and all others involved, and must not be divulged to third parties without the prior consent of the sponsor.

11.11 Subject Privacy

Investigators must ensure that the privacy of clinical trial subjects is protected. Clinical trial subjects may be identified in all documentation submitted to the sponsor only by their clinical trial subject number and initials, and not by the subject's name. The investigator must maintain proper custody of the name and address of the subject of the clinical trial in question and the identification code sheet that corresponds to the subject number. The subject identification code list is to be maintained by the Investigator in strict confidence and is not to be passed on to the Sponsor.

12. Paper Publication

The sponsor has exclusive rights to this study. The authors and manuscript will reflect the collaboration between multiple investigators and the staff of the clinical center and the sponsor, and the order of authorship will be established according to the scientific contribution of the investigators

to the protocol and the number of subjects enrolled. In principle, the scientific contribution of the investigators to the protocol will be the primary criterion, and the number of active cases enrolled will be the secondary criterion, and the above criteria will be used to determine the first author, the corresponding author, and the author rank order prior to writing the manuscript. Because there are many research centers participating in this study, individual centers or individual investigators will not be allowed to write articles for publication until the final report of the multicenter study has been completed, except with the consent of the sponsor. The final decision on manuscript and publication rests with the sponsor.

13. Study Documentation, CRFS, and Recod Keeping

13.1 Origional documents

In the trial, original information is defined as the following：

- Records related to the ICF, including instructions for subjects;
- Medical records, etc. as the basis for completing the eCRF;
- Records of the use of study medications;
- subject diary cards.

13.2 Document retention at Clinical center

13.2.1 Documents relating to ethics committees

The person responsible for data retention in the clinical center must retain EC meeting minutes and summaries until 5 years after the trial drug is approved for marketing. If the sponsor wishes to retain them for a longer period of time, the parties will discuss and decide on the duration and method of retention. The person responsible for data retention or the investigator will need to contact the sponsor if the trial unit makes any changes to document retention.

13.2.2 Documents relating to study

The person responsible for data retention at the clinical center must retain the following documents until 5 years after the trial drug has been approved for marketing. If the sponsor wishes to retain them for a longer period of time, the parties will discuss and decide on the duration and method of retention. The person responsible for data retention or the investigator will need to liaise with the sponsor if the trial unit makes any changes to document retention.

- Original documents;
- Originals or copies of trial contracts, ICFs, and other GCP-related documents provided by study clinical center staff;
- Trial protocol, GCP-related documents obtained from the EC, or other GCP-related documents obtained;

- Records of the administration of the medication used in the trial, and other records relevant to the conduct of the trial.

13.3 Retention of documents on sponsors

The sponsor will keep the following information (including documents and data) until 5 years after the approval of the test drug for marketing. Longer retention periods may be required in accordance with relevant regulations. It is the responsibility of the sponsor to inform the investigator/clinical center when this information is no longer required to be retained.

- Original or copy of the trial protocol, trial contract, study report, or GCP-related information provided by the sponsor;
- Case report forms, GCP-related notifications, or GCP-related information obtained from the investigator;
- Monitoring, audit-related records, or other relevant operational records;
- Data obtained during the trial;
- Relevant records required by GCP.

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15. Appendix

Appendix 1 Schedule of Assessments

Assessment \ Cycle Day（d）	Screening/Baseline		Cycle 1		Cycle 2~N[13,14]	End of Treatment (EOT)[15]	28-Day Follow-Up [16]	Long Term Follow-Up [17]
	-14 ~ -1	-7 ~ -1	C1D1	C1D8、15 (±3)	CxD1 (±3)	(+7)	(±7)	At the end of treatment or at the end of the main study
Written Informed Consent [1]	X							
Subject Demography	X							
Medical History	X							
Transplant History	X							
GVHD History	X							
cGVHD Prior Treatments	X							
Inclusion/Exclusion Criteria	X							
cGVHD severity assessment		X						
Efficacy Assessments								
Clinician-reported global cGVHD activity assessment		X			X	X		
Response Assessment [2]					X [2]	X		
Pulmonary Function Tests [2,3]		X			X [2,3]	X		
Patient-reported cGVHD acticity assessment[2]		X			X [2]	X		
Lee Symptom Scale Score [2]		X			X [2]	X		
PROMIS Global Health Score [2]		X			X [2]	X		
Document Corticosteroid Dosage	***Corticosteroid Dosage to be collected from the date the ICF is signed until 28 days after last dose of study drug.***							
Document other cGVHD therapies	***cGVHD therapies to be collected from the date the ICF is signed until 28 days after last dose of study drug.***							
Safety Assessments								
Complete PE [4]	X							
Symptom directed PE			X	X	X	X	X	
Vital signs [5]	X		X	X	X	X	X	

Cycle Day（d） Assessment	Screening/Baseline		Cycle 1		Cycle 2~N[13,14]	End of Treatment (EOT)[15]	28-Day Follow-Up [16]	Long Term Follow-Up [17]
	-14 ~ -1	-7 ~ -1	C1D1	C1D8、15 (±3)	CxD1 (±3)	(+7)	(±7)	At the end of treatment or at the end of the main study
Weight	X		X	X	X	X	X	
ECOG PS score	X		X		X	X	X	
Hematology [6]		X	X	X	X	X	X	
Urinalysis [7]		X	X		X	X	X	
Clinical Chemistry [8]		X	X	X	X	X	X	
Virology [9]	X							
12-Lead ECG [10]	X		X		X	X	X	
Ultrasonic cardiogram（LVEF）	X		X[18]			X	X	
Pregnancy test [11]		X	X		X	X	X	
Concomitant medications /procedures	X		X	X	X	X	X	
Adverse events	X		X	X	X	X	X	
Long term follow-up								X
Investigational Product								
Study Drug administration [12]			X	X	X			
Dispense/Collect Study Drug & Study Drug Diary			X	X[19]	X	X		
Pharmacokinetics	***See PK Table***							

cGVHD = chronic graft versus host disease；d = day；ECOG = Eastern Cooperative Oncology Group；GVHD = graft versus host disease；LVEF = left ventricular ejection fraction；PROMIS = Patient-Reported Outcomes Measurement Information System；PS = Performance Status

1. The informed consent form must be signed before any study procedures begin.
2. To be assessed on Day 1 of Cycles 2-5 and then on Day 1 of every other Cycle thereafter (i.e. Day 1 of Cycles 2, 3, 4, 5, 7, 9, 11 etc.)
3. Lung function assessment to be conducted at time of response assessments (see item 2). Pulmonary Function Tests (PFTs), to include FEV 1 , FVC, DL CO (corrected for Hb), TLC, and RV, will be performed at screening/baseline and Day 1 of Cycles 4, 7, 13，every 6 th Cycle thereafter and EOT. On Day 1 of other cycles with response assessments, spirometry (FEV 1 and FVC) is sufficient.
4. Assessment by organ and system. A comprehensive physical examination includes: height, general condition, head and neck, lymph nodes, skin, chest, abdomen, musculoskeletal system (including limbs and spine), and nervous system.
5. Vital sign includes temperature, respiratory rate, pulse/heart rate, blood pressure. Sitting blood pressure and heart rate to be obtained after 5 minutes of rest.
6. Hematology：hemoglobin (Hb), hematocrit (HCT), Red blood cell count (RBC), white blood cell count (WBC), white blood cell classification count (including neutrophils, lymphocytes, monocytes, basophils, eosinophils), platelets (PLT). If it is done within 3 days prior to C1D1, it does not need to be repeated on C1D1.

Assessment \ Cycle Day（d）	Screening/Baseline		Cycle 1		Cycle 2~N[13,14]	End of Treatment (EOT)[15]	28-Day Follow-Up [16]	Long Term Follow-Up [17]
	-14 ~ -1	-7 ~ -1	C1D1	C1D8、15 (±3)	CxD1 (±3)	(+7)	(±7)	At the end of treatment or at the end of the main study

7. Urinalysis：pH、urine protein (U-PRO), urine white blood cells (U-WBC), urine red blood cells (U-RBC), urine sugar (U-GLU), urine occult blood, urobilirubin, urine bilirubin, urine nitrite and urine ketone bodies (U-KET). If it is done within 3 days prior to C1D1, it does not need to be repeated on C1D1.
8. Clinical chemistry：aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyltransferase (γ-GGT), total bilirubin (TBIL), direct bilirubin (DBIL), albumin (ALB), total protein (TP); Creatinine (sCr), Urea (Urea) or urea nitrogen (BUN), uric acid (UA), potassium (K), sodium (Na), chlorine (Cl), calcium (Ca), phosphorus (P), magnesium (Mg), blood glucose (GLU). If it is done within 3 days prior to C1D1, it does not need to be repeated on C1D1.
9. Virology includes Hepatitis B Surface antigen (HBsAg), Hepatitis B Surface Antibody (HBsAb), Hepatitis B core antibody (HBcAb), Hepatitis Be antigen (HBeAg), Hepatitis Be antibody (HBeAb), Hepatitis C antibody (HCV-Ab), human immunodeficiency virus (HIV) antibody, Hepatitis B virus DNA (HBV-DNA) (if applicable), Hepatitis C virus RNA (HCV-RNA) (if applicable). If they are done at the site within 28 days prior to screening and reports can be provided, the investigator determines that the test can be used as a result of the screening period. When HBcAb or HCV-Ab is positive, HBV-DNA or HCV-RNA should be tested to rule out active infection.
10. 12-Lead ECG – see ECG Assessment table.
11. Female of childbearing age are tested for pregnancy. For this study, the reproductive age was defined as non-menopausal, and menopause included natural amenorrhea ≥12 months; Or natural amenorrhea ≥24 months after chemotherapy; Or natural amenorrhea ≥6 months and serum follicle-stimulating hormone (FSH) level > 40 IU/L; Or confirmed surgical records and/or pathology reports confirmed after bilateral oophorectomy. Serum pregnancy tests for women of childbearing age during the screening period must be negative. Urine pregnancy test can be performed as needed during the study treatment. Positive results are to be confirmed with serum testing. If the urine pregnancy result is positive, subjects should stop the study drug treatment and withdraw from the study, and the investigators will continue to follow up subjects until delivery and 30 days after delivery. Subjects who did not deliver were followed up until the end of the pregnancy.
12. On Day 1 of Cycles 1 to 7, subjects will take their dose at the clinic and then will be dispensed study drug for home administration. Instruct subjects to fill in the study drug dairy. From Cycle 8 onwards, the Day 1 dose may be taken at home or in the clinic.
13. The end of the main study is defined as 12 months after the last subject was enrolled.Subjects who have not yet experienced cGVHD progression at the end of the main study, and in the judgment of the investigator, the benefits of continued dosing outweigh the risks, may submit a written request and, upon approval by the sponsor's Medical Director and documentation of the subject's willingness to continue the treatment, the sponsor will continue to provide BN101/belumosudil medication at no cost until cGVHD progression, intolerable toxicity, initiation of a new cGVHD therapy, recurrence of hematological neoplasm, loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first.For subjects assessed as "Lack of Response - Mixed" and "Lack of Response - Progression"(see the main body of the protocol), if the investigator believed that these subjects could continue to benefit from treatment with BN101/belumosudil, the treatment may be continued after a written application was submitted, and approval from the Sponsor's Medical Director as well as documentation of the subject's willingness to continue treatment was obtained.
14. On the first day of cycle 7 (C7D1) and all subsequent odd cycles (C7D1, C9D1, C11D1, etc.), subjects will receive 2 cycles of study drugs and 2 copies of drug dairy and return to the clinic for efficacy and safety assessment every other treatment cycle, as well as dispense/collect study drugs until the end of the main study.
15. Subjects will return to the clinic for EOT assessment within 7 days after the final administration of the study drug or at the end of the main study (only for subjects who have not discontinued the study drug at the end of the main study). Subjects who withdraw from the trial early should also return to the clinic for EOT assessment. End-of-treatment visits are also required at the end of the main study if subjects have not discontinued study drug at the end of the main study. EOT

Assessment \ Cycle Day（d）	Screening/Baseline		Cycle 1		Cycle 2~N[13,14]	End of Treatment (EOT)[15]	28-Day Follow-Up [16]	Long Term Follow-Up [17]
	-14 ~ -1	-7 ~ -1	C1D1	C1D8、15 (±3)	CxD1 (±3)	(+7)	(±7)	At the end of treatment or at the end of the main study

visits should be done prior to new treatment.

16. Subjects will receive the assessment at 28 days (±7 days) after the last study drug administration. If subjects started a new cGVHD treatment within 28 days of the last study drug administration, this visit needs to be completed before receiving the new treatment.
17. Subjects who discontinue study therapy during the main study period will be contacted by phone approximately every 12 weeks to confirm survival, any changes in cGVHD therapy, and any antitumor therapy until the end of the main study period.
18. Subjects who have not yet experienced cGVHD progression at the end of the main study, and in the judgment of the investigator, the benefits of continued dosing outweigh the risks, may submit a written request and, upon approval by the sponsor's Medical Director and documentation of the subject's willingness to continue the treatment, the sponsor will continue to provide BN101/belumosudil medication at no cost until cGVHD progression, intolerable toxicity, initiation of a new cGVHD therapy, recurrence of hematological neoplasm, loss to follow-up, withdrawal of consent, or death, etc., whichever occurred first. During this time, the study will continue to collect participants' serious adverse events (SAEs) (up to 28±7 days after the last dose or start new cGVHD therapy), study drug use, and survival (or can be contacted by telephone).
19. During the treatment, it will be up to the investigator to decide whether to perform an echocardiogram according to the subject's condition.
20. C1D8 and C1D15 do not need to dispense/collect study drugs, only dispense/collect study drug diary.

Appendix 2 Pharmacokinetics Sampling

PK Sample Collection		
Sample	Blood (approximately 3 mL every time point)，separated plasma	
Extensive blood sampling: 12 subjects at selected sites		
Cycle 1	Day 1	Prior to BN101/belumosudil dosing, and at 1、1.5、2、3、4、6、8、12 hours post dose
	Day 2	Prior to BN101/belumosudil dosing
	Day 15	Prior to BN101/belumosudil dosing
Cycle 2 (or when withdrawing from the study early)	Day 1	Prior to BN101/belumosudil dosing，and at 1、1.5、2、3、4、6、8、12 hours post dose
	Day 2	Prior to BN101/belumosudil dosing
Cycle 3 (or when withdrawing from the study early)	Day 1	Prior to BN101/belumosudil dosing
Sparse PK: All Subjects		
Cycle 2 (or when withdrawing from the study early, except for those who were in the extensive blood sampling group)	Day 1	Prior to BN101/belumosudil dosing，and at 1.5、4 hours post dose
Cycle 4 (or when withdrawing from the study early)	Day 1	Prior to BN101/belumosudil dosing，and at 1.5、4 hours post dose

Appendix 3 Pharmacokinetic Blood Sample Collection Time Window

PK Time point	Time Window	
	Extensive blood sampling	**Sparse blood sampling**
Prior to BN101/belumosudil	-60 minutes to BN101/belumosudil dose	-60 minutes to BN101/belumosudil dose
1、1.5、2、3 hours post dose	± 10 minutes	± 10 minutes
4、6、8 hours post dose	± 15 minutes	NA
12 hours post dose	± 60 minutes	NA
Note：NA = not applicable		

Appendix 4 ECG Assessments

ECG Assessments		
Cycle 1	Day 1	Triplicate ECG within 60 minutes prior to BN101/belumosudil dosing and at 1.5 hours post dose (± 20 minutes), they should be taken at 1-2 minutes intervals
Cycle 2	Day 1	Triplicate ECG within 60 minutes prior to BN101/belumosudil dosing and at 1.5 hours post dose (± 20 minutes), they should be taken at 1-2 minutes intervals
Cycle 4	Day 1	Triplicate ECG within 60 minutes prior to BN101/belumosudil dosing and at 1.5 hours post dose (± 20 minutes), they should be taken at 1-2 minutes intervals
Cycle 7 and every 2 cycles thereafter (only until the end of the main study)	Day 1	Single ECG at 1.5 hours post dose (± 20 minutes)
EOT		Single ECG
28-Day Follow-up (only until the end of the main study)		Single ECG

Appendix 5 cGVHD Activity Assessment for Clinician

	Score 0	Score 1	Score 2	Score 3
Esophagus	No esophageal symptoms	Occasional dysphagia or odynophagia with solid food or pills during the past week	Intermittent dysphagia or odynophagia with solid and pills, but not for liquids or soft foods, during the past week	Dysphagia or odynophagia for almost
	☐	☐	☐	☐

☐Abnormality present but explained entirely by non-GVHD documented cause (specify):

☐Abnormality thought to represent GVHD PLUS other causes (specify):

	Score 0	Score 1	Score 2	Score 3
Upper GI	No symptoms	Mild, occasional symptoms, with little reduction in oral intake during the past week	Moderate, intermittent symptoms, with some reduction in oral intake during the past week	More severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week
	☐	☐	☐	☐

☐Abnormality present but explained entirely by non-GVHD documented cause (specify):

☐Abnormality thought to represent GVHD PLUS other causes (specify):

	Score 0	Score 1	Score 2	Score 3
Lower GI	No loose or liquid stools during the past week	Occasional loose or liquid stools, on some days during the past week	Intermittent loose or liquid stools throughout the day, on almost every day of the past week, without requiring intervention to prevent or	Voluminous diarrhea on almost every day of the past week, requiring intervention to prevent or correct

			correct volume depletion	volume depletion
	☐	☐	☐	☐

☐Abnormality present but explained entirely by non-GVHD documented cause (specify):

☐Abnormality thought to represent GVHD PLUS other causes (specify):

	Score 0	**Score 1**	**Score 2**	**Score 3**
Lungs	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring O_2)
	☐	☐	☐	☐
	Spirometry Not done ☐	FEV_1 （% Predicted）:	FEV_1 （L）:	FVC （% Predicted）:	FVC （L）:

☐Abnormality present but explained entirely by non-GVHD documented cause (specify):

☐Abnormality thought to represent GVHD PLUS other causes (specify):

	Score 0	**Score 1**	**Score 2**	**Score 3**
Eyes	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ⩽ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs). WITHOUT new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS
	☐	☐	☐	☐

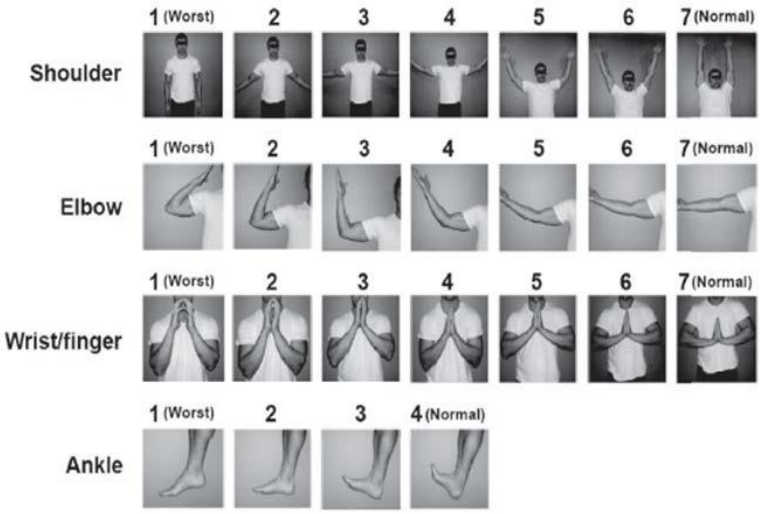
☐Abnormality present but explained entirely by non-GVHD documented cause (specify):

☐Abnormality thought to represent GVHD PLUS other causes (specify):

	Score 0	Score 1	Score 2	Score 3
Joints And Fascia	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.
	☐	☐	☐	☐

☐Abnormality present but explained entirely by non-GVHD documented cause (specify):

☐Abnormality thought to represent GVHD PLUS other causes (specify):

P-ROM Score		Score Not done ☐ Score Not done ☐ Score Not done ☐ Score Not done ☐

☐Abnormality present but explained entirely by non-GVHD documented cause (specify):

☐Abnormality thought to represent GVHD PLUS other causes (specify):

	Score 0	Score 1	Score 2	Score 3
Skin	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
	☐	☐	☐	☐

☐Abnormality present but explained entirely by non-GVHD documented cause (specify):

☐Abnormality thought to represent GVHD PLUS other causes (specify):

	Score 0	**Score 1**	**Score 2**	**Score 3**
Skin Features Score	No sclerotic features		Superficial sclerotic features "not hidebound" (able to pinch)	Check all that apply: ☐Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐Impaired mobility ☐Ulceration
	☐		☐	☐

If skin features score=3, BSA% of non-moveable sclerosis/fasciitis：

Other skin GVHD features (scored by BSA)

Check all that apply:

☐Maculopapular rash/erythema ☐Lichen planus-like features	☐Sclerotic features ☐Papulosquamous lesions or ichthyosis	☐Keratosis pilaris-like

How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible：

0	1	2	3	4	5	6	7	8	9	10
Symptoms not at all severe										Most severe symptoms possible

Mouth	Erythema	None	0	Mild or moderate erythema（<25%）	1	Moderate（≥25%）or Severe erythema（<25%）	2	Severe erythema（≥25%）	3
	Lichenoid	None	0	Lichen-like	1	Lichen-like	2	Lichen-like	3

			changes（<25%）		changes（25%~50%）		changes（>50%）	
Ulcers	None	0			Ulcers involving（≤20%）	3	Severe ulcerations（>20%）	6
Total score for all mucosal changes								

☐Abnormality present but explained entirely by non-GVHD documented cause (specify):

☐Abnormality thought to represent GVHD PLUS other causes (specify):

	Total serum bilirubin	ALT	ALP
Liver labs	(mg/dL)	(U/L)	(U/L)

☐Abnormality present but explained entirely by non-GVHD documented cause (specify):

☐Abnormality thought to represent GVHD PLUS other causes (specify):

Global severity rating

Where would you rate the severity of this patient's chronic GVHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:

0	1	2	3	4	5	6	7	8	9	10
Not at all severe										Most severe

Additional cGVHD details per organ

Lungs	Pulmonary Function Tests (PFTs)	diffusing capacity for carbon monoxide (DL_{CO}) (single breath, adjusted for hemoglobin)	Residual Volume (RV) (L)	Total lung capacity (TLC) (L)

OTHER SKIN GVHD FEATURES (NOT scored by BSA)

Check all that apply:

☐Hyperpigmentation	☐Poikiloderma	☐Hair Involvement
☐Hypopigmentation	☐Severe or generalized pruritus	☐Nail Involvement

Eyes	Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:	☐Yes	☐No	☐Not examined

OTHER cGVHD FEATURES	Other indicators, clinical features or complications related to chronic GVHD [check all that apply and assign a score to severity (0-3) based on functional impact where applicable; none: 0; mild: 1; moderate: 2; severe: 3]	
	☐Ascites (serositis) _____	☐Myasthenia Gravis _____
	☐Pericardial Effusion _____	☐Peripheral Neuropathy _____
	☐Pleural Effusion _____	☐Polymyositis _____
	☐Nephrotic syndrome _____	☐Others (specify):_____

Since starting BN101/belumosudil, would you say that this patient's cGvHD is:

	-3	-2	-1	0	1	2	3	Score
cGVHD Status	Very much worse	Moderately worse	A little worse	About the Same	A little better	Moderately better	Very much better	

Abstracted from: Lee SJ et al. (Biol Blood Marrow Transplant 2015; 21:984 – 999); Jagasia, et al (Biol Blood Marrow Transplant. 2015;21:389–401)

Appendix 6 cGVHD Response Assessment

Response Determination for Chronic GVHD Clinical Trials based on Clinician Assessments

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 ✖ULN
Lungs	• Normal %FEV1 after previous involvement • If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	• Increase by 10% predicted absolute value of %FEV1 • If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	• Decrease by 10% predicted absolute value of %FEV1 • If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

Abstracted from: Lee SJ, Wolff D, Kitko C, et al. Biol Blood Marrow Transplant 2015; 21:984 –999.

Appendix 7 cGVHD Lee Symptom Scale Score

By circling one number per line, please indicate how much you have been bothered by the following problems in the past 7 days:

Skin		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
1.	Abnormal skin color	0	1	2	3	4
2.	Rashes	0	1	2	3	4
3.	Thickened skin	0	1	2	3	4
4.	Skin ulcer	0	1	2	3	4
5.	Itchy skin	0	1	2	3	4
Eyes and Mouth		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
6.	Dry eyes	0	1	2	3	4
7.	Need to use eye drops frequently	0	1	2	3	4
8.	Difficulty seeing clearly	0	1	2	3	4
9.	Need to avoid certain foods due to mouth pain	0	1	2	3	4
10.	Ulcers in mouth	0	1	2	3	4
11.	Receiving nutrition from and intravenous line or feeding tube	0	1	2	3	4
Breathing		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
12.	Frequent cough	0	1	2	3	4
13.	Colored sputum	0	1	2	3	4
14.	Shortness of breath with exercise	0	1	2	3	4
15.	Shortness of breath at rest	0	1	2	3	4
16.	Need to use oxygen	0	1	2	3	4
Eating and Digestion		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
17.	Difficulty swallowing solid foods	0	1	2	3	4

18.	Difficulty swallowing liquids	0	1	2	3	4
19.	Vomiting	0	1	2	3	4
20.	Weight loss	0	1	2	3	4
Muscles and Joints		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
21.	Joint and muscle aches	0	1	2	3	4
22.	Limited joint movement	0	1	2	3	4
23.	Muscle cramps	0	1	2	3	4
24.	Weak muscled	0	1	2	3	4
Energy		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
25.	Loss of energy	0	1	2	3	4
26.	Need to sleep more/take naps	0	1	2	3	4
27.	Fevers	0	1	2	3	4
Mental Emotional		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
28.	Depression	0	1	2	3	4
29.	Anxiety	0	1	2	3	4
30.	Difficulty sleeping	0	1	2	3	4

Appendix 8 PROMIS Global Health Score

Please answer each of the following questions and mark the box by selecting an appropriate answer for each question.

		Excellent	Very good	Good	Fair	Poor
01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not At All**
06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
10	How often have you been bothered by emotional problems such as feeling anxious, depressed, or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very Severe**
08	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
07	How would you rate your pain on average?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		No Pain										Worst Imaginable Pain

Appendix 9 cGVHD Activity Assessment-Patient Self Report

Symptoms **Please rate how severe the following symptoms have been <u>in the last 7days</u>. Please fill in the circle below from 0 (symptoms has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
Your **skin itching** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
Your **skin and/or joint tightening** at their WORST?	○	○	○	○	○	○	○	○	○	○	○
Your **mouth sensitivity** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
Your **genital discomfort** at its WORST? (Women-vagina, vulva, or labia) (Men-penis)	○	○	○	○	○	○	○	○	○	○	○

Eyes	What is your main complaint with regard to your eyes?										
	Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe)	0	1	2	3	4	5	6	7	8	9	10

<u>Patient Global Ratings:</u>

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
1=mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe chronic GVHD symptoms possible.

0	1	2	3	4	5	6	7	8	9	10
cGVHD symptoms not at all severe										Most severe cGVHD symptoms possible

3. <u>Compared to a month ago,</u> overall would you say that your cGVHD symptoms are:

+3 = Very much better
+2 = Moderately better
+1 = A little better
0 = About the same
-1 = A little worse
-2 = Moderately worse
-3 = Very much worse

Abstracted from：Lee SJ, Wolff D, Kitko C, et al. Measuring Therapeutic Response in Chronic Graft-versus-Host Disease. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graftversus-Host Disease: IV. The 2014 Response Criteria Working Group Report. Biol Blood Marrow Transplant 2015;21:984 – 999.

Appendix 10 Eastern Cooperative Oncology Group (ECOG) Performance Status

Score	Description
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work.
2	Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours).
3	Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours).
4	Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair).
5	Death.

Appendix 11 Calculation Formula of Creatinine Clearance

Male：

Ccr=[(140-Age)×Weight(kg)]/[0.818×Scr (μmol/L)]

Female：

Ccr=[(140-Age)×Weight(kg)]/[0.818×Scr (μmol/L)] × 0.85

Annotation：

Ccr= Creatinine Clearance； Scr = Serum Creatinine

Scr (mg/dL) = Scr (μmol/L) × 0.01131

Appendix 12 Drugs that Induce and Inhibit CYP3A4

	Strong	Moderate	Weak
Inducers	Apalutamide Carbamazepine Enzalutamide Mitotane Phenytoin Rifampin St. John's wort	Bosentan Efavirenz Etravirine Phenobarbital Primidone	Armodafinil Modafinil Rufinamide
Inhibitiors	Boceprevir Cobicistat Conivaptan Danoprevir Dasabuvir Elvitegravir Grapefruit juice Indinavir Itraconazole Ketoconazole Lopinavir Paritaprevir Ombitasvir Posaconazole Ritonavir Saquinavir Telaprevir Tipranavir Telithromycin Troleandomycin Voriconazole	Aprepitant Ciprofloxacin Kaunivartan Crizotinib Cyclosporine Diltiazem Dronedarone Erythromycin Fluconazole Fluvoxamine Imatinib Tofisopam Verapamil	Chlorzoxazone Cilostazol Cimetidine Clotrimazole Fosaprepitant Istradefylline Ivacaftor Lomitapide Ranitidine Ranolazine Ticagrelor

This is not a comprehensive list, and all concomitant medications should be evaluated for possible interactions with BN101/belumosudil.

Data Source：

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Appendix 13 Drugs that Induce and Inhibit CYP1A2

	Strong	Moderate	Weak
Inducers	-	Phenytoin Rifampin Ritonavir Smoking Teriflunomide	-
Inhibitors	Ciprofloxacin Enoxacin Fluvoxamine	Methoxsalen Mexiletine Oral contraceptives	Acyclovir Allopurinol Cimetidine Peginterferon α-2a Piperine Zileuton

This is not a comprehensive list, and all concomitant medications should be evaluated for possible interactions with BN101/belumosudil.

Data Source：

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Appendix 9 Drugs that Prolong QT/QTc

Generic Name	
Aclarubicin	Hydroxychloroquine
Amiodarone	Ibogaine
Anagrelide	Ibutilid
Arsenic trioxide	Levofloxacin
Astemizole	Levomepromazine
Azithromycin	Levomethadyl acetate
Bepridil	Levosulpiride
Chloroquine	Mesoridazine
Chlorpromazine	Methadone
Chlorprothixene	Moxifloxacin
Cilostazol	Nifekalant
Ciprofloxacin	Ondansetron
Cisapride	Oxaliplatin
Citalopram	Papaverine HCl
Clarithromycin	Pentamidine
Cocaine	Pimozide
Disopyramide	Probucol
Dofetilide	Procainamide
Domperidone	Propofol
Donepezil	Quinidine
Dronedarone	Roxithromycin
Droperidol	Sevoflurane
Erythromycin	Sotalol
Escitalopram	Sparfloxacin
Flecainide	Sulpiride
Fluconazole	Sultopride
Gatifloxacin	Terfenadine
Grepafloxacin	Terlipressin
Halofantrine	Terodiline
Haloperido	Thioridazine
Dihydroquinidine	Vandetanib

This is not a comprehensive list, and all concomitant medications should be evaluated for possible interactions with BN101/belumosudil.

Data Source：https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf (30 Dec 2019)

Appendix 10 Equivalent Dose of Corticosteroid Hormone

Class of Drug	Name of Drug	Equivalent Dose（mg）
Short-acting	Hydrocortisone	20
	Cortisone	25
Medium-acting	Prednisone	5
	Prednisolone	5
	Methylprednisone	4
Long-acting	Triamcinolone acetonide	4
	Betamethasone	0.60
	Dexamethasone	0.75
Hydrocortisone 1 = Cortisone 0.8 = Prednisone 4 = Prednisolone 4 = Methylprednisone 5 = Triamcinolone acetonide 5 = Betamethasone 25 = Dexamethasone 20		

Annotation：
The ratio of anti-inflammatory effect is based on counting hydrocortisone as 1. The equivalent dose is counted with a standard of hydrocortisone.
Data Source：http://news.medlive.cn/imm/info-progress/show-150532_166.html