CLINICAL STUDY PROTOCOL

Protocol Title: Phase 2, single arm, Belumosudil and Ruxolitinib combination 3rd line therapy after 2nd line Ruxolitinib failure for chronic Graft vs Host Disease (cGvHD) treatment (**BELRUX**)

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
aGvHD	Acute graft-versus-host disease
ALP	Alkaline Phosphatase
ALT	Alanine Amino Transferase
APC	Antigen-presenting cell
AST	Aspartate Amino Transferase
BID	Twice a day
BSA	Body Surface Area
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
cGvHD	Chronic Graft versus Host Disease
d	Day
DSMB	Data Safety Monitoring Board
DLI	Donor Lymphocyte Infusion
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECP	Extracorporeal photopheresis
eCRF	Electronic Case Report Forms
EDC	Electronic data capture
FEV1	Forced Expiratory Volume in 1 second
FFS	Failure-free survival
GCP	Good Clinical Practice
GvHD	Graft versus Host Disease
h / hr	Hour
HBV	Hepatitis B Virus
HCT	Hematopoietic Stem Cell Transplantation
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPFB/TPD	Health Products and Food Branch/Therapeutic Products Directorate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
ITT	Intention To Treat
JAK	Janus kinase
Kg	Kilogram

L	Litre
LAR	Legally Acceptable Representative
min	Minute
ml	Millilitre
mLSS	Modified Lee Symptom Scale
MMF	Mycophenolate mofetil
NCI	National Cancer Institute
OD	Once a day
ORR	Overall Response Rate
PFTs	Pulmonary Function Tests
PI	Principal Investigator
PO	Per os/ By mouth / Orally
PPI	Proton pump inhibitor
PR	Partial Response
P-ROM	Photographic Range-Of-Motion
q	Every
QI	Qualified Investigator
RBC	Red Blood Cells
REB	Research Ethics Board
ROCK2	Rho-associated protein kinase-2
SAE	Serious Adverse Event
SOC	Standard of Care
Tregs	Regulatory T-cells
ULN	Upper Limit of Normal
μg	Microgram
WBC	White Blood Cell
WHO	World Health Organization

SYNOPSIS

Study Title:	Phase 2, single arm, Belumosudil and Ruxolitinib combination 3rd line therapy after 2nd line Ruxolitinib failure for chronic Graft versus Host Disease (cGvHD) treatment (**BELRUX**)
Primary Objective and Endpoint:	To evaluate the efficacy, tolerability and safety of combination treatment of belumosudil with ruxolitinib as a third line therapy for steroid refractory cGvHD 1. Efficacy will be assessed using failure-free survival (FFS) at 48 weeks in the belumosudil + ruxolitinib 3rd-line phase (i.e. after initiation of the combination following documented ruxolitinib 2nd-line failure for chronic GvHD).
Secondary Objective and Endpoints:	To evaluate the response achievement with combination treatment of belumosudil with ruxolitinib as third-line treatment for cGvHD, and to characterize response, safety and toxicity during both the ruxolitinib 2nd-line phase and the belumosudil + ruxolitinib 3rd-line phase. 1) Overall response rate (ORR) as per the NIH cGvHD Consensus Response Criteria after 24 and 48 weeks of combination treatment of belumosudil with ruxolitinib. 2) FFS at 24 weeks in the belumosudil + ruxolitinib 3rd-line phase; and FFS at 24 and 48 weeks (from initiation of ruxolitinib) in the ruxolitinib 2nd-line therapy. 3) Durable response rate in patients who achieve complete or partial response with combination treatment of belumosudil with ruxolitinib as assessed at 48 weeks from C1D1. Durable response is defined as sustained improvement in symptoms or absence of disease progression from the time of treatment initiation. 4) Cumulative incidence of ruxolitinib failure at 24 and 48 weeks and cause of ruxolitinib failure (progression of primary cGvHD, mixed response (CR/PR in one organ and progression/new onset in other organ), toxicity, NRM) & ORR at 24/48 weeks with ruxolitinib 2nd line therapy 5) Overall response rate (ORR) as per the NIH cGvHD Consensus Response Criteria after 24 and 48 weeks of ruxolitinib 2nd line therapy; FFS rate at 48 weeks of ruxolitinib 2nd line therapy; Cumulative incidence of ruxolitinib failure at 24 and 48 weeks and cause of ruxolitinib failure (progression of primary cGvHD, mixed response (complete/ partial response in one organ and progression/new onset in other organ), toxicity, Non-relapse mortality) and failure rate at 24 and 48 weeks following 2nd line

	ruxolitinib therapy following steroid refractory chronic GvHD & ORR at 24 and 48 weeks with ruxolitinib 2nd line therapy 6) Overall GvHD symptom burden improvement, serially measured using the modified Lee Symptom Scale (see Appendix D) evaluated separately for the ruxolitinib 2nd-line phase and the belumosudil + ruxolitinib 3rd-line phase
Exploratory Objectives and Endpoints:	To evaluate improvement in musculoskeletal involvement of sclerotic GvHD using the P-ROM score measurement. 1) Changes in the P-ROM score after 4, 8, 12, 24, and 48 weeks of combination therapy for patients who have developed sclerotic GvHD in musculoskeletal involvement of GvHD 2) Current failure-free survival (cFFS) at last follow-up (or at 72 weeks) from initiation of ruxolitinib (i.e. ruxolitinib 2nd-line therapy)
Study Design:	This is a phase II, non-randomized, open-label study in patients with moderate to severe cGvHD who have failed to respond or are intolerant to front line corticosteroid therapy. It has two phases: 1) ruxolitinib 2nd line therapy phase; 2) belumosudil and ruxolitinib combination 3rd line therapy phase. In the ruxolitinib 2nd line phase, patients will receive ruxolitinib monotherapy as 2nd line treatment for 48 weeks. Whenever the patients meet pre-determined criteria of ruxolitinib failure, the patient will be switched over to belumosudil and ruxolitinib combination 3rd line therapy. Patients will be monitored for documented individual efficacy/safety/toxicity as third line treatment in cGvHD patients. In ruxolitinib 2nd line phase, participants will begin on 10 mg BID of oral ruxolitinib monotherapy for one cycle (i.e. Cycle 1). Each cycle is equal to 28 days. Response will be assessed at Weeks 4, 8, 12, 24, 36, and 48. Participants will continue ruxolitinib monotherapy for up to 48 weeks unless the pre-specified criteria for ruxolitinib treatment failure (refer to section 2) are met at one of the scheduled response assessments. Upon documentation of ruxolitinib failure, patients will begin taking belumosudil in addition to ruxolitinib, at a dose of 200 mg OD or 200 mg BID (if on a PPI). Patients will remain on combination therapy for 48 weeks (i.e. 12 cycles), until progression of cGVHD, or intolerance to either agent, whichever occurs sooner. A visit will be conducted at the end of treatment, 28 days post- end of treatment as well as 24 weeks (6 months) post-end of treatment.

Duration:	The enrollment period of the study is expected to be 12-18 months. The maximum duration of the study will be 2.5 years. The screening period for each patient may last up to 14 days. Participants will receive ruxolitinib monotherapy until documented treatment failure or for up to 48 weeks, whichever occurs first. Upon documented treatment failure, belumosudil will be added to ongoing ruxolitinib therapy for up to 48 weeks (12 cycles). Participants will be followed for 24 weeks after the end of treatment to assess cGVHD progression, survival, and safety. If ruxolitinib monotherapy failure is not observed by 48 weeks, participants will come off study and continue ruxolitinib therapy as SOC.
Planned Total Sample Size:	A maximum of 53 patients will be enrolled.
Investigational Product Administration:	Belumosudil will be administered as an oral dose of 200 mg OD or 200 mg BID (if patient is on a proton pump inhibitor (PPI)) with ruxolitinib 10mg BID as 3rd line therapy after ruxolitinib failure based on pre-specified ruxolitinib failure criteria
Patient Inclusion/ Exclusion Criteria:	**Inclusion Criteria:** 1. 18 years of age or older at the time of enrollment. 2. Has previously been diagnosed with moderate to severe cGvHD OR mild cGvHD with high-risk features (defined as platelet counts < 100 x 10^9/L at screening). 3. Capable of providing informed consent. 4. Meets the criteria of steroid-refractory cGvHD after first line corticosteroids therapy at the time of enrollment, as follows: • Lack of response or disease progression after prednisone ≥1 mg/kg/day for ≥1 week **OR** • Disease persistence without improvement with prednisone >0.5 mg/kg/day or 1 mg/kg/every other day for ≥4 weeks **OR** • Increase in prednisone dose to >0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose. 5. Taking a steroid dose at the time of enrollment that is <0.5mg/kg/day of prednisone or equivalent. 6. Absolute neutrophil count ≥ 1.5 × 10^9/L within 2 weeks (14 days) of enrollment. 7. Platelet count ≥ 50 × 10^9/L within 2 weeks of enrollment. 8. ALT and AST ≤ 5 × ULN (<7.5 x ULN if due to liver GvHD) within 2 weeks of enrollment. 9. Total bilirubin ≤ 1.5 × ULN within 2 weeks of enrollment. 10. Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 using the MDRD-4 variable formula within 2 weeks of enrollment. 11. Female patients of childbearing potential will use 2 reliable methods of birth control (refer to Section 9.3) or be surgically

sterile, or abstain from heterosexual activity for the course of the study from the time of study enrollment until 3 months following the discontinuation of all study treatment and agree not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period. Patients of childbearing potential are those who have not been surgically sterilized (i.e. have a documented hysterectomy, or documented bilateral salpingectomy, or documented bilateral oophorectomy) or have not been free from menses for > 2 years. For individuals with permanent infertility due to an alternate medical cause other than the above (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis) investigator discretion should be applied to determining study entry eligibility.

Male patients will use an adequate method of contraception for the course of the study from the time of enrollment to 3 months after discontinuation of all study treatment. These participants must refrain from donating or cryopreserving sperm, be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent or must agree to use contraception (a male condom and an additional highly effective contraceptive method as described in Section 9.3) when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

12. Patients showing overlap syndrome with components of aGvHD at the time of enrollment are eligible to participate unless the acute component of their overlap syndrome is Grade 3 or 4.
13. Must be able and willing to comply with study procedures.

Exclusion Criteria:

1. Receiving ruxolitinib for active steroid refractory acute GvHD at the time of enrollment. Participants with a prior history of aGvHD are eligible only if the aGvHD has achieved CR or PR prior to screening and the participants subsequently developed steroid refractory cGvHD.
2. Have never been treated with systemic steroids as therapy for cGvHD.
3. Receiving >0.5 mg/kg/day of prednisone or equivalent corticosteroids at the time of enrollment.
4. Ongoing use of any of the following pharmaceutical agents, which cannot be discontinued prior to belumosudil treatment (PRN/as-needed use is permissible if it can be fully discontinued at least 7 days prior to enrollment and is not expected to resume during the study):
    - Strong CYP3A inducers
    - UGT1A1 substrates (e.g., raltegravir)

	• P-gp substrates (e.g., dabigatran) • OATP1B1/OATP1B3/BCRP substrates (e.g., rosuvastatin) 5. Has had prior treatment with a JAK inhibitor or ROCK2 inhibitor within 8 weeks of enrollment. Participants who received a JAK inhibitor for aGvHD are eligible only if they achieved CR or PR prior to screening. 6. Active uncontrolled bacterial, fungal, parasitic, or viral infection. Infections are considered controlled if appropriate therapy has been initiated and, at the time of screening, no signs of infection are present. 7. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection that requires treatment, or is at risk for HBV reactivation (i.e., positive HBsAg) within 4 weeks of enrollment. Participants with negative HBsAg and positive total HBc antibody may be included if HBV DNA is undetectable at the time of screening. Participants who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA. Participants whose immune status is unknown or uncertain must have results confirming immune status before enrollment. 8. Known active infection or history of human immunodeficiency virus (HIV). 9. Evidence of relapsed primary hematologic disease, or receipt of treatment for relapse after the allo-HCT was performed. Patients treated with Donor Lymphocyte Infusion (DLI) who have developed GvHD will not be excluded if the primary hematological disease has resolved. 10. Maintenance therapy for the primary hematologic disease started within 4 weeks before initiation of study treatment (Cycle 1 Day 1) or plans to start maintenance therapy after Day 1. 11. Participants on mechanical ventilation, requiring oxygen support or with a FEV1 < 30%. 12. History or current diagnosis of cardiac disease indicating significant risk of safety for participation in the study, such as uncontrolled or significant cardiac disease, including any of the following: a. Recent myocardial infarction (within 6 months of enrollment) b. New York Heart Association Class III or IV congestive heart failure c. Unstable angina (within 6 months of enrollment) d. Clinically significant (symptomatic) cardiac arrhythmias (e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker).

	13. Uncontrolled hypertension, defined as blood pressure that remains above 130/80 mmHg in spite of concurrent use of at least three antihypertensive agents of different classes. 14. Patients with known active CNS disease (malignant involvement of CNS). 15. Patients with active acute GvHD grade III-IV. 16. History or other evidence of severe illness or any other conditions that would make the patient, in the opinion of the treating Investigator, unsuitable for the study (such as malabsorption syndromes, poorly controlled psychiatric disease or coronary artery disease). 17. Known hypersensitivity to belumosudil, ruxolitinib or any of their excipients 18. Patients unable to swallow oral medications 19. Female participants who are pregnant or breastfeeding
Patient Screening Assessments:	• Written Informed Consent • Inclusion/Exclusion Criteria • Demographics • Medical History & Prior GvHD Treatments • Tuberculosis Skin Test / Interferon -gamma release assay • Physical Examination (includes height and weight) & ECOG performance status assessment • Vital Signs • 12-lead ECG • Urine pregnancy test in biologically female patients • Hematology • Serum Chemistry • Virology • Concomitant Medications • Correlative Sampling (optional) • P-ROM (Photographic Range-Of-Motion) assessment
Treatment and Post-Treatment Assessments:	Assessments to be completed on visits as per the Study Calendar Treatment Phase Phase 1: ruxolitinib 2nd line therapy (1, 4, 8, 12, 24, 36 and 48 weeks) Phase 2: belumosudil+ ruxolitinib 3rd line therapy (when ruxolotinib failure criteria met) on 1, 2, 4, 8, 12, 24, 36 and 48 weeks • Physical Examination & ECOG performance status assessment • Vital Signs • Hematology • Serum Chemistry • AE Assessment if required • Ruxolitinib and Belumosudil administration • Concomitant Medications • NIH consensus based GvHD organ specific score and global severity score (i.e. mild vs moderate vs severe grade)

	• NIH consensus based GvHD response assessment • Modified Lee Symptom Scale • P-ROM (Photographic Range-Of-Motion) assessment • Serum pregnancy test in biologically female patients • Pulmonary Function Test • IP return and accountability • Correlative Samples (as per the Study Calendar, optional) <u>End of Treatment Visit</u> • Physical Examination & ECOG • Vital Signs • Hematology • Serum Chemistry • AE Assessment • Concomitant Medications • NIH consensus based GvHD organ specific score and global severity score (i.e. mild vs moderate vs severe grade) • Modified Lee Symptom Scale • P-ROM (Photographic Range-Of-Motion) assessment • Pulmonary Function Test • IP return and accountability • Correlative Samples <u>Follow-up Visit</u> • Physical Examination & ECOG • Vital signs • P-ROM assessment • Hematology • Serum chemistry • P-ROM (Photographic Range-Of-Motion) assessment • Survival status • Concomitant Medications (new cGvHD therapies only)
Response:	1) Failure-free survival (FFS) will be evaluated using the Kaplan-Meier method. FFS at 48 weeks in the belumosudil + ruxolitinib 3rd-line phase is the primary endpoint; FFS is additionally evaluated at 24 weeks in the 3rd-line phase, and at 24 and 48 weeks (from initiation of ruxolitinib) in the ruxolitinib 2nd-line phase 2) Overall response rate (ORR) will be evaluated at 24 and 48 weeks in the belumosudil + ruxolitinib 3rd-line phase and, separately, at 24 and 48 weeks in the ruxolitinib 2nd-line phase 3) Durable response after response achievement will be evaluated only in the patients who achieved CR or PR during the treatment period (any response), following second-line ruxolitinib therapy

	and third-line combination therapy with belumosudil plus ruxolitinib
Safety Variables & Analysis:	The safety and tolerability of study treatment will be evaluated by means of AE reports, physical examinations, and laboratory safety evaluations. Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used for grading of AEs. In the ruxolitinib 2nd line therapy phase, as patients will be receiving standard of care treatment, toxicity will be managed as per the product monograph. In the ruxolitinib 3rd line combination with belumosudil therapy phase, protocol-defined dose modifications should be followed as per section 5.3. Interim safety data will be examined on an ongoing basis to ensure patient safety.
Statistical Analysis:	**Statistical Analysis:** This is a single-arm phase II study with a sample size of 53 patients (accounting for 10% dropout) to provide at least 80% power to detect an improvement in failure-free survival (FFS) at 48 weeks in the belumosudil + ruxolitinib 3rd-line phase from 67% (null, REACH3) to 90% (alternative), assuming a ruxolitinib failure rate of approximately 40–50% in the ruxolitinib 2nd-line phase, at a two-sided alpha of 0.05 **Populations:** - Intent-to-Treat (ITT): All enrolled patients. - Safety: All patients receiving ≥1 dose of belumosudil. - Efficacy: All patients completing ≥1 cycle of belumosudil with baseline assessment. **Analyses:** - Primary (FFS): Failure-free survival rate at 48 weeks in the belumosudil + ruxolitinib 3rd-line phase, estimated by the Kaplan-Meier method with 95% CI. - Secondary (Safety/Tolerability): Incidence and severity of AEs summarized by frequency, percentage, grade (CTCAE v5.0), and relationship to study drug. - Secondary (ORR at 48 weeks, FFS, Durable response): Kaplan-Meier estimates with 95% CI.

	- Secondary (Ruxolitinib failure): cumulative incidence of ruxolitinib failure and cause of failure at 24 and 48 weeks; failure rate and ORR for ruxolitinib 2nd line therapy summarized descriptively with 95% CI. - Secondary (Symptom burden): Repeated measures analysis using general linear model ($p<0.05$ for significance). - Exploratory (P-ROM changes): Descriptive summaries of changes at 4, 8, 12, 24 and 48 weeks. Descriptive statistics (frequencies/percentages for categorical; mean/SE/median for continuous) will be used. The final analysis will be performed once all participants have either completed at least 48 weeks of treatment or discontinued study treatment prior to Week 48. Data from all participating centers will be pooled. Demographic and baseline characteristics will be summarized descriptively (frequencies/percentages for categorical variables; mean/SD/median/min-max/25th-75th percentiles for continuous). Graphical summaries may be used. Dose modifications will be summarized by frequency, percentage, and reason. All tests will use a two-sided alpha=0.05 unless specified. Exploratory analyses may be added as appropriate. No interim analyses are planned. Study populations are defined in 11.2. Endpoint evaluations are detailed in 11.3, including: - Proportions with 95% CI for binary outcomes (e.g., ORR). - Kaplan-Meier method for time-to-event outcomes (e.g., FFS, durable response). - Repeated measures using general linear model for longitudinal data (e.g., symptom burden). - Descriptive statistics for changes in exploratory measures (e.g., P-ROM scores).

1. INTRODUCTION

1.1 Background

1.1.1 Chronic Graft versus Host Disease

Allogeneic Hematopoietic Stem Cell Transplantation (HCT) is a potentially lifesaving intervention for patients diagnosed with certain hematological disorders and cancers of the hematopoietic system. Major complications can develop in the post-transplant period and cause significant morbidity and mortality. One of the most common complications amongst these is acute and chronic graft versus host disease (GvHD). Chronic GvHD (cGvHD) affects anywhere from 30-70% of transplant recipients and significantly impacts short-term, intermediate, and long-term outcomes [1,2]. GvHD risk is affected by numbers of clinical factors, including but not limited to donor/recipient HLA mismatch, increased age (donor or recipient), sex, intensity of the pre-transplant conditioning regimen, and donor source [3]. The pathophysiology of cGvHD involves a complex interplay between the donor immune cells and the host tissues, which leads to the deregulation of immune pathways, chronic inflammation, tissue damage, and fibrosis. The process begins with the activation of donor T cells by recipient antigens, which then proliferate and differentiate into effector T cells and attack recipient tissues, initiating an inflammatory response [4]. Also, deregulated immune pathways contribute to chronic immune activation by recipient antigens and subsequent chronic inflammation.

The pathogenesis of cGvHD is understood to involve three phases, which occur simultaneously. The *inflammatory phase* includes the release of cytokines and chemokines, which recruit additional immune cells to the site of injury [4]. In the *immune deregulation phase*, these immune cells then amplify the inflammatory response and cause tissue damage, leading to the release of additional danger signals that further stimulate the immune response. Finally, in the *fibrotic phase*, chronic inflammation can lead to irreversible tissue fibrosis, which can impair organ function and cause long-term damage. The development of fibrosis is thought to be due to the activation of fibroblasts and myofibroblasts by the chronic inflammatory response. Understanding the different involvement of disease phases is fundamental for therapeutic drug selection with different action mechanisms.

1.1.2 Management of Chronic GvHD

The treatment paradigm of cGvHD is evolving, driven by improved understanding of its pathophysiology and the emergence of effective novel therapies. Systemic cGvHD therapy has three ideal aims, including (1) the induction of immunologic tolerance, (2) the reversal and limiting of organ damage and the preservation of affected organ function, and (3) the successful discontinuation of all systemic immunosuppression without the recurrence of GvHD and without relapse of hematological malignancy [2]. Systemic therapy is indicated for patients with moderate-to-severe grade cGvHD, which is defined

according to the NIH 2014 criteria as the involvement of three or more organs, moderate or severe grade organ involvement in any organ, or any highly morbid form of GvHD, such as lung or sclerotic GvHD [6]. Front-line therapy of moderate to severe cGvHD is treatment with corticosteroids with or without the addition of another systemic agent for steroid-sparing purposes, such as calcineurin inhibitors, which were reported to alter the natural course of the disease [7]. In patients who do not respond or remain steroid dependent there are several therapeutic options including ibrutinib, extracorporeal photopheresis (ECP), conventional immunosuppressive agents like mycophenolate mofetil (MMF), and novel agents such as ruxolitinib and belumosudil.

Ruxolitinib, a Janus kinase (JAK) inhibitor, is the only drug that demonstrated a clinical benefit and superior efficacy over the best available therapy in a phase III trial as a second-line treatment [8]. The REACH3 study and the Canadian real-world experience studies, have shown that ruxolitinib can lead to improvements in symptoms, overall response, and failure-free survival (FFS) while reducing the need for corticosteroids [9]. Accordingly, it is considered as a second-line option for steroid-refractory cGvHD in Canada and elsewhere [10]. Belumosudil is an orally available Rho-associated protein kinase-2 (ROCK2) selective inhibitor which is involved in the signalling pathways that lead to inflammation and tissue damage in cGvHD [11]. In July 2021, the FDA approved belumosudil in the US for the treatment of adult and pediatric patients aged 12 years and older with cGvHD after failure of at least two prior lines of systemic therapy. Belumosudil was also approved for the same indication in Canada in March of 2022.

1.2 Study Rationale

Contemporary systemic therapy for cGvHD usually lasts between one to three years. Initial treatment for moderate to severe cGvHD typically involves systemic corticosteroids, such as prednisone at a dose of 0.5-1 mg/kg/day, which is then tapered, sometimes in combination with calcineurin inhibitors. Although corticosteroids are the standard of care for the initial treatment of moderate to severe cGvHD, 50-60% of patients may become refractory to these drugs and may require additional systemic therapy beyond corticosteroids and calcineurin inhibitors within two years of starting treatment [12]. There are limited prospective comparative studies evaluating the effectiveness and safety of second-line therapies for cGvHD. As a result, no single treatment has been established as superior, and there is no standard of care once corticosteroid resistance develops.

Ruxolitinib is approved as standard second-line therapy for steroid-refractory cGvHD (SR-cGvHD). Ruxolitinib demonstrates efficacy relatively quickly due to its anti-inflammatory mechanism, making it useful for controlling the inflammatory processes seen early in cGvHD, while it does not appear to substantially impact established fibrotic disease. Accordingly, ruxolitinib failure occurs frequently in the clinical practice and has been reported at about 50% of patients fail ruxolitinib therapy within this timeframe. Recently EBMT panel presented a consensus-based guideline for ruxolitinib failure for chronic

GvHD management. The followings are the proposed criteria for ruxolitinib failure suggested by the EBMT panel.

- Progression by Day 28 from ruxolitinib initiation.
- Progression at Day 28 in only one organ, with a clinically meaningful partial response (PR) in other organs.
- Stable disease or a non–clinically meaningful partial response at any response assessment.
- Failure to achieve a partial remission 3 months as per investigator's discretion or at any response assessment thereafter.

However, it has not been prospectively validated whether this criteria correlates with long-term outcomes and how many patients are going to be classified as ruxolitinib failure. Also it is not completely clear how to manage this subgroup of patients with novel agents. The EBMT provisional recommendation suggests belumosudil without reservation as 3rd line therapy either as monotherapy or as add-on (thus combination of belumosudil and ruxolitinib).

Belumosudil is approved as third-line therapy for cGvHD in the United States and Canada, and as second-line therapy in select jurisdictions such as Japan and China. Real-world experience (RWE) suggests that combined use of belumosudil with ruxolitinib is feasible, effective, and tolerable, without evidence of clinically significant drug-drug interaction (DDI). However, this combination has not yet been systematically evaluated in a prospective study. The CTTC 2024 guideline identifies combination strategies as a promising future direction for cGvHD treatment [2], given the complementary mechanisms of action of the two agents: ruxolitinib provides robust anti-inflammatory activity, while belumosudil is uniquely effective in reversing established fibrosis associated with cGvHD.

While the EBMT provisional recommendation provide an objective, standardized, and clinically actionable definition of ruxolitinib failure, it has not been consistently applied in prior real-world or retrospective studies of ruxolitinib in SR-cGvHD, where "failure" has often been loosely defined post hoc rather than prospectively assessed at pre-specified timepoints. By anchoring failure assessment to Day 28 and subsequent 3-monthly intervals, this study allows for early identification of primary non-response (warranting prompt transition to alternative therapy) while also distinguishing patients with partial, organ-specific responses who may benefit from add-on therapy rather than a full change in treatment strategy.

Preliminary data support the combination of belumosudil with ruxolitinib in ruxolitinib-refractory cGvHD. In real-world experience, concurrent administration of the two agents has been feasible and well tolerated, with no clinically significant pharmacokinetic drug–drug interaction identified between belumosudil and ruxolitinib. Recently reported combination data in patients with ruxolitinib-refractory cGvHD ([24]; n=57, of whom approximately two-thirds had NIH severe-grade disease and had received five or more prior lines of therapy) demonstrated meaningful organ responses across multiple involved

sites together with durable failure-free survival, without a signal for increased toxicity relative to either agent alone. Together, these observations suggest that adding belumosudil to ruxolitinib at the time of ruxolitinib failure can rescue response and potentiate efficacy while preserving safety, providing the rationale for prospective evaluation of this combination as a defined third-line strategy.

Based on this rationale, the present study proposes a two-phase treatment strategy that reflects real-world sequential practice and current approval pathways, rather than upfront combination therapy:

Phase 1: Ruxolitinib monotherapy as second-line therapy - Patients will initiate ruxolitinib monotherapy as second-line treatment for SR-cGvHD, with response assessed at 4, 8, 12, 24, 36 and 48 weeks, for up to 48 weeks or until the pre-specified ruxolitinib failure criteria above are met, whichever occurs first.

Phase 2: Belumosudil/Ruxolitinib combination as third-line therapy - Patients who meet ruxolitinib failure criteria will transition to combination therapy with belumosudil added to ongoing ruxolitinib, administered as third-line treatment. Response will again be assessed at 2, 4, 8, 12, 24, 36 and 48 weeks for up to 48 weeks of combination treatment.

This design allows the study to first characterize the real-world failure rate and kinetics of ruxolitinib monotherapy as second-line therapy using standardized, prospectively applied failure criteria, then prospectively evaluate, for the first time, the efficacy, toxicity, and feasibility of adding belumosudil to ruxolitinib in patients who have failed ruxolitinib, reflecting its use as third-line therapy. This addresses a clear gap in the literature: no prospective study to date has evaluated this specific combination sequence using pre-defined, objective failure criteria, despite growing real-world use and guideline-level interest in combination strategies for cGvHD.

1.3 Rationale for starting dose and dosing schedule

Ruxolitinib will be administered orally to patients, as per standard of care (SOC), at a dose of 10 mg BID as indicated in the product monograph for patients with cGvHD. Patients may require dose reductions or modifications of ruxolitinib during the course of treatment based on side effect profile, clinical assessment, and laboratory assessments. No dose increases above 10 mg BID will be allowed in the study due to the very limited clinical experience with such doses in patients with GvHD. Participants will initiate treatment with ruxolitinib monotherapy (10 mg twice daily) as second-line therapy for steroid-refractory chronic graft-versus-host disease (SR-cGVHD). Response will be assessed at predefined time points (Weeks 4, 8, 12, 24, 36, and 48). Participants will continue ruxolitinib monotherapy for up to 48 weeks unless the pre-specified criteria for ruxolitinib treatment failure are met at one of the scheduled response assessments. Upon documentation of ruxolitinib failure, patients will receive the investigational medicinal product (IMP) belumosudil orally at a dose of 200 mg OD or 200 mg BID (if on a proton pump inhibitor (PPI)) as based on the published activity and safety data in the ROCKstar trial [11]. Several

real-world experience studies reported no significant toxicity profile or drug-drug interaction issue from combination of ruxolitinib and belumosudil [13,14]. Dose reductions and modifications are described in Section 5.3. Patients will remain on dual therapy for an additional 12 months until progression of cGVHD, or intolerance to either agent, whichever occurs sooner.

2. STUDY DESIGN

This is a phase II non-randomized, open-label study in patients with moderate to severe cGvHD who have failed to respond to, or are intolerant of first line therapy. Patients will receive ruxolitinib monotherapy as second-line therapy and will be assessed for response at Weeks 4, 8, 12, 24, 36, and 48. Upon documented ruxolitinib failure, patients transition to third-line combination therapy with two oral agents (belumosudil and ruxolitinib), each with documented individual efficacy in cGvHD. A maximum of 53 participants are expected to be enrolled in Canada.

Participants will begin on 10 mg BID of oral ruxolitinib monotherapy in 2nd line phase. Response will be assessed at predefined time points (Weeks 4, 8, 12, 24, 36, and 48). When ruxolitinib failure is documented at any assessment based on the below criteria, then the participants will be moved to belumosudil-ruxolitinib combination phase as 3rd line therapy.

Ruxolitinib Failure Criteria:

- Progression by Day 28 from ruxolitinib initiation.
- Progression at Day 28 in only one organ, with a clinically meaningful partial response (PR) in other organs.
- Stable disease or a non–clinically meaningful partial response at any response assessment.
- Failure to achieve a partial remission by 3 months as per investigator's discretion or at any response assessment thereafter

In the belumosudil-ruxolitinib combination phase as 3rd line, belumosudil will be added to ongoing ruxolitinib, at a dose of 200 mg OD or 200 mg BID (if on a PPI). Patients will remain on dual therapy for upto 48 weeks (i.e. 12 cycles), until progression of cGVHD, or intolerance to either agent, whichever occurs sooner. A safety visit will be conducted at the end of treatment, 28 days following end of treatment, as well as a remote follow up visit conducted 24 weeks following end of treatment.

The endpoints will include failure-free survival at 48 weeks after initiation of combination therapy with belumosudil and ruxolitinib 3rd-line phase, overall response rate at 24 and 48 weeks after initiation of combination therapy, and failure-free survival measured from the start of ruxolitinib monotherapy to evaluate the impact of rescue treatment with combination therapy in patients who experience treatment failure on ruxolitinib alone. Failure-free survival is defined as the absence of any of the following events: (1) initiation of additional systemic therapy or a switch in treatment for chronic graft-versus-host

disease (cGVHD), (2) progression/relapse of primary disease, and (3) death due to non-relapse mortality.

2.1 Estimated Study Duration

The enrollment period of the study is expected to be approximately 12–18 months. The maximum duration of the study will be 2.5 years. The screening period may last up to 14 days. In Phase 1 (ruxolitinib monotherapy for 2nd line), participants will receive ruxolitinib monotherapy and will be assessed for response at Weeks 4, 8, 12, 24, 36, and 48. Participants with documented treatment failure at any assessment will initiate combination therapy with belumosudil and ruxolitinib, which will continue for up to 48 weeks (12 cycles). Patients will be followed for evidence of progression of cGVHD, survival, and unexpected toxicity (if any) for 24 weeks after the end of treatment visit. If ruxolitinib monotherapy failure is not observed by 48 weeks, participants will come off study and continue ruxolitinib therapy as SOC.

2.2 Study Schema

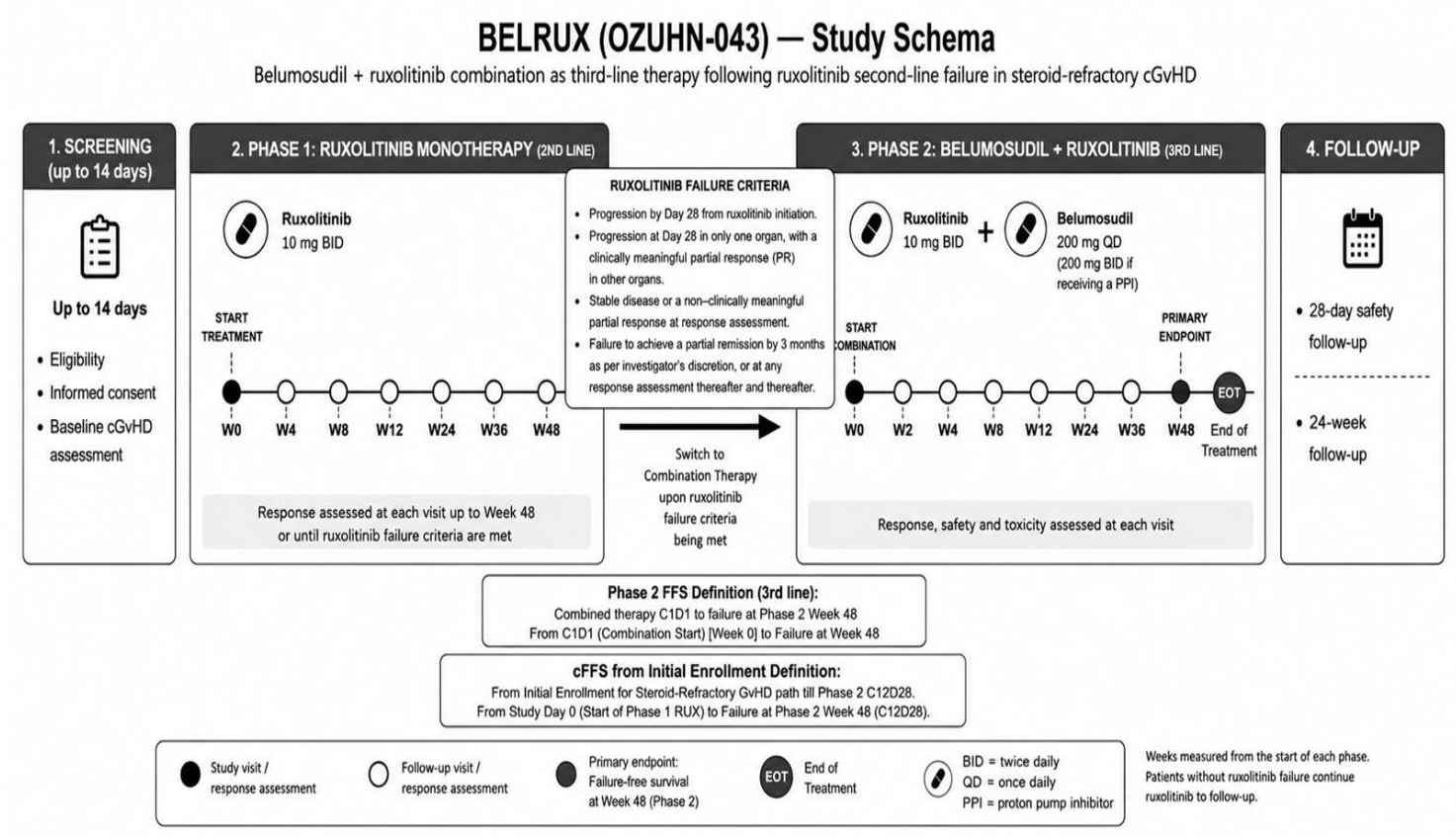

Figure 1. Participant treatment schema

3. OBJECTIVES

Primary Objectives	Primary Endpoint
To evaluate efficacy, tolerability and safety of combination treatment of belumosudil with ruxolitinib as third line therapy for steroid-refractory cGvHD.	1. **Efficacy will be assessed using failure-free survival (FFS) at 48 weeks following combination treatment of belumosudil with ruxolitinib 3rd line phase (i.e., after initiation of the combination following documented Ruxolitinib 2nd line failure for chronic GvHD). FFS is defined as the time from treatment initiation of combination therapy until the occurrence of treatment failure, progression/relapse of primary disease or non-relapse mortality whichever occurs first.**
Secondary Objectives	**Secondary Endpoints**
To evaluate the response achievement with combination treatment of belumosudil with ruxolitinib as third-line treatment for cGvHD, and to characterize response, safety and toxicity during both the ruxolitinib 2nd-line phase and the belumosudil + ruxolitinib 3rd-line phase.	1. ORR as per the NIH cGvHD Consensus Response Criteria after 24 and 48 weeks of combination treatment of belumosudil with ruxolitinib. 2. FFS at 24 weeks of combination of belumosudil and ruxolitinib 3rd-line phase; and FFS at 24 and 48 weeks (from initiation of ruxolitinib) in the ruxolitinib 2nd-line therapy 3. Durable response rate in patients who achieve complete or partial response with combination treatment of belumosudil with ruxolitinib as assessed at 48 weeks from C1D1. Durable response is defined as sustained improvement in symptoms or absence of disease progression from the time of treatment initiation. 4. Cumulative incidence of ruxolitinib failure at 24 and 48 weeks and cause of ruxolitinib failure (progression of primary cGvHD, mixed response (CR/PR in one organ and progression/new onset in other organ), toxicity, NRM) & ORR at 24/48 weeks with ruxolitinib 2nd line therapy

	5. Overall response rate (ORR) as per the NIH cGvHD Consensus Response Criteria after 24 and 48 weeks of ruxolitinib 2nd line therapy; Cumulative incidence of ruxolitinib failure at 24 and 48 weeks and cause of ruxolitinib failure (progression of primary cGvHD, mixed response (complete/ partial response in one organ and progression/new onset in other organ), toxicity, Non-relapse mortality) and failure rate at 24 and 48 weeks following 2nd line ruxolitinib therapy following steroid refractory chronic GvHD & ORR at 24 and 48 weeks with ruxolitinib 2nd line therapy 6. Overall GvHD symptom burden improvement, serially measured with a modified Lee Symptom Scale (see Appendix D) evaluated separately for the ruxolitinib 2nd-line phase and the belumosudil + ruxolitinib 3rd-line phase.
Exploratory Objectives	**Exploratory Endpoints**
To evaluate improvement in musculoskeletal involvement of sclerotic GvHD using the P-ROM score measurement.	1. Changes in the P-ROM score after 4, 8, 12, 24, and 48 weeks of combination therapy in patients who have developed sclerotic GvHD in musculoskeletal involvement of GvHD 2. Current failure-free survival (cFFS) at last follow-up (or at 72 weeks) from initiation of ruxolitinib (ruxolitinib 2nd-line phase).

4. PATIENT SELECTION

This trial will be conducted in compliance with the protocol, GCP and applicable regulations. Eligibility status must be confirmed by an Investigator or designate prior to enrollment. It is important that no exception is to be made to the eligibility criteria. Questions related to eligibility requirements must be discussed with Ozmosis and/or QI **prior** to enrollment.

4.1. Inclusion Criteria

1. For inclusion in this study, patients must fulfill all the following criteria:18 years of age or older at the time of enrollment.
2. Has previously been diagnosed with moderate to severe cGvHD OR mild cGvHD with high-risk features (defined as platelet counts < 100 x 10^9/L at screening).

3. Capable of providing informed consent.
4. Meets the criteria of steroid-refractory cGvHD after first line corticosteroids therapy at the time of enrollment, as follows:
    - Lack of response or disease progression after prednisone ≥1 mg/kg/day for ≥1 week **OR**
    - Disease persistence without improvement with prednisone >0.5 mg/kg/day or 1 mg/kg/every other day for ≥4 weeks **OR**
    - Increase in prednisone dose to >0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose.
5. Taking a steroid dose at the time of enrollment that is ≤0.5mg/kg/day of prednisone or equivalent
6. Absolute neutrophil count ≥ 1.5 × 10^9/L within 2 weeks (14 days) of enrollment.
7. Platelet count ≥ 50 × 10^9/L within 2 weeks of enrollment.
8. ALT and AST ≤ 5 × ULN (<7.5 x ULN if due to liver GvHD) within 2 weeks of enrollment.
9. Total bilirubin ≤ 1.5 × ULN within 2 weeks of enrollment.
10. Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 using the MDRD-4 variable formula within 2 weeks of enrollment.
11. Female patients of childbearing potential will use 2 reliable methods of birth control (refer to Section 9.3) or be surgically sterile, or abstain from heterosexual activity for the course of the study from the time of study enrollment until 3 months following the discontinuation of all study treatment and agree not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period. Patients of childbearing potential are those who have not been surgically sterilized (i.e. have a documented hysterectomy, or documented bilateral salpingectomy, or documented bilateral oophorectomy) or have not been free from menses for > 2 years. For individuals with permanent infertility due to an alternate medical cause other than the above (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis) investigator discretion should be applied to determining study entry eligibility.

    Male patients will use an adequate method of contraception for the course of the study from the time of enrollment to 3 months after discontinuation of all study treatment. These participants must refrain from donating or cryopreserving sperm, be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis)

and agree to remain abstinent or must agree to use contraception (a male condom and an additional highly effective contraceptive method as described in Section 9.3) when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

12. The patients showing overlap syndrome with components of aGvHD at the time of enrollment can be enrolled unless their acute component of overlap syndrome is Grade 3 or 4 acute GvHD.

13. Must be able and willing to comply with study procedures.

4.2. Exclusion Criteria

1. Receiving ruxolitinib for active steroid refractory acute GvHD at the time of enrollment. Participants with a prior history of aGvHD are eligible only if the aGvHD has achieved CR or PR prior to screening and the participant subsequently developed steroid refractory cGvHD.
2. Have never been treated with systemic steroids as therapy for cGvHD.
3. Receiving >0.5 mg/kg/day of prednisone or equivalent corticosteroids at the time of enrollment.
4. Ongoing use of any of the following pharmaceutical agents, which cannot be discontinued prior to belumosudil treatment (PRN/as-needed use is permissible if it can be fully discontinued at least 7 days prior to enrollment and is not expected to resume during the study):
   - Strong CYP3A inducers
   - UGT1A1 substrates (e.g., raltegravir)
   - P-gp substrates (e.g., dabigatran)
   - OATP1B1/OATP1B3/BCRP substrates (e.g., rosuvastatin)
5. Has had prior treatment with a JAK inhibitor or ROCK2 inhibitor within 8 weeks of enrollment. Participants who received a JAK inhibitor for aGvHD are eligible only if they achieved CR or PR prior to screening.
6. Active uncontrolled bacterial, fungal, parasitic, or viral infection. Infections are considered controlled if appropriate therapy has been initiated and, at the time of screening, no signs of infection are present.
7. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection that requires treatment, or is at risk for HBV reactivation (i.e., positive HBsAg) within 4 weeks of enrollment. Participants with negative HBsAg and positive total HBc antibody may be included if HBV DNA is undetectable at the time of screening. Participants who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA. Participants whose immune

status is unknown or uncertain must have results confirming immune status before enrollment.

8. Known active infection or history of human immunodeficiency virus (HIV).
9. Evidence of relapsed primary hematologic disease, or receipt of treatment for relapse after the allo-HCT was performed. Patients treated with Donor Lymphocyte Infusion (DLI) who have developed GvHD will not be excluded if the primary hematological disease has resolved.
10. Maintenance therapy for the primary hematologic disease started within 4 weeks before initiation of study treatment (Cycle 1 Day 1) or plans to start maintenance therapy after Day 1.
11. Participants on mechanical ventilation, requiring oxygen support or with a FEV1 < 30%.
12. History or current diagnosis of cardiac disease indicating significant risk of safety for participation in the study, such as uncontrolled or significant cardiac disease, including any of the following:
    a. Recent myocardial infarction (within 6 months of enrollment).
    b. New York Heart Association Class III or IV congestive heart failure.
    c. Unstable angina (within 6 months of enrollment).
    d. Clinically significant (symptomatic) cardiac arrhythmias (e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker).
13. Uncontrolled hypertension, defined as blood pressure that remains above 130/80 mmHg in spite of concurrent use of at least three antihypertensive agents of different classes.
14. Patients with known active CNS disease (malignant involvement of CNS).
15. Patients with active acute GvHD grade III-IV.
16. History or other evidence of severe illness or any other conditions that would make the patient, in the opinion of the treating Investigator, unsuitable for the study (such as malabsorption syndromes, poorly controlled psychiatric disease or coronary artery disease).
17. Known hypersensitivity to belumosudil, ruxolitinib or any of their excipients.
18. Patients unable to swallow oral medications.
19. Female participants who are pregnant or breastfeeding.

4.3. Patient Screening and Enrollment

The screening period will commence once the informed consent form (ICF) is signed. Adequate time must be allowed for the patient to ask questions and make a voluntary decision. The ICF must be signed before any study-specific samples are taken or study-specific assessments are conducted. Data regarding screen-failures will be captured in the electronic data capture (EDC) system. In these cases, a new consent form must be signed to allow re-screening. Re-screening is permitted to occur for those who may have initially screen failed due to slightly elevated liver enzymes that, in the opinion of the treating investigator, were the result of GvHD. Re-screening for these patients can occur at any time. Re-screened participants will not be granted a new study identification number.

Prior to screening any patients, each site must have submitted all necessary regulatory documentation to Ozmosis and the site must have been activated by Ozmosis. Access to the electronic case report forms (eCRFs) will only be granted once this has been received.

All patients will be screened and confirmed to be eligible by a Qualified Investigator (QI), and consenting will occur according to the site's ethics board approved process, **prior** to the patient's enrollment into this study.

All eligibility criteria must be met at the time of enrollment. Any questions should be addressed with Ozmosis **prior** to enrollment.

No patient can receive protocol treatment until eligibility has been confirmed and the Patient Enrollment Form has been submitted to Ozmosis. The screening period is 14 days. The Patient Enrollment Form must be completed, and signed by a Site Investigator prior to enrollment. There are 2 sections to the Patient Enrollment Form:

- SCREENING (top section): This section is completed by the site and should be e-mailed to ozmclinical@ozmosisresearch.ca or faxed to 416-634-8333 at the time of screening.
- ENROLLMENT (bottom section): This section is completed by the site at the time of enrollment. The site will submit the signed and completed Patient Enrollment Form to Ozmosis by e-mailing to ozmclinical@ozmosisresearch.ca or fax to 416-634-8333. Only after this has been submitted to Ozmosis can the patient receive investigational product(s)/treatment.

The protocol treatment is to be given within 3 working days of patient enrollment.

5. STUDY TREATMENT

5.1. Study Drug Administration

The Investigational Medicinal Product (IMP), Belumosudil, will be provided by Sanofi as 200 mg tablets.

Ruxolitinib will be dispensed as either 5 or 10 mg tablets, and will be obtained through the site's local pharmacy, as it will be administered per SOC.

All patients will receive open-label IMP. Responsibility for treatment of patients rests with the QI. Prior to initiating ruxolitinib (Cycle 1 Day 1), a tuberculosis skin test or interferon-gamma release assay should be performed in accordance with the approved ruxolitinib product monograph to screen for latent tuberculosis infection, with results interpreted cautiously in immunocompromised patients. Positive results should prompt appropriate evaluation and management per institutional guidelines before starting isoniazid therapy. If the patient had been already treated with isoniazid prophylaxis for 6 months due to prior history of tuberculosis skin test or interferon-gamma release assay, this test will be exempted.

There will be 2 phases for the treatment as follows:

Phase 1: Ruxolitinib monotherapy as second-line therapy: Patients will initiate ruxolitinib monotherapy as second-line treatment for SR-cGvHD and will be assessed for ruxolitinib failure criteria as mentioned in Section 2.

Phase 2: Belumosudil/Ruxolitinib combination as third-line therapy: Patients who meet ruxolitinib failure criteria will transition to combination therapy with belumosudil added to ongoing ruxolitinib, administered as third-line treatment.

Eligible participants in this study will be started on ruxolitinib monotherapy orally at the standard recommended dose of 10 mg BID in ruxolitinib 2nd line phase (Phase 1). Response will be assessed at predefined time points (Weeks 4, 8, 12, 24, 36, and 48). Participants will continue ruxolitinib monotherapy for up to 48 weeks, unless the pre-specified criteria for ruxolitinib treatment failure are met at one of the scheduled response assessments. When ruxolitinib failure is documented at any assessment based on the pre-specified criteria, then the patient will be moved forward to belumosudil-ruxolitinib combination 3rd line phase (Phase 2).

Belumosudil will be added to ongoing ruxolitinib, at a dose of 200 mg OD or 200 mg BID (if on a PPI). Patients will remain on dual therapy for up to 48 weeks (i.e. 12 cycles), until progression of cGVHD, or intolerance to either agent, whichever occurs sooner.

Ruxolitinib should be taken as per standard of care. Participants should take belumosudil orally with their morning or evening meal or within 5 minutes of completing the meal, taken at the same time each day. Tablets should be swallowed whole and not crushed, chewed or cut. Given there are no significant known drug interactions between ruxolitinib and belumosudil, they can be taken at the same time during combination therapy. The QI should instruct the patient to take the investigational product exactly as prescribed to

promote compliance. Participants should make every effort to take the study drugs at the same scheduled time daily as described above.

Participants will be given a study drug diary to record the details of each dose of ruxolitinib and belumosudil both in Phase 1 and Phase 2.

5.2. Missed or Lost Doses

Vomited doses should not be repeated or made up. In the event that the patient misses or forgets the planned dose of study drug, the following guidance should be followed:

Missed Belumosudil with QD Scheduling

- If less than 12 hours of time have elapsed after the missed scheduled dose, the drug should be taken. The patient should then resume the regular planned daily dosing schedule the following day.
- If more than 12 hours of time have elapsed after the missed scheduled dose, the drug should be skipped for that day. The patient should then resume the regular planned dosing schedule the following day.

Missed Belumosudil with BID Scheduling

- For patients taking belumosudil on a BID dosing schedule, if a morning or evening dose is delayed for less than 6 hours of time, the dose should be taken as soon as possible. The patient should then take the next dose as planned, resuming the regular dosing schedule.
- If a morning or evening dose is delayed for more than 6 hours of time, the patient should skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing.

Note that if the patient skips more than 7 consecutive days of both belumosudil and ruxolitinib, the patient should be discontinued from the study unless approved by the sponsor and treating Investigator.

Doses held due to toxicity or missed will not be made up at a later time.

5.3. Dose Modifications

Ruxolitinib

Ruxolitinib is a Health Canada–approved standard-of-care therapy for second-line SR-cGvHD; therefore, no study-specific dose-modification rules are prescribed for ruxolitinib. Dose reductions, interruptions and management of ruxolitinib-related toxicity (including cytopenias) should follow the approved ruxolitinib product monograph and institutional standard of care. For any patient who develops severe or worsening cytopenias

necessitating abrupt interruption of ruxolitinib, a flare of cGvHD is expected to occur. To avoid a significant cGvHD flare during abrupt ruxolitinib interruption, the patient's corticosteroid dose should be maintained or increased to > 0.4 mg/kg/day methylprednisolone (or equivalent prednisone to > 0.5 mg/kg/day) for a minimum 7 days after abrupt cessation of ruxolitinib. Ruxolitinib dosing may be restarted or increased following recovery of the hematologic parameter(s) to what are considered acceptable levels per standard of care. The objective for restarting or escalating after a reduction for hematologic safety is to find the highest safe dosing regimen of ruxolitinib for each patient. If the reduced dose is tolerated for 4 weeks, the dose may be re-escalated to the previous dose.

Belumosudil

Table 1 and 2 below outlines the instances where belumosudil dose reduction are recommended as well as the corresponding recommended dose reduction.

Table 1. Guideline for management of treatment-emergent toxicities

Toxicity	Recommended Action
Grade ≥3 LFTs (AST, ALT or total bilirubin)	• Hold Belumosudil dosing until resolution to Grade 1 or below levels • Consider resuming Belumosudil after resolution to Grade 1 or below levels. If resuming, then resume at one dose decrement • If toxicity (Grade ≥3) recurs, discontinue Belumosudil
Other Grade ≥3 clinically significant toxicities considered related to Belumosudil	• Hold Belumosudil dosing until toxicity has resolved to Grade 1 or below levels. If resuming Belumosudil after resolution to Grade 1 or below levels, then resume at one dose decrement • If toxicity recurs, hold dose as above then consider resuming Belumosudil at one dose decrement

Dose interruption for up to 14 days for toxicity management is permitted. Patients requiring pauses of more than 14 days will be discontinued from the study unless approved by the Sponsor.

Table 2. Belumosudil Dose Decrements

Belumosudil Dose	Dose Reduction
200mg BID	200mg QD
200mg QD	200mg QOD

If the reduced dose is tolerated for 1 complete cycle, the dose may be re-escalated to the previous dose.

In practice, when overlapping toxicities occur (most commonly cytopenias, liver function test abnormalities, or infections), the treating physician will exercise clinical judgment to

prioritize dose modification based on the dominant contributing agent, severity of the toxicity, and organ-specific involvement. As a general guiding principle:

- For hematologic toxicities (e.g., thrombocytopenia, neutropenia): ruxolitinib can be dose-reduced or interrupted first, as it is the primary agent associated with JAK2-mediated cytopenias, per the product monograph with investigator's discretion.

- For liver function test elevations (e.g., bilirubin, ALT/AST): belumosudil will be dose-reduced or interrupted first, consistent with its dose modification tables (Table 1 and Table 2), unless the QI determines ruxolitinib is the more likely contributor based on timing and clinical context.

Table 3. Dose modification for clinically relevant hematologic side effects

Toxicity	Ruxolitinib	Belumosudil
Neutropenia (ANC)		
Grade 1-2 (ANC LLN-1x10^9/L)	Maintain the dose	Maintain the dose
Grade 3 (ANC 0.5-1x10^9/L)	Reduce the dose to half, If resolve to Grade 2 or lower in 7 days, escalate to the initial dose If not resolve in 7 days, hold Ruxolitinib until recover. When recover, restart it at one dose decrement.	Maintain the dose If not resolve to Grade 2 or lower in 7 days, hold Belumosudil until recover. When recover, restart it at initial dose
Grade 4 (ANC <0.5x10^9/L)	Hold the dose If resolve to Grade 2 or lower in 7 days, restart at the half of initial dose If not resolve in 7 days, hold Ruxolitinib until recover. When recover, restart it at one dose decrement.	Hold the dose If resolve to Grade 2 or lower in 7 days, restart at the half of initial dose If not resolve in 7 days, hold Ruxolitinib until recover. When recover, restart it at one dose decrement.
Thrombocytopenia (transfusion allowed if needed)		
Grade 1-2 (Platelet LLN-50x10^9/L)	Maintain the dose	Maintain the dose
Grade 3 (ANC 25-50x10^9/L)	Reduce the dose to half, If resolve to Grade 2 or lower in 7 days, escalate to the initial dose If not resolve in 7 days, hold Ruxolitinib until	Maintain the dose If not resolve to Grade 2 or lower in 7 days, hold Belumosudil until recover. When recover, restart it at initial dose

	recover. When recover, restart it at one dose decrement.	
Grade 4 (ANC <25x10^9/L)	Hold the dose If resolve to Grade 2 or lower in 7 days, restart at the half of initial dose If not resolve in 7 days, hold Ruxolitinib until recover. When recover, restart it at one dose decrement.	Hold the dose If resolve to Grade 2 or lower in 7 days, restart at the half of initial dose If not resolve in 7 days, hold Ruxolitinib until recover. When recover, restart it at one dose decrement.

Table 4. Dose modification for clinically relevant non-hematologic side effects

Toxicity	**Ruxolitinib**	**Belumosudil**
LFTs (AST, ALT or total bilirubin)		
Grade 1-2	Maintain the dose	Maintain the dose
Grade 3-4	Maintain the dose If not resolve to Grade 2 or lower in 7 days, hold Ruxolitinib until recover. When recover, restart it at initial dose	Hold Belumosudil dosing until resolution to Grade 2 or below levels Consider resuming Belumosudil after resolution to Grade 2 or below levels. If resuming, then resume at one dose decrement If toxicity (Grade ≥3) recurs, discontinue Belumosudil
Other Grade ≥3 clinically significant toxicities considered related to Belumosudil		
Grade 1-2	Maintain the dose	Maintain the dose
Grade 3 (ANC 25-50x10^9/L)	Maintain the dose If not resolve to Grade 2 or lower in 7 days, hold Ruxolitinib until recover. When recover, restart it at initial dose	Hold Belumosudil dosing until toxicity has resolved to Grade 2 or below levels. If resuming Belumosudil after resolution to Grade 2 or below levels, then resume at one dose decrement If toxicity recurs, hold dose as above then consider resuming Belumosudil at one dose decrement

Table 5. Recommendation for Dose Decrease of both Belumosudil and Ruxolitinib

Previous dose	Recommended dose for dose decrease
Belumosudil	
200mg BID	200mg QD
200mg QD	200mg QOD
200mg QOD	discontinue
Ruxolitinib	
10mg BID	5mg BID (or 10mg QD)
5mg BID	5mg QD
5mg QD	discontinue

5.4. Dose Tapering at End of Treatment/Discontinuation

Patients whose cGVHD has not progressed at the time of study treatment completion or discontinuation of combination treatment of belumosudil and ruxolitinib, for reasons other than AEs, should be tapered off belumosudil by reducing the dose every 2 weeks (14 days) as described below:

Starting dose of 200mg BID belumosudil → 200mg QD → 200mg QOD → Discontinue

OR

Starting dose of 200mg belumosudil QD → 200mg QOD → Discontinue

The belumosudil tapering process is to be initiated following the end of the 12 cycles of combination treatment (i.e., at EOT), and should last 4 weeks.

Tapering of ruxolitinib should be done slowly as per the product monograph, with documented CR or PR for at least 2 months, starting with a 50% dose reduction every 2 months (56 days). Initial dose reduction is to 5 mg orally BID. If sustained cGvHD response is observed (i.e. no worsening of cGvHD signs and symptoms), patient is further tapered by a second 50% dosage reduction to 5 mg orally QD for an additional 2 months (56 days), prior to cessation. The tapering process can be initiated prior to the EOT visit if the patient is responding well.

5.5. Patient Compliance and Dropout

To the extent possible, patients must strictly follow the continuous daily dosing schedule during the course of study treatment. Patients, in Phase 1 and Phase 2, that skip more than 7 consecutive days of both drugs, in the absence of investigational product related toxicity, will be discontinued from the study unless approved by both the Sponsor and treating Investigator.

Compliance to study medication dosing will be documented using patient diaries and pill counting. Patients will record the date, time and number of pills consumed in the diary on a daily basis. The Principal Investigator (PI) or designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs. Reasoning for missed doses should be documented in the patient diaries when possible, as well as within the study drug administration form in the eCRF. The PI / designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients.

5.6. Premature Withdrawal/Discontinuation Criteria

At the discretion of the QI, a patient may be removed from the study for the following reasons:

- Progression in Phase 2 of cGVHD as defined by NIH Consensus Criteria
- Noncompliance with study procedures
- Need for treatment with medications, such as a new systemic agent for cGVHD, not allowed by the study protocol
- Recurrence of underlying malignancy, as defined by established disease specific criteria, or other intercurrent illness that interferes with study assessments
- Unacceptable toxicity related to study participation
- Investigator decision.
    - Note that patients in Phase 2 should be withdrawn from the study if there has been no response after 12 months of treatment, if in the judgement of the Investigator there has been no clinical benefit for the patient, e.g., in terms of organ score improvements, improvements in Lee symptom scores or reductions of corticosteroid / tacrolimus doses.
- Other treatments become available
- Patient preference / withdrawal of consent or loss to follow-up
- Termination of the study by the sponsor
- Pregnancy in a female participant will lead to definitive treatment discontinuation in all cases.

Patients with a Lack of Response or Mixed response may continue treatment with belumosudil and ruxolitinib, and can remain on study if the treating Investigator considers continued treatment to be in the patient’s best interest, but only after approval from the Sponsor and documentation of patient’s willingness to continue. The rationale for continued treatment in such instances must be clearly documented. For clarity, Lack of Response or Mixed response will be considered as progression event for analysis purposes.

Patients may withdraw from the study at any time. Patients who discontinue from the study will be encouraged to return to the study site to undergo the evaluations listed for the End of Treatment Visit and for follow-up visits. In the instances where a reason for withdrawal of consent is given, this will be captured in the eCRF. Patient data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent.

If the reason for withdrawal is the occurrence of an AE, the patient will be followed by the QI until such events resolve, stabilize, and, according to the QI's judgment, there is no need of further follow-up. The reason for withdrawal from the study will be documented in the electronic case report form.

Ozmosis must be notified within 24 hours of a patient's discontinuation from the study.

5.7. Patient Replacement

Enrolled participants withdrawn from the study before receiving any study drug will be replaced.

5.8. Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be established for this study. The DSMB will comprise of experts in stem cell transplantation and the management of GVHD, independent of the study. A list of the DSMB members can be found in the DSMB charter.

The DSMB will monitor the safety aspects of the trial and will review safety data on a bi-annual basis. Additional meetings may be scheduled as necessary and if any of the safety stopping rules indicated below are met. Please refer to the DSMB charter for additional details.

5.9. Safety Stopping Rules

Accrual will be on hold and a meeting held with the PI, investigators and Data Safety Monitoring Board (DSMB) if the following occurs:

1. If there is a death or unacceptable toxicity (SAE Grade ≥4) attributed as: possibly, probably or definitely related to the study drug.
2. If the first 3 patients enrolled experience significant toxicity (i.e. Grade ≥3 AEs lasting 4 weeks or longer) attributed as: possibly, probably or definitely related to the study drug.

A decision will be made by the Sponsor and DSMB regarding whether the study will be re-opened for the next patient in the study or not. If there is disagreement in the SAE causality assessment or whether or not to re-open accrual between the different parties,

the final decision will rest on the DSMB. Ozmosis will notify all sites and applicable parties on the decision and whether accrual has re-opened. Only when it is deemed safe can the next patient start the treatment phase of the study.

6. INVESTIGATIONAL PRODUCT

Please refer to the most recent version the Investigator's Brochure (IB) for belumosudil for updated information. Given that ruxolitinib is a standard drug of choice for second line therapy, and is being administered as per SOC, please refer to the product monograph for additional, current information.

6.1. Drug Characteristics and Description

Ruxolitinib is an orally available JAK-2 inhibitor which is a standard of care drug for second line therapy of cGvHD treatment.

Belumosudil inhibits ROCK2 and ROCK1 with 50% inhibitory concentration (IC_{50}) values of approximately 100 nM and 3 μM, respectively. ROCK2 has been shown to be activated in Th17-skewed milieu, leading to the upregulation of STAT3 phosphorylation and the consequent increased expression of Th17-specific transcription factors, such as RORγt and IRF4 [15, 16]. Moreover, selective ROCK2 inhibition restores immune homeostasis and shifts the Th17/Treg balance toward Tregs via a STAT5-dependent mechanism [17, 18]. Belumosudil also acts on the actin/myosin cytoskeletal network/impacts collagen formation/mediates stress fiber formation and regulates the transcription of pro-fibrotic genes, including CTGF and α-SMA [19]. In vivo, belumosudil has demonstrated efficacy in a variety of clinically relevant animal models of disease including chronic GvHD, systemic sclerosis, idiopathic pulmonary fibrosis and other autoimmune diseases [18, 19].

The first marketing authorization for belumosudil was obtained in the US in July 2021. The US FDA approved belumosudil (REZUROCK®) for the treatment of patients 12 years and older with cGVHD after failure of at least 2 prior lines of systemic therapy. Belumosudil was also approved for the same indication in Canada in March 2022.

6.2. Formulation

Belumosudil, the investigational drug product, will be provided as a pale-yellow film-coated, oblong tablet containing 242.5 mg belumosudil mesylate salt (equivalent to 200 mg belumosudil free base), for oral administration.

6.3. Storage & Handling

Belumosudil tablets are to be stored at a controlled room temperature of 20°C to 25°C (68°F-77°F) with excursions permitted between 15°C and 30°C (59°F-86°F). Supplies should be protected from moisture, freezing, strong light, and excessive heat within the provided containers. Supplies will be shipped under ambient conditions and should be

stored in the site pharmacy. Based on current long-term and accelerated stability data, a shelf-life of 36 months is assigned for the belumosudil tablets when stored under 25°C/60% relative humidity (RH).

Ruxolitinib will be supplied, stored, and handled as per standard of care.

All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

6.4. Packaging and Labelling

For this protocol, 200 mg belumosudil tablets will be supplied to participating sites in a white, wide-mouth high density polyethylene container with child-resistant, induction-seal screw cap lid containing integral desiccant.

The study drug will be labeled consistent with the regulatory requirements and local site guidelines.

6.5. Product Accountability and Destruction

The PI (or an authorized designee) at each participating site must maintain a careful record of the inventory of the investigational product received using a drug accountability form. Investigational product accountability records will be available for review by the study monitor as applicable according to the monitoring plan. The local site pharmacies will follow the appropriate GCP for the storage and dispensing of the medication to the study patient.

The investigational product should not be used for any purpose outside the scope of this protocol, nor can investigational product be transferred or licensed to any party not participating in the clinical study. Sponsor’s data for investigational product are confidential and proprietary and shall be maintained as such by the QIs. The investigational product may be destroyed as per site’s destruction policies and documentation of investigational product destruction will be filed in the trial master file. The investigational product may be returned to the Sponsor if requested by the Sponsor.

In accordance with regulatory requirements, study sites must document the amount of investigational product received from and returned to the sponsor, the amounts of investigational product dispensed to study patients, and the amount returned by study patients. Product accountability records must be maintained throughout the course of the study.

6.6. Drug Supply and Ordering

The investigation product, Belumosudil, and funding for the study are being provided by Sanofi Canada. As ruxolitinib will be administered per standard of care, it should be

obtained through to the site's local pharmacy. Sites must request study drug by submitting an order form to the drug depot, copying Ozmosis, in order for the study drug to be shipped to the site pharmacy. The PI (or designee) will verify and acknowledge receipt of all investigational product shipments by signing and returning all required forms.

7. MEASUREMENT OF DRUG EFFECTS

7.1. Safety Assessment

The adverse effects of the study drugs will be assessed from adverse events, vital signs and by clinically significant changes in the laboratory evaluations and ECGs.

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI CTCAE. This study will utilize the CTCAE Version 5.0 for adverse event reporting.

7.2. Post-Baseline cGvHD Response Assessment

The response assessment will be performed by the treating investigator according to the detailed schedule found in the study calendar. At each post-baseline visit, the response evaluation of each organ should be made by comparing the actual organ assessment versus the baseline status documented at C1D1. All organs that should be evaluated and a high level summary of evaluation criteria as per NIH consensus guideline[20] are listed in Table 6. Table 7 summarizes the rules for overall response assessment based on organ specific evaluation at each post-baseline visit.

Table 6. Organs included in cGVHD response assessment

Organ	Evaluation by	Criteria for response assessment
Skin	NIH Skin Score, considering %BSA involvement and sclerotic features	Change of skin score
Eyes	NIH Eye Score	Change of Eye score
Mouth	NIH Modified OMRS (Sum of scores for erythema, lichenoid and ulcers)	Change of OMRS
Esophagus	NIH Esophagus Score	Change of Esophagus score
Upper GI	NIH Upper GI Score	Change of Upper GI score
Lower GI	NIH Lower GI Score	Change of Lower GI score
Liver	Lab results for ALT, alkaline phosphatase, and Total bilirubin	Change of values for ALT, alkaline phosphatase, and Total bilirubin
Lungs	NIH Lung score AND %FEV1	Change of %FEV1
Joints and fascia	NIH Joint and Fascia Score and PROM scores	Change of Joint and Fascia Score and PROM scores

Table 7. Response determination for cGvHD based on all organs*

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 Oral Mucosa Rating Score 0 after previous involvement	Decrease in NIH Modified Oral Mucosa Rating Score of 2 or more points	Increase in NIH Modified Oral Mucosa Rating Score 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 one or more	Decrease by 50%	Increase by 2x ULN
Lungs	-Normal %FEV1 after previous involvement -If pulmonary function tests (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 one 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

* At least one organ must be involved at baseline. Organ specific responses versus baseline status

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

7.3. Response Duration

Response duration will be defined as the time from the first documented achievement of complete response (CR) or partial response (PR), whichever occurs first (as defined in Table 7), until the first documented date of loss of response or disease progression. The smallest measurements recorded during the study, including baseline, will serve as the reference for assessing progression.

7.4. Optional Sub-Study Correlative Sample Collection

All patients who agree to participate in this study, will be presented with the option to participate in an optional sub-study that will involve the collection of additional blood samples. The correlative blood samples will be obtained as per the frequency in the Study Calendar. These samples will be sent to a tissue biobank in Toronto, Canada and stored here for up to 10 years for future research purposes. Access to samples in long term storage (for patents who consented) will be restricted to representatives delegated by the PI. Samples will be de-identified by using a unique patient number. Further details will be provided in the study laboratory manual, including sample shipment details.

8. STUDY CALENDAR

Phase 1 – ruxolitinib monotherapy as 2nd line treatment

	Screening	Treatment						
Visit Name	Screening	C1D1 Week 1 [j]	C2D1 Week 4[i]	C3D1 Week 8	C4D1 Week 12	C7D1 Week 24	C10D1 Week 36	C12D28 Week 48
Visit Window	-14 days	Within 3 days of enrolment	+/- 4 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days
Informed consent***	X							
Inclusion/Exclusion Criteria	X							
Demographics	X							
Prior GvHD Medication & Medical History	X							
Tuberculosis Skin Test / Interferon -gamma release assay[l]	X							
Ruxolitinib Dispensing[i]		X	X	X	X	X	X	X[l]
Physical Examination[a] & ECOG performance status assessment	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X
P-ROM assessment	X	X	X	X	X	X	X	X
12 Lead ECG[c]	X							
Pregnancy Test[d]	X	X						
Hematology[e]	X	X	X	X	X	X	X	X
Serum Chemistry[f]	X	X	X	X	X	X	X	X
Virology[h]	X							
Pulmonary Function Test		X			X	X	X	X
Modified Lee Symptom Scale		X	X	X	X	X	X	X
NIH consensus based GvHD organ specific score and global severity score[k]		X	X	X	X	X	X	X
IP return and accountability			X	X	X	X	X	X

Adverse Events[j]		Continuous						
Concomitant medications review	x	Continuous						
Correlative Samples (optional sub-study)[g]		X						X

***Consent should be done prior to any study specific screening assessment, according to the site ethics board approved process and site institutional timelines. Site should follow their site guidelines for consenting window (timeframe for prior to screening and prior to enrollment). Patient enrollment with Ozmosis@UHN is required. Please refer to section "Patient Enrollment".

a. Complete physical examinations will be done at Screening and on C1D1 (i.e. weight, height, HEENT, Cardiovascular, Dermatological, Musculoskeletal, Respiratory, GI, Genitourinary, Neurological, Endocrine Metabolic, Blood Lymphatic, Other). Symptom directed physical exams will be performed for all subsequent visits as per study calendar. See Appendix A for ECOG Performance Status Scale

b. Vital signs: Pulse rate, blood pressure, temperature and respiratory rate will be measured. Vitals will be measured prior to dosing.

c. 12-lead ECG will be performed as per the timepoints in the study calendar and more frequently as indicated clinically (i.e. in the event of cardiovascular AEs, patient is hypokalemic, etc.).

d. A negative urine pregnancy test is required for female patients at the time of screening. A negative serum pregnancy test is required for female patients of childbearing potential on C1D1 prior to treatment.

e. Hematology will include: hemoglobin, hematocrit, RBC count, platelet count, absolute neutrophil count and differential WBC count.

f. Serum chemistry will include: total proteins, albumin, calcium, phosphorous, total cholesterol, random plasma glucose, uric acid, BUN/urea, GFR, creatinine, total bilirubin, ALP, sodium, potassium, magnesium, serum bicarbonate, chloride, AST, ALT, LDH. These electrolytes and creatinine levels are to be checked more frequently as indicated clinically.

g. Peripheral blood samples for correlative studies will be collected for plasma and mononuclear cells isolation at the timepoints indicated. Patient must have provided consent to participate in this optional sub-study. See the study lab manual for additional sampling details.

h. HIV, HBsAg, HBV DNA, HCV antibody, and HCV RNA.

i. Ruxolitinib may continue on past the C12D28 visit as per standard of care and if, in the opinion of the treating investigator, the patient is receiving clinical benefit. Tapering of ruxolitinib should be done slowly as per the product monograph with documented CR or PR, starting with a 50% dose reduction every 2 months (56 days). Initial dose reduction is to 5 mg orally BID. If sustained cGvHD response is observed (i.e. no worsening of cGvHD signs and symptoms), patient is further tapered by a second 50% dosage reduction to 5 mg orally QD for an additional 2 months (56 days), prior to cessation.

j. The protocol treatment is to begin within 3 working days of patient enrollment. Any screening assessments performed within 24 hours of C1D1 can be used to fulfill C1D1 requirements and do not need to be repeated.

k. See Tables 2 and 3, as well as Appendix C. Response assessment will be assessed at week 4, 8, 12, 24, 36 and 48 weeks.

l. Prior to initiating ruxolitinib (Cycle 1 Day 1), a tuberculosis skin test or interferon-gamma release assay should be performed in accordance with the approved ruxolitinib product monograph to screen for latent tuberculosis infection, with results interpreted cautiously in immunocompromised patients. Positive results should prompt appropriate evaluation and management per institutional guidelines before starting isoniazid therapy. If the patient had been already treated with isoniazid prophylaxis for 6 months due to prior history of tuberculosis skin test or interferon-gamma release assay, this test will be exempted

Phase 2: Belumosudil-ruxolitinib combination therapy as 3rd line treatment

		Treatment							End of Treatment and Follow Up		
Visit Name	C1D1 Week 0	C1D14 Week 2	C2D1 Week 4[i]	C3D1 Week 8	C4D1 Week 12	C7D1 Week 24	C10D1 Week 36	C12D28 Week 48	EOT Visit [k]	28 Day Safety FU Visit	6 Month FU Visit [g]
Visit Window	+/- 2 days	+/- 2 days	+/- 4 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 28 days
Ruxolitininb[i]	x	x	x	x	x	x	x	x			
Belumosudil Dispensing[j]	X[h]	X	X	X	X	X	X	X[j]	Taper & Discontinue		
Physical Examination[a] & ECOG performance status assessment	X	X	X	X	X	X	X	X	X	X	
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	
P-ROM assessment			X	X	X	X		X	X	X	
12 Lead ECG[c]	X										
Hematology[d]	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry[e]	X	X	X	X	X	X	X	X	X	X	
Pulmonary Function Test	X				X	X	X	X	X		
Modified Lee Symptom Scale	X		X	X	X	X	X	X	X		
NIH consensus based GvHD organ specific score and global severity score[m]	X	X	X	X	X	X	X	X	X		
IP return and accountability		X	X	X	X	X	X	X	X[j]		
Survival Status										X	X
Adverse Events[h]		Continuous									
Concomitant medications review		Continuous									x[l]
Correlative Samples (optional sub-study)[f]	X								X		

a. Complete physical examinations will be done at Screening and on C1D1 (i.e. weight, height, HEENT, Cardiovascular, Dermatological, Musculoskeletal, Respiratory, GI, Genitourinary, Neurological, Endocrine Metabolic, Blood Lymphatic, Other). Symptom directed physical exams will be performed for all subsequent visits as per study calendar. See Appendix A for ECOG Performance Status Scale
b. Vital signs: Pulse rate, blood pressure, temperature and respiratory rate will be measured. Vitals will be measured prior to dosing.

c. 12-lead ECG will be performed as per the timepoints in the study calendar and more frequently as indicated clinically (i.e. in the event of cardiovascular AEs, patient is hypokalemic, etc.).
d. Hematology will include: hemoglobin, hematocrit, RBC count, platelet count, absolute neutrophil count and differential WBC count.
e. Serum chemistry will include: total proteins, albumin, calcium, phosphorous, total cholesterol, random plasma glucose, uric acid, BUN/urea, GFR, creatinine, total bilirubin, ALP, sodium, potassium, magnesium, serum bicarbonate, chloride, AST, ALT, LDH. These electrolytes and creatinine levels are to be checked more frequently as indicated clinically.
f. Peripheral blood samples for correlative studies will be collected for plasma and mononuclear cells isolation at the timepoints indicated. Patient must have provided consent to participate in this optional sub-study. See the study lab manual for additional sampling details.
g. Visit may be conducted remotely over the phone if preferred
h. In the event that at the intended C1D1 visit assessment the participant is experiencing Grade ≥3 AE(s), treatment with belumosudil should not begin. This visit will be considered an unscheduled visit and the C1D1 visit should be rescheduled. The participant can continue on ruxolitinib alone and should be followed for resolution of the Grade ≥3 AE(s). If the Grade ≥ 3 AE(s) improve to Grade ≤2 or resolve completely within 4 weeks, the participant will still be eligible to receive belumosudil. In this case, they should come back in for a true C1D1 visit and can complete all the necessary assessments as well as belumosudil dosing. If the Grade ≥3 AE(s) does not recover within 4 weeks, the participant will move on to the End of Treatment visit and discontinue study. If there are any questions or concerns about the patient status and treatment in these scenarios, this should be discussed with the sponsor.
i Ruxolitinib may continue on past the C12D28 visit as per standard of care and if, in the opinion of the treating investigator, the patient is receiving clinical benefit. Tapering of ruxolitinib should be done slowly as per the product monograph with documented CR or PR, starting with a 50% dose reduction every 2 months (56 days). Initial dose reduction is to 5 mg orally BID. If sustained cGvHD response is observed (i.e. no worsening of cGvHD signs and symptoms), patient is further tapered by a second 50% dosage reduction to 5 mg orally QD for an additional 2 months (56 days), prior to cessation.
j. Patients whose cGVHD has not progressed at the time of study treatment completion or discontinuation of combination treatment of belumosudil and ruxolitinib for reasons other than AEs should be tapered off belumosudil by reducing the dose every 2 weeks (14 days) as described below:
Starting dose of 200mg BID → 200mg QD → 200mg QOD → Discontinue OR Starting dose of 200mg QD → 200mg QOD → Discontinue
k. For those participants who completed all treatment visits, the C13D28 visit can be considered the End of Treatment Visit.
l. Only subsequent therapies used to treat cGvHD need to be captured during the period from the 28-day safety follow up and the 6 month follow up visit
m. See Tables 2 and 3, as well as Appendix C. Response assessment will be assessed at week 4, 8, 12, 24, 36 and 48 weeks.

9. CONCOMITANT MEDICATIONS

All concomitant medications (including herbal or alternative medicines) taken by the patient from the time of consent through the duration of protocol therapy will be recorded in the eCRF. Initiation of new systemic cGvHD therapy will be considered a new line of treatment and as study treatment failure.

Subsequent cGvHD therapies occurring during the follow up period (24 weeks) will also be captured.

9.1. Permitted concomitant medications

Patients may take their usual medications unless specifically prohibited by the Investigator team or listed as prohibited concomitant medications. Patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per local institutional guidelines.

9.2. Prohibited concomitant medications

Non-drug therapies with the intent of altering the immune response will not be permitted. Herbal or alternative medicines are also prohibited. Patients should not receive any form of chemotherapy, steroids (other than those initiated as first-line therapy and tapered off in the course of the trial) or COX2 inhibitors once beginning combination treatment.

9.2.1 Medications prohibited with belumosudil

The following medications are prohibited to be taken with belumosudil:

- Strong CYP3A inducers
- UGT1A1 substrates (e.g., raltegravir)
- P-gp substrates (e.g., dabigatran)
- OATP1B1/OATP1B3/BCRP substrates (e.g., rosuvastatin)

9.2.2 Medication interactions with ruxolitinib

Please discuss all medication interactions with ruxolitinib with your care team, as per the standard of care treatment. However, the following interactions should be noted:

- Moderate CYP2C9 inhibitors (dose reduction recommended)
- Drugs that decrease heart rate/prolong PR interval (avoiding concomitant use is recommended)

9.3. Prevention of Pregnancy

Female patients of childbearing potential must use 2 reliable methods of birth control or be surgically sterile, or abstain from heterosexual activity (complete abstinence) for the

course of the study from study enrollment until 3 months following the last dose of any study therapy and agree not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period. These patients must have a negative urine pregnancy test at screening, as well as a negative serum pregnancy on C1D1 prior to the administration of study intervention. The patient must be excluded from participation if the either pregnancy result is positive. Female patients of childbearing potential are those who have not been surgically sterilized (i.e. have a documented hysterectomy, or documented bilateral salpingectomy, or documented bilateral oophorectomy) or have not been free from menses for > 2 years. For individuals with permanent infertility due to an alternate medical cause other than the above (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis) investigator discretion should be applied to determining study entry eligibility.

Male patients should agree to use a reliable method of contraception, or be surgically sterile, or abstain from heterosexual activity (complete abstinence), from study enrollment until 3 months following the last dose of any study therapy. These participants must refrain from donating or cryopreserving sperm, be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent **or** must agree to use contraception (a male condom and an additional highly effective contraceptive method as described below) when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

Acceptable and reliable methods of contraception are:

- Condoms with contraceptive foam
- Oral, implantable or injectable contraceptives
- Contraceptive patch,
- Intrauterine device
- Intrauterine hormone-releasing system
- Diaphragm with spermicidal gel
- A sexual partner who is azoospermic (vasectomized or due to a medical cause), surgically sterilized or post-menopausal (in this instance, no additional contraception methods are required)

Complete abstinence is defined as complete avoidance of heterosexual intercourse during study treatment and for at least 1 month after completion of study treatment. Patients who choose complete abstinence are not required to use a second method of contraception. Acceptable alternate methods of effective contraception must be discussed in the event that the patient chooses to forego complete abstinence.

10. SAFETY AND REPORTING REQUIREMENTS

This study will be conducted in accordance with Health Canada regulatory requirements and ICH Good Clinical Practice Guidelines. Adverse Events (AEs) and Serious Adverse Events (SAEs) data will be reported and collected.

10.1. Adverse Event Definitions

An **adverse event** (AE) is any untoward medical occurrence in a clinical investigation patient who is administered a drug or biologic (medicinal product) during the course of a study, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Each AE is to be classified by the investigator as serious or non-serious.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after administration of the study product unless they reoccur after the patient has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

A laboratory test abnormality considered clinically relevant (e.g. causing the patient to withdraw from the study, requiring treatment or causing apparent clinical manifestations) or judged relevant by the Investigator should be reported as an AE.

10.2. Adverse Event Documentation

Adverse events will use the descriptions and grading scales found in the revised NCI CTCAE. This study will utilize the CTCAE Version 5.0 for AE reporting.

All AEs must be recorded in the eCRFs. Documentation must be supported by an entry in the patient's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the QI, action taken and outcome.

10.3. Attribution Definitions

For all AEs, relationship to **each of the** study drugs will be reported on the appropriate AE eCRF page. The PI must judge whether **each of the** study drugs caused or contributed to the AE in which case it is considered to be an adverse drug reaction (ADR), and report it as either:

Related (definitely, probably or possibly): there is a reasonable possibility that the investigational product caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for the determination of relatedness:

- There is a plausible time sequence between onset of the AE and investigational product administration;
- There is a plausible biological mechanism through which the investigational product may have caused or contributed to the AE.

Not related (unrelated, unlikely related): It is highly unlikely or impossible that the investigational product caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for a determination of not related:

- Another cause of the AE is evident and most plausible; the temporal sequence is inconsistent between the onset of the AE and investigational product administration; a causal relationship is considered biologically implausible.

10.4. Serious Adverse Event

A **Serious Adverse Event (SAE) or Reaction** is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly / birth defect
- Is an important medical event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (example: intensive treatment in an emergency room or at home for bronchospasm, convulsions that do not result in hospitalization). Medical and scientific judgment should be exercised in deciding whether some events should be considered as serious because their quick reporting to the sponsor may be of interest for the overall conduct of the study.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an adverse event in which the patient was at risk of death at the time of the event. It does not refer to an adverse event that hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met:

- The admission results in a hospital stay of less than 12 hours.

OR

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to day 1 of the study or for prophylactic insertion of a gastric feeding tube).

OR

- The admission is not associated with an adverse event (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfil the criteria of 'medically important' and as such may be reportable as a serious adverse event dependent on clinical judgement. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Important medical event: Any AE may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition.

Any death (regardless of cause) that occurs from the time of administration of the first dose of study therapy until 28 days after the final administration of the investigational product, and any death occurring after this time that is judged at least possibly related to prior treatment with the investigational product, will be promptly reported.

An AE is **unexpected** when the nature or severity of the AE is not consistent with the applicable product information (i.e. investigator's brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). An AE is considered to be associated with the use of the drug if the attribution is classified as "possible", "probable" or "very likely".

10.5. Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. AESIs may be added, modified, or removed during a study by protocol amendment.

AESIs for this study include:

- Grade ≥ 3 infections: Severe infections (e.g., bacterial, viral, or fungal) that are life-threatening or require significant medical intervention.
- Secondary malignancies: New cancers that develop during the study, potentially linked to the treatment.
- Grade ≥ 3 blood pressure changes: Severe hypertension or hypotension that could pose significant health risks.
- Grade ≥ 3 ALT, AST, and bilirubin: Severe liver function abnormalities, indicated by elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin, suggesting potential liver toxicity.

- Symptomatic overdoses: Any symptoms resulting from taking higher-than-prescribed doses of ruxolitinib or belumosudil, requiring immediate attention.

These AESIs are monitored closely to ensure participant safety and to gather data on the safety profile of the combination therapy for cGvHD.

10.6. Adverse Event Reporting Criteria

AEs are to be recorded within the CRF. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, grade, action taken with respect to the investigational product, corrective treatment or therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was related to the investigational product.

The severity of all AEs will be graded according to the NCI CTCAE, version 5.0. For each event, the highest severity grade attained since the last assessment period will be reported.

10.7. Adverse Event Reporting Period and Follow up of AEs, SAEs, and AESIs

The AE reporting period begins at the time the patient receives their first dose of study treatment in phase 2 combination Belumosudil and Ruxolitinib therapy (i.e., C1D1 in phase 2). The SAE reporting period begins at the time the patient receives their first dose of study treatment in phase 1 Ruxolitinib monotherapy (i.e., C1D1 in phase 1). All AEs, SAEs and AESIs must be followed until resolution or 28 days following the last dose of study treatment, whichever comes first. The QI shall provide follow-up information when available in a new follow-up SAE form. Resolution status of such an event should be documented on the eCRF.

Patients withdrawn from the study due to an AE will be followed until the AE has resolved. In the case of an SAE, the patient will be followed until clinical recovery or until progression has been stabilized or judged to be chronic. After discontinuation from protocol treatment, all patients will be followed for any ongoing or late toxicities. Patients will be seen for a Safety Follow up visit, 28 ± 7 days after discontinuing treatment. Safety Follow up procedures will be completed as indicated in the Study Calendar.

The AE reporting period will end once 28 days have passed since the patient's last dose of study drug. Therefore, SAEs occurring after the last dose of study treatment that have been deemed by the QI as at least possibly related to protocol treatment, must be reported if it occurs within 28 days after discontinuation of the investigational products. In addition, any known untoward event of any severity that occurs subsequent to the AE reporting period that the Investigator assesses as at least possibly related to the study therapy (i.e., the relationship cannot be ruled out) should also be reported as an AE. On-

going and non-resolved toxicities are followed until resolution back to baseline or ≤ Grade 1 after off treatment, or until considered stable by the QI.

10.8. Serious Adverse Event Reporting to Ozmosis

All SAEs defined as per Section 10.4 and all AESIs defined as per Section 10.5 must be recorded on case report forms. In addition, they must be reported to Ozmosis according to the following instructions:

1. Within 24 hours of becoming aware of the event, report initial information (on trial specific SAE report form) by fax or e-mail to:

   Ozmosis Research Inc.
   Fax: 416-634-8333
   E-mail: ozmsafety@ozmosisresearch.ca

   - The initial information should always contain:
     - Name of reporter/Site Investigator,
     - Patient identification,
     - AE Term,
     - Investigational product dose and start/stop dates

2. On the next working day *if the initial report in step #1 did not contain complete information*: Fax or email completed trial-specific SAE form.
3. Follow-up SAE and AESI reports should be submitted to Ozmosis as soon as possible.

All SAEs must be followed until resolved, become chronic, or stable unless the patient is lost to follow up. Resolution status of such an event should be documented on the eCRF.

10.9. Exceptions and Non-Reportable SAEs

Progressive disease, death due to progressive disease, and relapse of primary malignancy, will not be reportable as an SAE in this study. Relapse of the underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected relapse. Clinical symptoms of relapse may be reported as an AE if the symptom cannot be determined as exclusively due to the relapse of the underlying malignancy or does not fit the expected pattern of relapse for the disease under study. If there is any uncertainty of an AE being due only to cancer it should be reported as an AE or SAE.

Elective procedures requiring hospitalization will not be considered SAE's if they were pre-planned prior to signing consent; however, other events may occur during this hospitalization that may be considered serious or non-serious adverse events and will

need to be captured according to the protocol SAE reporting period if hospitalization is prolonged.

10.10. Procedures for Expedited Reporting

Responsibility for Reporting SAEs to Health Canada

Ozmosis, acting on behalf of Sponsor, will be responsible for notifying Health Canada in an expedited manner of adverse events which are considered *serious* and *unexpected* and *related* to the protocol treatment (or for which a causal relationship with the protocol treatment cannot be ruled out). Follow-up of SAEs as documented and submitted by the clinical site on the Ozmosis. SAE form will be forwarded to Health Canada by Ozmosis, where applicable.

Responsibility for Reporting SAEs (including Pregnancies as applicable) and AESIs to Sponsor

Ozmosis Research Inc. will be responsible for submitting all SAEs and AESIs (initial and/or follow-up reports) to the Sponsor using the SAE Report Form and pregnancies using the Pregnancy Report Form. The form must be emailed to Sponsor at the latest within 24 hours after Ozmosis receives it from the site. The foregoing is applicable to all SAEs, irrespective of causality.

Reporting of SAEs to Local Ethics Boards

SAEs occurring within a site should also be reported to local ethics boards according to their local policies.

Ozmosis will notify all PIs of all SAEs that are reportable to regulatory authorities in Canada from this trial or from other clinical trials as reported to the Sponsor. PIs (or their designee) must notify their ethics boards and file the report with their Investigator Site File.

Documentation that SAEs have been reported to REBs must be kept on file at the site and Ozmosis.

Reporting of SAEs to Pharmaceutical Company

Ozmosis, acting on behalf of the Sponsor, will notify Sanofi of all reportable SAEs (i.e. SAEs requiring reporting to Health Canada), any misuse/abuse of ASC, or any ASC exposure during pregnancy within 15 days of receipt of reports from the sites.

10.11. Reporting of Pregnancy

Pregnancies occurring in study patients/sexual partner(s) will be treated procedurally as SAEs. Pregnancies occurring in study patients or their sexual partner(s) after study

treatment should be reported separately on Pregnancy Report Form and the patient has to discontinue the trial medications.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

Pregnancy in itself, occurring in female patients, and female partners of male patients is not regarded as an AE unless there is a suspicion that the IPs under study may have interfered with the effectiveness of a contraceptive medication.

The QIs are required to report to Ozmosis any pregnancy occurring in female patients, and female partners of male patients. Women of childbearing potential will be instructed to contact the investigator or study staff immediately if they suspect they might be pregnant (e.g. missed or late menstrual period) at any time during study participation.

The investigator must immediately notify Ozmosis if a study subject becomes pregnant and discontinue study. Any drug exposures during pregnancy must immediately be reported to Ozmosis, who will inform Sanofi Canada within 15 days.

11. STATISTICAL ANALYSIS

The final analysis will be performed once all participants have either completed at least 48 weeks of treatment or discontinued study treatment prior to Week 48. Data from all participating centers will be pooled to ensure an adequate sample size for analysis. Demographic and baseline disease characteristics will be summarized descriptively. Categorical variables will be presented as frequencies and percentages, and continuous variables as mean, SD, median, minimum, and maximum; for selected parameters, the 25th and 75th percentiles will also be provided. Graphical summaries of the data may also be presented.

The number of participants with dose modifications (reductions, interruptions, or permanent discontinuations) and the corresponding reasons will be summarized. All dosing data will be listed. Categorical variables will be summarized as frequencies and percentages, while continuous variables will be summarized using mean, SD, median, 25th and 75th percentiles, minimum, and maximum.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. Additional exploratory analyses of the data will be conducted as deemed appropriate.

There are no planned interim analyses for this study.

11.1. Study Design and Justification for Sample Size

The primary endpoint is failure-free survival (FFS) at 48 weeks in the belumosudil + ruxolitinib 3rd-line phase. Based on REACH3, the FFS with ruxolitinib in SR-cGvHD is approximately 67% (null hypothesis); the alternative hypothesis for the belumosudil + ruxolitinib combination is an FFS rate of 90% at 48 weeks. Assuming a ruxolitinib failure rate of approximately 40–50% by 48 weeks in the ruxolitinib 2nd-line phase, a total of up to 53 patients will be enrolled (approximately 48 evaluable plus 10% to account for drop-out), providing at least 80% power to reject the null hypothesis at a two-sided alpha of 0.05.

Success of the trial will be defined as demonstration of an FFS at 48 weeks in the belumosudil + ruxolitinib 3rd-line phase that is significantly superior to the null FFS of 67%, translating into a clinically meaningful improvement over best available therapy in patients with ruxolitinib-refractory cGvHD.

11.2. Study Population

The following study populations are defined and will be analysed as specified below. The population evaluable for safety will be the safety population.

The Intent to Treat (ITT) population: The total population of patients enrolled in the study

Safety population (evaluable for adverse events): All enrolled patients who received at least one dose of belumosudil

Efficacy population (evaluable for response): All enrolled patients who complete at least one cycle of belumosudil treatment with adequate baseline disease assessment.

11.3. Evaluation of Study Endpoints

11.3.1 Evaluation of the Primary and Secondary Endpoints

Failure-free survival (FFS) will be evaluated using Kaplan-Meier method. The FFS rate will be evaluated at 48 (primary endpoint) and 24 weeks after 3rd line combination therapy (secondary endpoint), as well as 24/48 weeks after ruxolitinib monotherapy 2nd line treatment (secondary endpoints), respectively. The composite endpoint of failure is defined as 1) GvHD progression or loss of response requiring switch of systemic GvHD treatment, 2) progression/relapse of primary hematologic disease and 3) non-relapse mortality.

Overall response rate (ORR) will be evaluated at 24 and 48 weeks after combination therapy (i.e. 28 and 48 weeks after belumosudil-ruxolitinib 3rd line therapy), and at 24 and 48 weeks after ruxolitinib 2nd line monotherapy, respectively. The proportion of responders and its 95% confidence interval (using exact binomial methods) will be calculated.

Durable response after response achievement will be evaluated only in the patients achieved CR or PR (any response). The Kaplan-Meier estimate will be calculated from the date of CR/PR achievement to the date of losing response/progression or death from any cause.

GvHD symptom burden improvement, measured serially measured by the modified Lee Symptom Scale, will be evaluated using repeated measure based on the general linear model. If p-value is less than 0.05, it demonstrates statistically significant change over time within subject.

The Modified Lee symptom score (mLSS) will be used to reflect a symptom burden in cGvHD study patients. The symptoms will be assessed serially and will be evaluated using repeated measure based on the general linear model. If p-value is less than 0.05, it demonstrates statistically significant change over time within subject. The score assesses 7 different organs/areas including skin, eye/mouth, breathing, eating/digestion, muscle/joints, energy, and mental/emotional health. The sum of these domains will calculated to derive the total mLSS. Clinically meaningful improvement in mLSS is defined as a reduction of ≥7 points in overall mLSS. Longitudinal change in mLSS is analyzed by repeated measures using generalized linear model over time, evaluating within-subject and between-subject effects. In addition, the proportion of the patients showing clinically meaningful improvement in mLSS is analyzed longitudinally at 12, 24, and 48 weeks. In addition, the best improvement in mLSS is also calculated in each subject and plotted.

Safety and tolerability (secondary endpoint) will be assessed throughout the treatment duration using CTCAE v5.0 grading. Adverse events will be summarized descriptively, including:

- Incidence (number and percentage) of AEs, SAEs, and AESIs by grade, system organ class, preferred term, and relationship to study drug (belumosudil, ruxolitinib, or combination).

- Frequencies and percentages for AEs leading to dose modifications, interruptions, or discontinuations.

- Time-to-first AE (for key events) using Kaplan-Meier estimates if appropriate. No formal hypothesis testing will be performed for safety; results will be presented in tabular and graphical formats.

11.3.2 Evaluation of the Exploratory Endpoint

The exploratory objectives are two folds: 1) longitudinal monitoring of P-ROM score; 2) current failure-free survival (cFFS)

11.3.2.1. Longitudinal monitoring of P-ROM score

P-ROM score is to evaluate the improvement of sclerotic GvHD in musculoskeletal involvement of GvHD using the P-ROM score measurement. This will be evaluated by measuring changes in the P-ROM score after 4, 8, 12, 24, and 48 weeks of combination 3rd line therapy and ruxolitinib 2nd line monotherapy for patients who have developed steroid refractory chronic GvHD.

Current failure-free survival (cFFS) is to determine therapeutic intervention of combination (Belumosudil+ruxolitinib) could restore GvHD control in the patients failing ruxolitinib therapy. It will be measured from initiation of ruxolitinib (i.e. ruxolitinib 2nd-line therapy) for steroid refractory chronic GvHD, over ruxolitinib failure, till 1) treatment failure to belumosudil-ruxolitinib 3rd line combination, 2) progression/relapse of primary disease, 3) non-relapse mortality.

11.3.2.2. Current failure-free survival (cFFS)

11.3.2.2.1. Background: Previous concept of current leukaemia-free survival in CML after allogeneic HCT

Allogeneic haematopoietic cell transplantation (allo-HCT) is curative for a substantial proportion of patients with chronic myeloid leukaemia (CML), but relapse remains a principal cause of treatment failure. A defining feature of CML after allo-HCT is the availability of highly effective salvage therapy: donor lymphocyte infusion (DLI), and subsequently tyrosine kinase inhibitors, can re-establish durable molecular remission in a large fraction of patients who relapse. Conventional leukaemia-free survival (LFS), defined as survival without any evidence of relapse at any time after transplant, treats every relapse as a permanent, terminal event and therefore classifies a patient who relapses but is successfully salvaged as a treatment failure - systematically underestimating the true cumulative benefit of the transplant-plus-salvage strategy. To address this, Craddock, Klein and colleagues introduced current leukaemia-free survival (CLFS), defined as the probability that a patient is alive and free of leukaemia at the most recent assessment, whether in the original post-transplant remission or in a remission re-established after treatment of relapse [21,22]. In 189 consecutive patients transplanted for CML in chronic phase, the 5-year LFS was 36% whereas the 5-year CLFS was 49%, indicating that salvage therapy (predominantly DLI) added approximately 13% to long-term disease-free survival - a contribution invisible to conventional LFS.

11.3.2.2.2. Methodological rationale of a "current" failure-free survival endpoint

Standard time-to-event endpoints such as LFS or failure-free survival (FFS) are, by construction, monotonically non-increasing and treat the first qualifying event as absorbing: once a patient "fails," they can never re-enter the event-free state, even if a subsequent intervention fully restores disease control. Where effective salvage exists, this produces a curve that falls at each first failure but can never rise, and so cannot credit

successful re-treatment. The "current" formulation removes this limitation - the estimated probability of occupying a controlled state is allowed to decrease when a patient fails and to increase again when a subsequent remission or disease control is achieved, so that the curve tracks the patient's actual, dynamic status over time ([22]. The gap between the current and the conventional estimate directly quantifies the incremental value of the salvage intervention. This is precisely the situation in steroid-refractory chronic graft-versus-host disease (cGvHD) treated with ruxolitinib, where a substantial proportion of patients fail second-line ruxolitinib but can regain control with an effective subsequent therapy.

11.3.2.2.3. Rationale for adopting current failure-free survival in this study

The two-phase design of this study mirrors the relapse-and-salvage paradigm in which CLFS was developed. Patients begin ruxolitinib as second-line therapy for steroid-refractory cGvHD (the ruxolitinib 2nd-line phase); an anticipated 40–50% will meet criteria for ruxolitinib failure and transition to the belumosudil + ruxolitinib combination as third-line therapy (the belumosudil + ruxolitinib 3rd-line phase). Under a conventional FFS definition measured from the start of ruxolitinib, the addition of a new systemic agent - ruxolitinib failure prompting the combination - is itself a failure-defining event, so every patient who progresses to the combination is scored as a permanent failure regardless of the subsequent outcome. Such an analysis cannot capture the central hypothesis of the study: that the belumosudil + ruxolitinib combination can restore GvHD control in patients failing ruxolitinib. We therefore adopt current failure-free survival (cFFS) as a secondary endpoint, measured from the initiation of ruxolitinib second-line therapy. cFFS captures ruxolitinib failure as an event but permits the patient to re-enter the failure-free ("controlled") state when the combination re-establishes response, thereby estimating the probability that a patient is alive and in GvHD control - on ruxolitinib alone, or on the salvage combination - at any given time. In this analogy, the belumosudil + ruxolitinib combination is to ruxolitinib failure what DLI is to post-transplant relapse, and cFFS quantifies the benefit of the salvage combination at the level of the overall treatment strategy. The primary endpoint of the study remains FFS at 48 weeks within the belumosudil + ruxolitinib 3rd-line phase; cFFS is reported as a supportive, strategy-level secondary endpoint.

11.3.2.2.4. Statistical method and failure components

The patient's course is represented as a multistate process analogous to the model of Klein and colleagues ([21, 5]). The principal states are: control on ruxolitinib second-line therapy (the initial failure-free state, analogous to first remission); ruxolitinib failure (analogous to relapse); receipt of the belumosudil + ruxolitinib combination; restored control on the combination (a second failure-free state, analogous to second remission); and the absorbing failure states of death, relapse of the underlying malignancy, non-

relapse mortality, or non-response requiring a further line of systemic therapy. For failure-free survival, an event is defined as death from any cause, relapse of the underlying malignancy, or initiation of an additional/next line of systemic immunosuppressive therapy beyond the phase-defining regimen; documented ruxolitinib failure per the pre-specified EBMT criteria marks the transition between phases. Current failure-free survival is the probability of occupying either failure-free state - controlled on ruxolitinib, or controlled on the combination after ruxolitinib failure - at time *t*, measured from the start of ruxolitinib. Two equivalent estimators will be used, following Klein et al. The first is a multistate Markov model in which cFFS(*t*) is the sum of the occupancy probabilities of the two control states. The second is a model-free estimator constructed as a linear combination of three Kaplan–Meier functions[23]: $cFFS(t) = S_1(t) + S_2(t) - S_3(t)$, where $S_1(t)$ is the conventional FFS function (event: death or first failure while on ruxolitinib), $S_2(t)$ treats death at any time or a second failure after the combination as events, and $S_3(t)$ treats death before - or achievement of - restored control on the combination as events; the difference $S_2(t) - S_3(t)$ estimates the probability of currently being in the salvage-restored control state (the fraction "rescued" by the combination). Standard errors will be obtained by the method of Pepe (1991). Because the two estimators coincide until the first patient is salvaged and are otherwise closely concordant (in the original CML series they differed by roughly a percentage point at 3 and 5 years), the multistate model will serve as the primary analysis of cFFS and the model-free estimator as a sensitivity analysis.

11.4. Final Analysis and Reporting

The final analysis will be conducted when the accrual target has been met, and all patients have completed their final study visit. Any deviation from the original statistical plan will be described in the final report.

12. STUDY SIGNIFIANCE

Despite advancements in the treatment of cGvHD with corticosteroids, many patients do not respond adequately to first-line therapy. Approximately 50–60% of patients with moderate to severe cGvHD stop responding to steroids within two years, and no standard second-line treatment exists. Current options, like rituximab or photopheresis, lack central approval and consistent success, leaving patients with high morbidity, reduced quality of life, and increased mortality risk. Ruxolitinib and belumosudil, approved for steroid-refractory cGvHD, show promising response rates (over 70%), but complete, lasting responses are rare. Patients often rely on prolonged steroids or immunosuppression, leading to complications. This study tests combining ruxolitinib and belumosudil as an upfront third-line therapy to improve outcomes in this patient population. No studies have

yet to explore combining these non-first-line agents for cGvHD. This trial design will provide valuable data on the safety and efficacy of combining these drugs, potentially paving the way for larger, randomized trials, leading to better disease control in an underserved group facing both cGvHD and treatment-related complications. Insights into how these drugs work together could also deepen understanding of cGvHD's inflammatory and fibrotic processes, informing the development of new therapies. Ultimately, the study could benefit transplant patients worldwide by potentially offering better disease management and advancing medical knowledge in a challenging field.

13. ETHICS

13.1. Informed Consent

Patient / Legally acceptable representative (LAR) (as applicable) consent (including Pregnancy and Pregnancy Partner consents as applicable) must be obtained according to local site and/or ethics board requirements prior to any study-specific screening procedures. It will be the responsibility of the PI to obtain the necessary clearance, and to indicate in writing to Ozmosis that such clearance has been obtained, before the trial can commence at that site. Sample English consent forms for the trial will be provided. A copy of the initial full ethics board approval and approved consent forms must be sent to Ozmosis. The patient/LAR must sign consent prior to registration/enrollment.

13.2. Research Ethics Board (REB)

Each participating site will have on file with Ozmosis, a list indicating the composition of its ethics board consistent with regulatory guidelines. This list will be updated as appropriate.

For Canadian sites, a Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation may be included in the signed local ethics approval document. This documentation must be received by Ozmosis before the site can be locally activated.

Initial approval: Site is required to obtain full board ethics approval of the protocol and consent form by the appropriate ethics board prior to commencement of the clinical trial at each site.

Continuing approval: Annual (or as required by the ethics board) re-approval may be required for as long as patients are being followed on protocol. It will be investigator's responsibility to apply for and obtain the re-approval.

Amendment: All protocol amendments will be confirmed in writing and submitted, as appropriate, for review by the ethics board and health authorities. Amendments will be reviewed and approved by applicable regulatory authorities prior to central

implementation of the amendment, and by ethics boards prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial patients or when the change(s) involve(s) only logistical or administrative aspects of the trial.

Ethics board refusals: If an ethics board refuses to approve this protocol (or an amendment/revision to this protocol), Ozmosis must be notified immediately of the date of refusal and the reason(s) for the refusal. Notification will then be made to the regulatory authorities.

SAEs, safety updates and investigator brochure updates: During the course of the study SAEs, safety updates or investigator brochure updates may be sent to sites for reporting to their ethics board. If/when this occurs documentation of ethics board submission of this information must be forwarded to Ozmosis.

14. RESPONSIBILITIES of the INVESTIGATOR

One QI will oversee the trial at each clinical site. The QI performs the study in accordance with this clinical trial protocol, ICH Guidelines for Good Clinical Practice and the applicable Health Canada regulations and local REB requirements.

The QI may appoint other individuals as he/she deems appropriate to assist in the study's conduct. All appointed designates will be listed and provided to Ozmosis. The appointed designates will be supervised by and under the QI's responsibility.

For ensuring compliance with the clinical trial protocol, ICH GCP and applicable regulatory requirements, the QI agrees to permit study monitoring/auditing by or on the behalf of Ozmosis and inspection by applicable regulatory authorities. The investigator agrees to allow the auditors/inspectors to have direct access to his/her study records, including source data/documents.

15. DOCUMENTATION, RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS

15.1. Documentation of Patient's Participation

A statement acknowledging the participation of a patient in this clinical trial must be documented in the patient's medical records along with the signed ICF.

15.2. Regulatory Requirements

The following documents are required:

- All PIs must complete and sign the Health Canada Qualified Investigator Undertaking form. The completed forms must be returned to the Ozmosis prior to any drug shipment.

- Ozmosis will submit a completed Health Canada Clinical Trial Site Information Form to Health Canada after local activation of each participating Canadian site.

- All applicable regulatory documents as listed in the Site Activation Checklist provided by Ozmosis to the sites.
- A copy of the initial full board approval letter from the ethics board. Continuing approval (full board) will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purposes.

15.3. Patient Confidentiality and Access to Source Data/Documents

Any research information obtained about the patient in this study will be kept confidential. A patient will not be identified by name. The patient's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from the patient's participation in the study may be disclosed with their consent to the health care providers for the purpose of obtaining appropriate medical care. The patient's medical records/charts, tests will be made available to Ozmosis, the Sponsor's partners, the Canadian regulatory authority Health Canada, the ethics board and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A patient's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study PI and will not be transferred outside of the hospital.

A patient may take away his/her permission to collect, use and share information about them at any time. If this situation occurs, the patient will not be able to remain in the study. No new information that identifies the patient will be gathered after that date. However, the information about the patient that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

15.4. Confidentiality of the Study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the ethics board. The PI shall permit the Sponsor, authorized agents of the sponsor, CRO and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source

documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of the Sponsor.

15.5. Study Data at the End of Registration of Clinical Trial

Prior to the first patient being registered/enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered (e.g. clinicaltrials.gov) appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

15.6. Data Reporting and Data Management

The data will be collected on electronic CRFs during this study. All data for this trial will be analyzed using the Medidata Rave database. Data management will be conducted by Ozmosis.

Please see the study-specific eCRF Completion Guidelines for additional details. The timelines and details for submission of eCRFs are included in these guidelines.

15.7. Maintenance of Study Records

To enable evaluations and/or audits from regulatory authorities, Ozmosis or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eCRFs and hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of treatment disposition. The Investigator should retain these records for 15 years after study close-out as required by Canadian regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the PI relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another QI, another institution, or to the Sponsor. The investigator must obtain the Sponsor’s written permission before disposing of any records.

16. QUALITY ASSURANCE AND QUALITY CONTROL

As per the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the Sponsor will be responsible for implementing and maintaining quality assurance and quality control systems.

16.1. Monitoring/Auditing

Ozmosis will organize monitoring to be conducted as per the Monitoring Plan.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Products and Food Branch Inspectorate. Other audits may be conducted by the study sponsor and Ozmosis, and/or other regulatory authorities.

17. ADMINISTRATIVE PROCEDURES

17.1. Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments authorized by the Sponsor. All protocol amendments will be approved by the ethics board prior to implementation. QIs must not implement any deviation from, or change to the protocol, except where it is necessary to eliminate an immediate hazard to trial patient or when the change(s) involves only logistical or administrative aspects of the trial.

An amendment may require a change to the ICF. The investigator must receive REB approval/favorable opinion of the revised ICF before implementing the change.

17.2. Protocol Deviations and Violations

All violations or deviations are to be reported to the site's ethics board (as per ethics board guidelines). All ethics board correspondence is to be forwarded to Ozmosis. The site must notify Ozmosis and/or the Sponsor immediately of any protocol violations.

17.3. Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the QIs must contact all participating patients immediately after notification is provided by the Sponsor. Standard therapy and follow-up for patients will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed.

The ethics board will be informed promptly by the site and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

18. SCIENTIFIC REPORTING AND PUBLICATION

This clinical trial protocol was developed by the PIs with the assistance of Ozmosis.

For publications, the first author will be the Principal Investigator of the study. Additional authors will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the Principal Investigator.

Results of the study will be disseminated through publications and presentations at international meetings. Any other publication or presentation related to the study and the results by any investigator or patient must receive prior approval from the sponsor. No other publication or presentation is permitted before the primary publication or presentation by the sponsor.

The information developed during the conduct of this clinical study is considered confidential.

19. APPENDICES

19.1. Appendix A: Eastern Cooperative Oncology Group Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

19.2. Appendix B: Common Terminology Criteria for Adverse Events

CTCAE, can be accessed at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

19.3. Appendix C: Grading of cGvHD Severity

cGVHD Severity	Definition
Mild cGVHD	1 or 2 organs involved with no more than score 1 plus Lung score 0
Moderate cGVHD	3 or more organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1
Severe cGVHD	At least 1 organ with a score of 3 OR Lung score of 2 or 3

Key points:
1. In skin: higher of the two scores to be used for calculating global severity.
2. In lung: FEV1 is used instead of clinical score for calculating global severity.
3. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
4. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).
Reference: Jagasia et al 2015.

19.4. Appendix D: Modified Lee Symptom Scale

By circling one (1) number per line, please indicate how severe your symptoms have been in the past 7 days:

Skin:		**No symptoms**	**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.	Sores on skin	0	1	2	3	4
5.	Itchy skin	0	1	2	3	4
Eyes and Mouth:		**No symptoms**	**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
Breathing:		**No symptoms**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
11.	Frequent cough	0	1	2	3	4
12.	Coloured sputum	0	1	2	3	4
13.	Shortness of breath with exercise	0	1	2	3	4
14.	Shortness of breath at rest	0	1	2	3	4
Eating and Digestion:		**No symptoms**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
15.	Difficulty swallowing solid foods	0	1	2	3	4
16.	Difficulty swallowing liquids	0	1	2	3	4
17.	Vomiting	0	1	2	3	4
18.	Weight loss	0	1	2	3	4

Muscles and Joints:	**No symptoms**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**

19.	Joint and muscle aches	0	1	2	3	4
20.	Limited joint movement	0	1	2	3	4
21.	Muscle cramps	0	1	2	3	4
22.	Weak muscles	0	1	2	3	4
Energy:		**No symptoms**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
23.	Loss of energy	0	1	2	3	4
24.	Need to sleep more/take naps	0	1	2	3	4
25.	Fevers	0	1	2	3	4
Mental and Emotional:		**No symptoms**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
26.	Depression	0	1	2	3	4
27.	Anxiety	0	1	2	3	4
28	Difficulty sleeping	0	1	2	3	4

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