Official Title: A Phase II Trial of Tildrakizumab for Prevention of Acute Graft-Versus-Host Disease

NCT Number: NCT04112810

Protocol Date: 10-31-2022

A Phase II Trial of Tildrakizumab for Prevention of Acute Graft-Versus-Host Disease

William Drobyski, MD
Lyndsey Runaas, MD

Current Version Number and Date

Version 1.0, Version date: 08-08-2019

Version 2.0, Version date: 09-16-2019

Version 3.0, Version date: 05-19-2020

Version 4.0, Version date: 08-07-2020

Version 5.0, Version date: 09-08-2021

Version 6.0, Version date: 09-07-2022

Version 7.0, Version date: 10-31-2022

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MCW OnCore® No.: PRO00035737 **FDA IND No.:** 145778

Principal Investigator
Lyndsey Runaas, MD
Assistant Professor
Division of Hematology and Oncology
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
Phone: (414) 805-4600
Email: lrunaas@mcw.edu

Principal Investigator [Study PI]
William R. Drobyski, MD
Professor
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, WI 53226
Phone: (414) 805-4600
Email: wdrobysk@mcw.edu

Sub-investigator:
Bryon D. Johnson, PhD
Professor
Director of BMT and Cell Therapy Laboratory
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, WI 53226
Research Lab Phone: (414) 955-4123
Email: bjohnson@mcw.edu

Biostatistician:
Aniko Szabo, PhD
Associate Professor of Biostatistics
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
Email: aszabo@mcw.edu

Funding Sponsor:
Sun Pharmaceutical Industries, Inc.
2 Independence Way
Princeton NJ 08540
(609) 720-8021
www.sunpharma.com

DSMC Manager:
Jennifer Bollmer, PhD
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
Phone: (414) 805-1947
Email: jbollmer@mcw.edu

VERSION HISTORY

Version 1, Version Date 08/08/2019

Initial submission of the protocol.

Version	Date
Version 1	08-08-2019
Version 2	09-16-2019
Version 3	05-19-2020
Version 4	08-07-2020
Version 5	09-08-2021
Version 6	09-07-2022
Version 7	10-31-2022

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PROTOCOL SUMMARY

Title	A Phase II Trial of Tildrakizumab for Prevention of Acute Graft-Versus-Host Disease
IND Sponsor	Sponsor-investigator
Principal Investigator	William Drobyski, MD, and Lyndsey Runaas, MD
Clinical Trial Phase	Phase II
Study Population	Adult patients undergoing a myeloablative allogeneic HSCT for hematologic malignancies.
Main Eligibility Criteria	**Inclusion Criteria:** 1. Age ≥18 years. 2. Patients with any hematologic malignancy for which alloHCT is indicated. Patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) must be in complete remission at the time of alloHCT.* 3. Myeloablative conditioning (MAC) regimen, based on CIBMTR criteria.* 4. T cell-replete peripheral blood graft. 5. Patients must have a matched related or unrelated donor (at least 6/6 match at HLA-A, -B and -C for related donors and at least 8/8 match at HLA-A, -B, -C and -DRB1 for unrelated donors). 6. Cardiac function: Left ventricular ejection fraction ≥45%. 7. Estimated creatinine clearance ≥40 mL/minute (using the Cockcroft-Gault formula and actual body weight). 8. Pulmonary function: DLCO ≥40% (adjusted for hemoglobin) and FEV1 ≥50%. 9. Liver function: total bilirubin <3 x upper limit of normal and ALT/AST <5 x upper normal limit. 10. Female subjects must meet one of the following*: • Postmenopausal for at least one year before enrollment, **OR** • Surgically sterile (i.e., undergone a hysterectomy or bilateral oophorectomy), **OR** • If subject is of childbearing potential (defined as not satisfying either of the above two criteria), agrees to practice two acceptable methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study agent, **OR** o Agrees to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. 11. Male subjects, even if surgically sterilized (i.e., status post vasectomy), must agree to one of the following*:

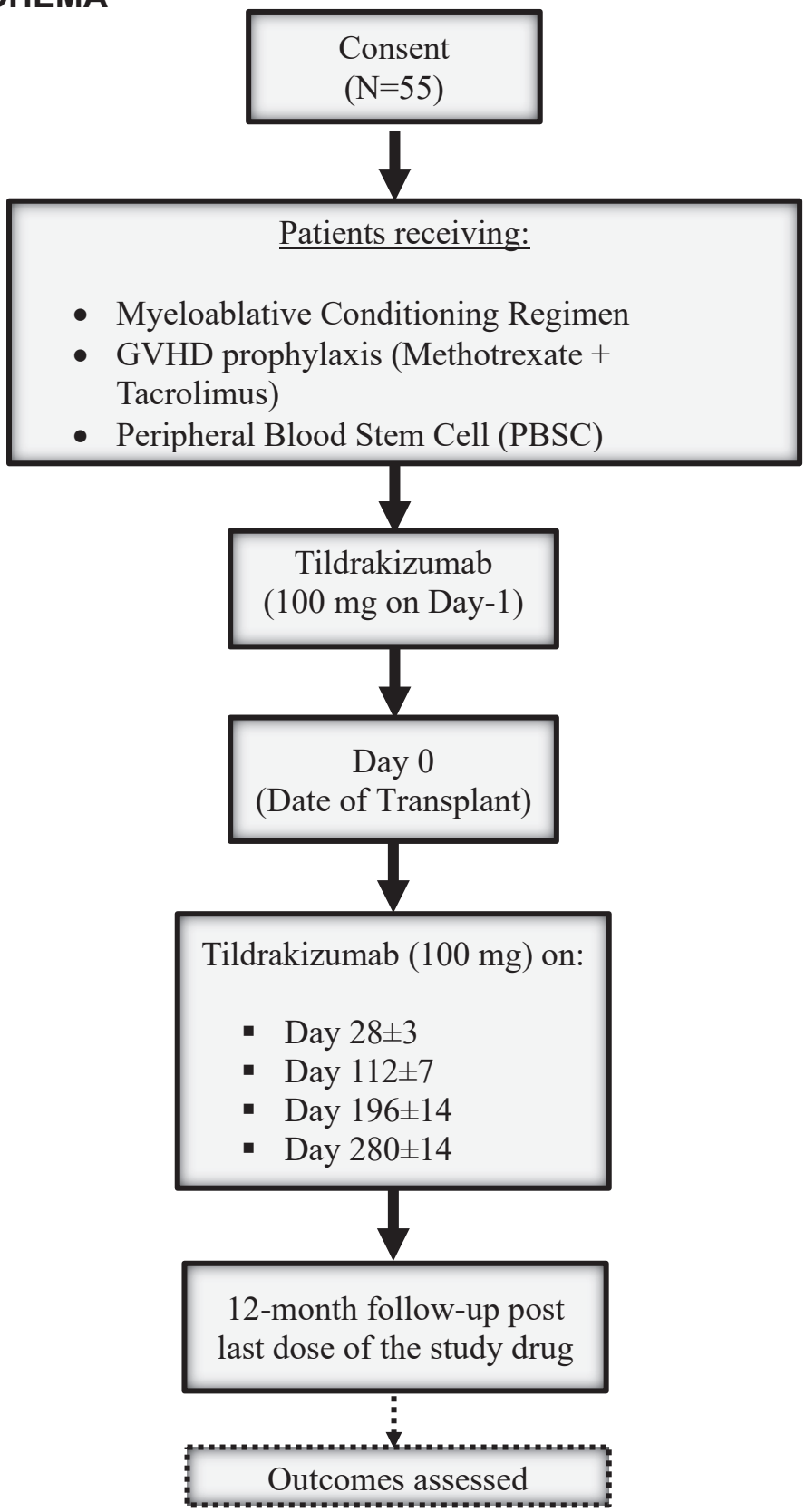
	• Practice effective barrier contraception during the entire study period and through 60 calendar days after the last dose of study agent, **OR** • Agrees to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. 12. Signed informed consent: Voluntary written consent must be given before patient registration and performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care. 13. Planned posttransplant maintenance therapy is allowed. 14. Prior autologous transplant is allowed. **Exclusion Criteria** 1. Prior allogeneic HCT. 2. Active CNS involvement with malignancy. 3. Patients receiving cord blood or haploidentical allograft. 4. Patients undergoing *in vivo* or *ex vivo* T cell-depleted alloHCT. 5. Karnofsky performance score <60% or ECOG > or = 2. 6. Patients with uncontrolled bacterial, viral, or fungal infections (currently on treatment and with progression of infectious disease or no clinical improvement) at time of enrollment. 7. Active hepatitis B or C virus infection or known human immunodeficiency virus (HIV) positive. 8. Use of rituximab, alemtuzumab, anti-thymocyte globulin (ATG), or other monoclonal antibody planned as part of conditioning regimen for GVHD prophylaxis. 9. Participation in another GVHD prophylaxis clinical trial. 10. Any current uncontrolled cardiovascular conditions, including uncontrolled ventricular arrhythmias, NYHA class III or IV congestive heart failure, uncontrolled angina, or electrocardiographic evidence of active ischemia or active conduction system abnormalities. 11. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol. Eligibility criteria will be determined prior to transplant. If a patient meets criteria during this pretransplant period but is no longer eligible at time of first administration of tildrakizumab, they will be removed and replaced on study. *Further defined in Section 4.5.
Study Rationale	GVHD remains a major cause of morbidity and mortality following MAC alloHCT. Proinflammatory cytokines play a central role in initiation and development of acute GVHD and as such, inhibition of these cytokines has been examined for both prevention and treatment of GVHD. IL-23 is a proinflammatory cytokine, which our lab has shown to have a unique and selective role in induction of colonic inflammation during acute GVHD and that this cytokine serves as a critical mediator linking conditioning regimen-

	induced mucosal injury and endotoxin lipopolysaccaraide (LPS) translocation to subsequent proinflammatory cytokine production and GVHD-associated pathological damage. Moreover, additional studies have demonstrated that blocking the IL-23 signaling pathway has not abrogated the graft-versus-tumor effect. Tildrakizumab is a commercially available anti-IL23 antibody FDA approved for the treatment of moderate to severe psoriasis with good tolerance. We hypothesize that blocking IL23, with tildrakizumab, will reduce GVHD rates for patients undergoing MAC alloHCT without having an impact on relapse rates, thus improving GVHD-free relapse-free survival (GRFS).
Primary Objectives	Probability of GVHD-free relapse-free survival (GRFS). An event for this outcome is defined as **either**: • grade III–IV acute GVHD • systemic therapy requiring chronic GVHD • relapse • or death at 12 months after matched related/unrelated donor peripheral blood HSCT using myeloablative conditioning regimen.
Primary Endpoint	GVHD-free relapse-free survival (GRFS).
Secondary Objectives	1. Cumulative incidence of mild, moderate, and severe chronic GVHD, according to the NIH criteria, and limited or extensive GVHD by conventional criteria. 2. Cumulative incidence of grade III–IV acute GVHD at days 100 and 180. 3. Probability of lower GI tract GVHD. 4. Incidence of primary and secondary graft failure. 5. Probability of non-relapse mortality (NRM) post HSCT. 6. Cumulative incidence of relapse/progression of the primary malignancy. 7. Probability of overall survival (OS) post HSCT. 8. Assess the pharmacokinetic (PK) profile of multi-dose tildrakizumab. 9. Incidence of infections. 10. Donor cell chimerism. 11. Effect of GVHD prophylaxis on gut microbiome diversity: difference in the level of microbiome diversity during transplant and association of baseline gut microbiome diversity with development of aGVHD, cGVHD and overall survival.
Secondary Endpoint(s)	1. Chronic GVHD. 2. Acute GVHD. o Grade II–IV. o Grade III–IV. 3. Acute GI GVHD. 4. Graft failure and hematopoietic recovery. 5. Non-relapsed mortality (NRM). 6. Disease relapse or progression. 7. Progression-free survival. 8. Overall survival. 9. Pharmacokinetics.

	10. Infectious risk. 11. Donor cell chimerism. 12. Microbiome diversity pre-engraftment and evolution during transplant.
Study Design	This is a phase II open-label trial designed to evaluate the efficacy of tildrakizumab in improving GRFS after myeloablative allogeneic hematopoietic cell transplantation for hematologic malignancy.
Study Agent/ Intervention Description	Patients enrolled on this clinical trial will receive tacrolimus initiating at day -3 at doses to maintain therapeutic levels per institutional preference and continued until at least day +90 post-transplant. Methotrexate will be administered intravenously and dosed at 15 mg/m^2 days +1, and 10 mg/mg^2 on days +3, +6, and +11. Tildrakizumab will be administered subcutaneously at a dose of 100 mg on day -1, day 28 ± 3, day 112 ± 7, day 196 ± 14, and day 280 ± 14.
Number of Subjects	55 patients
Subject Participation Duration	Patients will be followed for at least 12 months following alloHCT.
Duration of Follow-up	Patients will be followed for at least 12 months following alloHCT.
Estimated Time for Study Completion:	The study will reach study completion 30 months from the time the study opens to accrual.
Statistical Methodology:	The study will test the primary hypothesis that GRFS at 12 months exceeds the historical control value of 20% at a two-sided 10% significance level. The target sample size will be 55 patients with a known outcome (i.e., GVHD, relapse, or death status at 12 months). With this sample size the study will have 80% power to detect an increase in GRFS at 12 months to 35%, 94% power to detect an increase to 40%, and 54% power to detect an increase to 30%. Justification for the 15% increase in GRFS probability as a clinically meaningful endpoint derives from the recently published BMT Clinical Trials Network 1203 GVHD prevention trial which compared three different prophylaxis regimens to standard therapy with tacrolimus and methotrexate and was powered to detect a 15% increase in GRFS To achieve the target sample size, we will enroll 55 patients to allow for a 10% loss to follow-up. It is estimated that 30 months of accrual will be adequate. This is based on our historical rate of approximately 50 myeloablative allogeneic stem cell transplants per year over the past three years. Assuming a conservative

	40% enrollment rate, approximately 30 months should be sufficient to enroll our target of 55 patients. **Analysis of primary endpoint** The GRFS will be estimated using the Kaplan-Meier estimator and plotted with a 95% confidence band. An event for this outcome is defined as grade III–IV acute GVHD, chronic GVHD requiring systemic therapy, relapse, or death. Patients who are alive without GVHD will be censored at the last follow-up. The 12-month GRFS will be compared to the prespecified historical control value of 20% using a one-sided *z*-test. **Analysis of secondary endpoints** Demographic and other baseline data, such as disease characteristics, as well as outcome measures, will be presented overall and separately for URD and MRD patients. Categorical data, such as gender, race, etc., will be presented by frequencies and percentages. Descriptive summary statistics (e.g., frequency, mean, median, range and standard deviation) will be used to present numeric data. Time-to-event outcomes with and without competing risks will be analyzed using Kaplan-Meier and Nelson-Aalen estimates, respectively, and presented with 95% confidence intervals. Binary outcomes will be analyzed using proportions with 95% confidence intervals. Bacterial community composition will be characterized using OTU counts generated, as described above. OTU counts will be converted to measures of relative abundance to account for variation in sequencing coverage between samples. Statistical analysis will be carried out using the statistical software package R (www.r-project.org). Alpha (α) diversity (richness and evenness of taxa within a population) will be reported using the Shannon Index [46] and Chao1 richness estimator.[47] Beta (β) diversity (overlap in taxa shared between populations) will be analyzed using the Bray-Curtis dissimilarity metric[48] in conjunction with multivariate statistical analysis methods that will include Principal Components Analysis (PCA) and Permutational Multivariate Analysis of Variance (PERMANOVA).[49] Changes in abundance of individual taxa will also be analyzed using traditional univariate statistical methods.

STUDY SCHEMA



STUDY CALENDAR

Study Assessments	Baseline	Pre-Transplant	(Post-Transplant) (in Days)							Follow-Up	
	Day – 30 to -1	Day -1	28± 3	56 +/- 7 days	100 +/- 14 days	112± 7	180+/- 14 days	196± 14	280± 14	12 month post HCT (+/- 30 days)	
Informed consent	X										
Tildrakizumab administration – 100 mg subcutaneously		X	X			X		X	X		
History, physical exam, weight, height*	X		X	X	X	X	X	X	X	X	
ECOG Performance Status and HCT-CI*	X										
HLA typing (donor and recipient)*	X										
CBC with differential[1], Comprehensive metabolic panel[2*]	X		X	X	X	X	X	X	X	X	
Infectious disease markers[3*]	X										
LVEF[4*]	X										
DLCO and FEV1[4*]	X						X			X	
Disease evaluation[5*]	X				X					X	
Pregnancy test[6*]	X										
GVHD assessments[7*]			X	X	X	X	X	X	X	X	
AE assessments[8]	X		X	X	X	X	X	X	X	X	
Chimerism[9*]			X								
CMV NAAT peripheral blood*			X	X	X	X					
EBV PCR peripheral blood			X	X	X	X					
Immune reconstitution*			X		X		X			X	

	STUDY CALENDAR											
Study Assessments	**Baseline**	**Pre-Transplant**	**(Post-Transplant) (in Days)**							**Follow-Up**		
	Day – 30 to -1	**Day -1**	**28± 3**	**56 +/- 7 days**	**100 +/- 14 days**	**112± 7**	**180+/- 14 days**	**196± 14**	**280± 14**	**12 month post HCT (+/- 30 days)**		
Pharmacokinetic Labs and ADA testing		See footnote 10 for details and timepoints										
Research (stool) sample collection		x		See footnote 11 for details and timepoints								
Research blood and plasma	X		See footnote 12 for details and timepoints									

*Indicates evaluations are currently performed as standard of care at the MCW BMT program.

1. CBC with differential will be performed as appropriate during hospitalization for alloHCT on clinic visits and at minimum performed on days indicated on the schedule of events.
2. Comprehensive metabolic panel will be performed as appropriate during hospitalization for alloHCT, on clinic visits and at minimum performed on days indicated on the schedule of events.
3. Infectious disease titers include: CMV, hepatitis panel (hepA ab, hepB SAb, hepB SAg, hepB Core Ab, hepC Ab), HIV and HTLV I/II antibody.
4. May be performed within three months of transplant.
5. Evaluation of the malignant disease: for acute leukemia, CML, and MDS, these include a bone marrow aspirate and biopsy for morphology, cytogenetics/FISH and molecular testing as appropriate.
6. Pregnancy test must be performed <30 days before the start of the transplant conditioning for females of childbearing potential and may be performed per institutional practices.
7. GVHD assessments performed per the standard operating procedures at the MCW BMT Program and at minimum on days listed above. The GVHD assessment will include a review of all abnormalities experienced **during the entire assessment period** and the **highest grade** for each abnormality during the assessment period will be recorded.
8. The AE assessment will include a review of **all** toxicities experienced **during the entire assessment period** and the **highest grade** for each AE during the assessment period will be recorded on the AE forms.
9. Chimerism in whole blood fractionated as CD3 and CD33.
10. PK labs should be drawn prior to drug administration (prior to D-1) during initial admission, D+30 +/- 2 days, D+60 +/- 7 days and D+90 +/- 14 days. Each PK analysis requires five tubes of blood, each with 2–3 mL for a total of 10–15 mL blood drawn per PK analysis. Samples should stored at -70 degrees and batched prior to transmission to Labcorp Drug Development.
    ADA/NAB testing will be run off same samples as necessary to allow for better understanding of the PK profile differences seen.
11. First stool sample for microbiome studies will be collected after admission in the hospital pre-transplant (d-1) Subsequent stool samples will be collected on D+1 +/-2 days, D+7 +/- 2 days, , and every seven days thereafter through neutrophil engraftment (defined as three consecutive days of ANC >500). The last stool sample should be collected AFTER neutrophil engraftment. Stool sample will also be collected at the time of onset of acute or chronic GVHD.

	STUDY CALENDAR										
Study Assessments	**Baseline**	**Pre-Transplant**	**(Post-Transplant) (in Days)**							**Follow-Up**	
	Day – 30 to -1	**Day -1**	**28± 3**	**56 +/- 7 days**	**100 +/- 14 days**	**112± 7**	**180+/- 14 days**	**196± 14**	**280± 14**	**12 month post HCT (+/- 30 days)**	
	12. Blood samples will be collected at the following time points: Baseline (screening) and days 7±3, 14±3, 21±3, 28±7, 60±14, 90±14, 196±30, 365±30 post-transplants and at the time of development of GVHD (if it occurs). For each time point, one 10-ml red top tube and one 10-ml purple top tube will be collected.										

LIST OF ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse Event
aGVHD	Acute Graft-Versus-Host Disease
ALP	Alkaline Phosphatase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CDK	Cyclin-Dependent Kinases
cGVHD	Chronic Graft-Versus-Host Disease
CR	Complete Response
CRC	Clinical Research Coordinator
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Cell
CTO	Clinical Trials Office
DFS	Disease-Free Survival
DLT	Dose-Limiting Toxicity
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration

GI	Gastrointestinal
GVHD	Graft-Versus-Host Disease
GVL	Graft-Versus-Leukemia
HCT	Hematocrit
HGB	Hemoglobin
HSCT	Hematopoietic Stem Cell Transplantation
IL-23	Interleukin-23
IP	Investigational Product
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
MCWCC	Medical College of Wisconsin Cancer Center
NCI	National Cancer Institute
NRM	Non-Relapsed Mortality
ORR	Overall Response Rate
PBMC	Peripheral Blood Mononuclear Cells
PD	Disease Progression
PK	Pharmacokinetics
PR	Partial Response
PRRs	Pattern Recognition Receptors
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation
ULN	Upper Limit of Normal
UP	Unanticipated Problem

UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
WBC	White Blood Cell (Count)

1 BACKGROUND

Allogeneic hematopoietic stem cell transplantation (HSCT) is an intensive treatment modality that often represents the only curative therapy for patients with aggressive hematologic malignancies or other marrow failure syndromes. More than 8,000 allogeneic HSCTs were performed in the United States in 2016.[1] Despite this, the procedure continues to carry a high morbidity and mortality rate. One of the principal contributors to transplant-related mortality is graft-versus-host disease (GVHD).[2] GVHD develops in approximately 40–50% of patients undergoing an HLA matched related HSCT and 50–70% of recipients receiving a matched unrelated donor HSCT. [3,4] This is despite standard GVHD prophylactic medications administered to all transplant recipients. Once established, GVHD proves resistant to frontline therapies with corticosteroids in more than 50% of patients,[5] and survival is significantly diminished for these patients. [6,7]

1.1 Graft-versus-Host Disease

GVHD is an immunological phenomenon whereby donor lymphocytes respond to host peptides expressed on polymorphic human leukocyte antigens (HLA) molecules. This results in a clinical syndrome which can be described as an inflammatory response directed predominantly against the skin, intestine, and liver. The interaction between donor lymphocytes and polymorphic HLAs on host tissues is amplified by the significant tissue damage that occurs in transplant recipients as a result of the conditioning regimen. This leads to a significant cytokine and chemokine signaling, which furthers this destructive cascade.

GVHD has been divided into two phases, termed acute and chronic, which are distinguishable based on both temporal characteristics as well as unique clinical and pathological manifestation.[8-10] Acute GVHD (aGVHD) typically occurs in the first 100 days of transplant and targets a restricted set of organs including the skin, gastrointestinal (GI) tract, and liver, leading to cell apoptosis.[11] Chronic GVHD, alternatively, tends to occur after the first 100 days of transplant and can impact almost any organ system, with protean manifestations that have similarities to what occurs during autoimmune diseases.

The pathophysiology underlying acute GVHD is often considered a “cytokine storm” with a three-phase process: (1) the conditioning regimen results in systemic inflammation due to release of pro inflammatory cytokines such as IL-1, IL-6, TNF-α, and INF-γ; (2) donor T-cell priming and differentiation as a response to presentation by host antigens to APC; (3) effector phase of tissue apoptosis mediated by inflammatory cytokines and T/NK cells effectors.[2]

Compelling data in experimental models have shown that the GI tract plays a primary role in the amplification of acute GVHD.[12,13] Damage to the gastrointestinal mucosa from the conditioning regimen results in the release of damage- and pathogen-associated molecular patterns (DAMPs and PAMPs),[13,14] which activate cells of the innate immune system through the ligation of pattern recognition receptors (PRRs).[15] This ultimately leads to the generation of clonally expanded alloreactive T cells, which mediate further damage, creating an inflammatory positive feedback loop. From a clinical perspective, involvement of the GI tract is a major cause of morbidity and can result in significant complications, including protracted diarrhea, requirement for parenteral nutrition, and infectious complications due to translocation of bacteria across a damaged mucosal barrier.[16] Given the pivotal role that the GI tract plays in GVHD biology, strategies designed to reduce inflammation in this target organ have the potential to significantly decrease morbidity and mortality associated with this disease.

Owing to the central role of proinflammatory cytokines in the initiation and development of acute

graft-versus-host disease, inhibiting these cytokines has been looked at for both prevention and treatment of GVHD.

1.2 Interleukin-23

IL-23 is a member of the IL-12 family, signals through STAT3, and is secreted by dendritic cells (DCs), as well as other antigen presenting cells (APCs) such as macrophages and monocytes.[i] [17] This cytokine shares a p40 subunit with IL-12, but also contains an IL-23-specific p19 component. The p19/p40 complex binds to the IL-12Rβ1 subunit that is also a component of the IL-12 receptor along with a unique IL-23 receptor subunit that together is present on memory/activated T cells, DCs and macrophages.[18] Early studies demonstrated that IL-23 plays a critical role in disorders such as experimental allergic encephalomyelitis (EAE),[19] collagen-induced arthritis,[20] and inflammatory bowel disease[21] implicating this cytokine as a pivotal mediator in the pathogenesis of inflammatory disorders and autoimmunity.

1.3 IL-23 and GVHD

Studies in our laboratory using preclinical murine bone marrow transplantation models have demonstrated that IL-23 has a unique and selective role in the induction of colonic inflammation during acute GVHD and serves as a critical mediator linking conditioning regimen-induced mucosal injury and lipopolysaccharide (LPS) translocation to subsequent proinflammatory cytokine production and GVHD-associated pathological damage.[11,22] Specifically, transplantation of IL-23–deficient marrow grafts or administration of a p19-specific antibody significantly reduced the severity of acute GVHD, which was attributable to the preferential reduction in colonic GVHD, and a decrease in the production of proinflammatory cytokines within this tissue site. Secretion of IL-23 by donor, and not host, APCs was shown to be a critical event in the induction of GVHD of the colon. In subsequent studies, we identified that the proinflammatory effects of IL-23 were mediated through $CD4^+$ T cells that expressed the IL-23 receptor.[23] Specifically, these studies identified a unique colitogenic $CD4^+$ $IL\text{-}23R^+$ T-cell population that constitutively expresses the β2 integrin, CD11c, has a biased central memory phenotype and memory T-cell transcriptional profile, possesses innate-like properties by gene expression analysis, and has increased expression of the gut-homing molecules, α4β7 and CCR9. Adoptive transfer of these cells resulted in increased overall mortality, proinflammatory cytokine production and pathology specifically in the colon. Collectively, these findings defined a novel organ-specific role for IL-23 in the pathophysiology of GVHD and demonstrated that IL-23 could direct tissue-specific pathology within the context of a systemic inflammatory disorder. Moreover, additional studies demonstrated that blockade of the IL-23 signaling pathway did not abrogate the graft-versus-leukemia effect when tested in both acute and chronic models of leukemia.[23] Thus, targeting the IL-23 pathway for GVHD prevention in murine models resulted in separation of GVH and GVL reactivity. Thus, with a series of publications in well-characterized mouse models, we believe that we have established that IL-23 has a pivotal role in the pathophysiology of GVHD in the GI tract. In addition, there have been a number of studies that have suggested that donors with IL23R polymorphisms which result in attenuated IL-23 secretion have a protective effect on the occurrence of moderate-to-severe acute GVHD in transplant recipients.[24]

1.4 Tildrakizumab

Tildrakizumab (Iluyma™) is a humanized monoclonal antibody that specifically binds to the IL-23p19 subunit of IL-23 to neutralize its function.[25] The drug has been evaluated in clinical trials for patients with moderate to severe psoriasis with good effect.[25,26] The drug was well tolerated, with maximum-tolerated dose (MTD) of 10 mg/kg^{-1} once monthly. The responses were achieved

at all dose level (0.05–10 mg/kg^{-1}), maximum responses were achieved at dose level 3 and 10 mg/kg^{-1}.

The most common adverse events reported were headache, nasopharyngitis, upper respiratory infection, and cough. There was no dose increase related adverse events. Among the serious adverse events reported was convulsion, which was attributed secondary to tildrakizumab, occurred 17 days after the 10 mg/kg^{-1} doses, but there were several reported confounding factors; alcohol consumption, lack of sleep and use of benzodiazepines. In terms of pharmacokinetic, the drug had slow systemic clearance with long half-life of around three weeks. Another significant finding of the study was that the IL-23p19 expression almost completely disappeared from the affected tissue after tildrakizumab treatment, suggesting that the drug possesses direct effect on IL-23 producing cells. Based on this data, tildrakizumab was FDA approved for treatment of moderate to severe plaque psoriasis in March 2018.

1.5 Tildrakizumab and Treatment of GVHD

To date, tildrakizumab has not been tested for prevention or treatment of GVHD but based on aforementioned data suggesting a pivotal role for IL-23 in the pathophysiology of GVHD, coupled with the very favorable safety profile of tildrakizumab; we propose to conduct a phase II study evaluating the efficacy of tildrakizumab plus standard immunosuppressive therapy in preventing GVHD in patients undergoing a myeloablative HSCT. The FDA approval for use of this agent in patients with plaque psoriasis, with a well-reported safety profile, justifies not embarking on a phase I study in this population. However, as we were well aware that patients undergoing MAC alloHCT patients represent a uniquely vulnerable patient population with potential for unexpected and potentially life-threatening adverse effects, we initially proposed a safety run-in phase of six patients to ensure these patients appropriately engrafted and did not experience any unexpected adverse events before proceeding to the full phase II study.

1.6 Correlative Studies

Given the known cytokine dysregulation that is seen in the setting of allogeneic HSCT, especially in acute GVHD,[27] we intend to perform correlative studies to understand the impact of anti-IL-23 antibody treatment on the proinflammatory cytokine milieu that is typically seen post-allogeneic HSCT. This testing may help us better understand the changes that are happening within the immune system to inhibit graft-versus-host disease (GVHD).

1.7 Studies of the Microbiome in Transplant Patients

The microbiome, consisting of a varied community of microbes (bacteria, viruses, fungi, microeukaryotes, and sometimes multicellular parasites), exists in niches across the human body. The skin, lung, nares, vagina, and gastrointestinal tract are among the most heavily colonized, with the largest number of microorganisms inhabiting the colonic lumen. While the majority of the over trillion organisms that live within a healthy human colon are nonpathogenic members of the phyla Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, alterations in the balance of these microorganisms have been associated with adverse outcomes ranging from GVHD and infection to relapse post-HCT. [28] This clinical association between intestinal microorganisms and HCT outcomes has been investigated for decades and has informed the still controversial practices of infection prophylaxis, gut decontamination, the “neutropenic diet,” and isolation of patients in laminar air flow rooms. Single-institution studies have demonstrated that low microbial diversity in the stool after allogeneic HCT is associated with poor survival. [29,30]

Additionally, specific alterations have been associated with increased risk of acute GVHD, infectious outcomes and most recently, relapse. [31-33] While these findings are compelling, the generalizability of these proposed microbial biomarkers is unclear. This is particularly important as there is known geographic variation of the intestinal microbiome and practice variability in antibiotic use for prophylaxis and treatment from institution to institution, in part due to different antibiograms.

Novel methods in microbiome research are likely to facilitate translational breakthroughs — these methods allow (1) detailed taxonomic classification of microorganisms at the strain level, (2) metabolic characterization of the small molecules and proteins that a microbial community makes, (3) measurement of microbial genomic evolution in clinical time courses, and (4) culturing of previously fastidious organisms from the microbiome for *in vitro* investigation and cultivation as potential therapeutic live bacterial clinical interventions. Given recent reports suggesting that alterations in the microbiome can impact the efficacy of immunologic therapies, it is imperative that the link between the microbiome and transplant outcomes is investigated.[34,35]

1.7.1 Microbiome and Outcomes after Allogeneic Transplantation using Tildrakizumab as GVHD Prophylaxis

The study will test the secondary hypothesis that the use of IL-23 blockage (tildrakizumab), which has been shown to lower gastrointestinal GVHD rates, preserves the gut microbiome diversity (determined by 16s rRNA sequencing analysis of the sequential stool sample collected pre- and post-transplant until neutrophil engraftment). Additional analyses on patient samples will be conducted to answer the key question concerning the impact of the gut microbiome on transplant outcome. Aliquots preserved additionally will establish a cohort of stool samples collected prospectively for future sequencing by shotgun metagenomic sequencing and metabolomic analysis. Previous GVHD prophylaxis studies performed at this institution have also evaluated microbiome diversity in this setting. Continuing these important exploratory evaluations will help to add to our knowledge base in this arena and will contribute importantly to future research.

2 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

In this study, we hypothesize that IL-23 inhibition through repeated treatment with tildrakizumab, when added to standard GVHD prophylaxis, will result in an improvement in GVHD-free relapse-free survival (GRFS) for adult patients undergoing a myeloablative allogeneic HSCT for hematologic malignancies.

2.1 Primary Objectives

The primary endpoint of this trial is to determine the probability of GVHD-free relapse-free survival (GRFS). An event for this outcome is defined as either grade III–IV acute GVHD, systemic therapy-requiring chronic GVHD, relapse, or death at 12 months after matched related/unrelated donor peripheral blood HSCT using myeloablative conditioning regimen. Patients who are alive without GVHD will be censored at the last follow-up.

2.2 Secondary Objectives

1. Cumulative incidence of mild, moderate and severe chronic GVHD according to the NIH criteria and limited or extensive GVHD by conventional criteria.
2. Cumulative incidence of grade II–IV acute GVHD at days 100 and 180.
3. Cumulative incidence of grade III–IV acute GVHD at days 100 and 180.
4. Probability of lower GI tract GVHD.
5. Incidence of primary and secondary graft failure.
6. Probability of non-relapse mortality (NRM) post HSCT.
7. Cumulative incidence of relapse/progression of the primary malignancy.
8. Probability of overall survival (OS) post HSCT.
9. Assess the pharmacokinetic (PK) profile of multi-dose tildrakizumab.
10. Incidence of infections.
11. Donor cell chimerism.
12. Effect of GVHD prophylaxis on gut microbiome diversity: difference in level of microbiome diversity during transplant and association of baseline gut microbiome diversity with development of aGVHD, cGVHD and overall survival.

2.3 Rationale for the Outcome Measures Selection

Ample evidence suggests that IL-23 has a pivotal role in the pathophysiology of GVHD and preclinical studies suggest that blocking the IL-23 pro-inflammatory pathway can prevent GVHD. In this study, we will treat patients with tildrakizumab, which is a humanized monoclonal antibody that specifically binds to the IL-23p19 subunit of IL-23. We hypothesize that targeting IL-23 will reduce the incidence of GVHD and improve morbidity and mortality after transplantation.

2.4 Primary Endpoint

The primary endpoint of this trial is GRFS. An event for this outcome is defined as grade III–IV acute GVHD, chronic GVHD requiring systemic therapy, relapse or death. Patients who are alive without GVHD will be censored at the last follow-up.

2.5 Secondary Endpoint(s)

1. **Chronic GVHD**
   The cumulative incidence of chronic GVHD by NIH Consensus criteria (Appendix 2) will be determined. Development of chronic GVHD will be considered an event for this endpoint. The highest grade of chronic GVHD will be recorded. In addition, the time of onset of chronic GVHD and the time to highest chronic GVHD grade will be recorded. Death but not disease relapse will be considered a competing event.

2. **Acute GVHD**
   Cumulative incidences of grades II–IV and III–IV acute GVHD will be determined at day +100 and day +180 post-HCT. Acute GVHD will be graded according to Appendix 2. The time of onset of grade II–IV acute GVHD and time to development of the highest grade until day +180 will be recorded. Development of acute GVHD will be considered an event for this endpoint. Death but not disease relapse will be considered a competing event.

3. **Graft failure**
   Graft failure will be assessed as a secondary endpoint, including primary and secondary graft failure. Primary graft failure is defined as no neutrophil recovery to > 500 cells/μL by day 28 post-HCT. Secondary graft failure will be assessed according to neutrophil count after initial hematologic recovery. Secondary graft failure is defined as initial neutrophil engraftment followed by subsequent decline in absolute neutrophil counts <500 cells/μL, unresponsive to growth factor therapy, but cannot be explained by disease relapse or drugs.

4. **Hematopoietic recovery**
   Hematopoietic recovery will be assessed according to neutrophil and platelet counts recovery after HSCT. Neutrophil recovery or engraftment is defined as achieving an absolute neutrophil count (ANC) ≥500/mm^3 for three consecutive measurements on three different days. The first of the three days will be designated the day of neutrophil engraftment. The competing event is death without engraftment. Platelet recovery is defined by either the first day of a sustained platelet count >20,000/mm^3 for three days with no platelet transfusion in the preceding seven days. The first day of sustained platelet count above these thresholds will be designated the day of platelet engraftment.

5. **Non-relapsed Mortality (NRM)**
   NRM is defined as death after alloHCT without relapse. The cumulative incidence of NRM will be estimated at day +100 and one year after alloHCT. An event for this endpoint is death without evidence of disease progression or relapse. Disease progression or relapse will be considered a competing event.

6. **Disease Relapse or Progression**
   Relapse is defined by either morphological, cytogenetic or radiologic evidence of the pretransplant hematologic malignancy. Institution of any therapy to treat persistent, progressive or relapsed disease, including the withdrawal of immunosuppressive therapy or donor lymphocyte infusion, will be considered evidence of relapse/progression. NRM will be considered a competing event.

7. **Progression-Free Survival**
   The event for this endpoint is relapse/progression or death. The time to this event is measured from transplant to death or relapse/progression, whichever comes first. Patients who are alive and disease-free will be censored at last follow-up.

8. **Overall Survival**
   The event for this endpoint is death from any cause. The time to this event is measured from the time of transplant to death from any cause or for surviving patients, to last follow-up. Survivors will be censored at last follow-up.

9. **Pharmacokinetics and ADA/NAB testing**
   Pharmacokinetic sampling will be performed by Sun Pharmaceutical Industries Ltd., which will outsource these samples to Labcorp Drug Development. Given the long half-life of tildrakizumab, samples will be collected on week 0 (prior to administration of tildrakizumab), and then on days 30, 60, and 90. Each PK analysis draw requires five tubes of blood, each with 2–3 mL per tube, for a total of 10–15 mL of blood per PK analysis. PK samples should be stored at -70 degrees. Samples can be batched and shipped to Labcorp Drug Development.

ADA testing is testing for anti-drug antibodies, while Nab testing is testing for neutralizing antibodies to give a more complete picture along with the PK testing. ADA testing typically includes 3 tiers- screen, confirm and titer where screen/confirm are qualitative (positive or negative) and titer is semi-quantitative. The Nab method for tildrakizumab is screen tier only and qualitative (positive or negative), in which only samples that test positive are confirmed in the ADA assay. The purpose of having ADA/Nab testing alongside the PK testing is to better understand the PK profile differences seen. For instance, if PK serum concentrations are lower for an individual then a high ADA response would provide more clarity regarding the serum levels. Nab testing then would give additional insight into the mode of action of the immunogenicity.

10. **Incidence of infections**

The incidence of grade ≥3 (CTCAE v5) viral, fungal, and bacterial infections will be determined. The cumulative incidence of CMV viremia post-alloHCT will be described.

11. **Donor cell chimerism**

Chimerism will be evaluated using sorted whole blood in CD3+ and CD33+ fractions. Mixed chimerism is defined as the presence of donor cells, as a proportion of total cells to be >5% and <95%. Full donor chimerism is defined as ≥95% of donor cells. Donor cells of ≤5% will be considered as graft rejection. Donor cell chimerism will be assessed for all patients at day +28 (baseline) for both CD3+ and CD33+ fractions. The proportion of patients with each level of chimerism listed above will be described. CD3+ donor cell chimerism will be used to define the donor/recipient chimerism status.

12. **Microbiome**

To address this question, we will obtain stool samples from each patient prior to transplantation as a baseline and then at weekly intervals through the period of engraftment (defined as an absolute neutrophil count >500/mm^3 for three consecutive days). In addition, stool samples will be obtained at the time of GVHD onset in any affected patients. Fresh fecal samples will be collected and immediately preserved in RNAlater solution to facilitate optimal sample preservation, consistency of sample quality and ease of sample transport. Genomic DNA will be isolated from 200 mg of fecal sample using the Qiagen Powerlyzer Powersoi® kit as described.[40] Bacterial composition and abundance will be validated by quantitative PCR analysis. Composition of the microbiota will be determined through sequencing of the 16S rRNA gene V4 region (Diversigen, Baylor College of Medicine, Waco, TX). PCR products will be generated using a dual-indexing amplification strategy, then sequenced on the MiSeq platform (Illumina, San Diego, CA).

RNA gene sequence data will be utilized for bioinformatic analysis. 16S primers will be removed from the Illumina reads with the Trimmomatic program. Paired-end sequences will then be assembled using the FLASH algorithm,[42] and chimeric sequences will be removed using UCHIME.[43] The remaining clean 16S sequences will be clustered into operational taxonomic units (OTUs) using the UPARSE pipeline.[44] A sequence identity of 97% will be used to generate OTUs representing distinct bacterial species. The taxonomic identity of reference sequences will be determined using the RDP Classifier with an 80% confidence threshold. Bacterial community composition will be characterized using OTU counts generated as described above. OTU counts will be converted to measures of relative abundance to account for variation in sequencing coverage between samples. Statistical analysis will be carried out using the statistical software package R (www.r-project.org). Alpha (α) diversity (richness and evenness of taxa within a population) will be reported using the Shannon Index[46] and Chao1 richness estimator.[47] Beta (β) diversity

(overlap in taxa shared between populations) will be analyzed using the Bray-Curtis dissimilarity metric[48] in conjunction with multivariate statistical analysis methods that will include Principal Components Analysis (PCA) and Permutational Multivariate Analysis of Variance (PERMANOVA).[49] Changes in abundance of individual taxa will also be analyzed using traditional univariate statistical methods.

2.6 Correlative Studies

We intend to perform correlative studies to understand the impact of anti-IL-23 antibody treatment post allogeneic hematopoietic progenitor cell transplantation. This testing should help us better understand the changes that are happening within the immune system to inhibit graft-versus-host disease (GVHD). We propose obtaining labs at a minimum of nine time points as follows:

I) Baseline blood and plasma samples (at screening).
II) Blood and plasma samples at the following time points: days 7±3, 14±3, 21±3, 28±7, 60±14, 90±14, 196±30, 365±30 post-transplant.
III) Samples at the time of development of GVHD (if it occurs).

3 STUDY DESIGN

3.1 General Description

This is a phase II, open-label, single-arm trial designed to evaluate the efficacy of tildrakizumab in improving GVHD relapse-free survival.

Prior to embarking on the phase II portion of the study, we proposed a run-in of six patients to assess the safety and tolerability of tildrakizumab in patients undergoing MAC alloHCT. These six patients received the same dosing schema as the other patients in our proposed phase II study. The first three patients were followed through day 28 to ensure no evidence of primary graft failure. We saw no evidence of primary graft failure, thus, an additional three patients (similar to a 3+3 trial design) were treated on study and again, monitored through day 28 for evidence of primary graft failure. No evidence of graft failure was seen in these six patients. Thus, additional patients will be enrolled in the trial until the trial has reached full accrual or activated a stopping rule.

3.2 Treatment Schema

Patients enrolled on this clinical trial will receive tacrolimus initiating at day -3 at doses to maintain therapeutic levels per institutional preference and continued until at least day +90 post-transplant. Methotrexate will be administered intravenously and dosed at 15 mg/m^2 days +1, and 10 mg/mg^2 on days +3, +6 and +11. Tildrakizumab will be administered subcutaneously at a dose of 100 mg on day -1, day 28±3, day 112±7, day 196±14, and day 280±14.

Number of patients who will be enrolled in the study: 55.

3.3 Rationale for Treatment Schema

We propose early administration of tildrakizumab for acute GVHD prevention based on the fact

that immediately following MAC, tissue injury ensues resulting in release of inflammatory mediators that provoke acute GVHD. We hypothesize that it is critical to have tildrakizumab present in order to block this inflammatory milieu, as outlined in Section 1.3. We propose continued administration of tildrakizumab to mediate a beneficial effect not only on the risk of aGVHD but also on cGVHD. The FDA-approved dosing of tildrakizumab for moderate to severe plaque psoriasis, based on a half-life of 21 to 24 days, is week 0, week 4 and every 12 weeks thereafter. We have maintained this dosing schedule [day -1 = week 0, day 28=week 4, day 112, day 196, day 280 are on the every-12-week schedule] and continued the tildrakizumab dosing through the period at highest risk for development of acute GVHD, conventionally thought to occur prior to day 100, and into the period of time during which chronic GVHD can occur, traditionally after day 100.

3.4 Study Completion

The study will reach study completion 24 months from the time the study opens to accrual.

4 SUBJECT PARTICIPATION, DISCONTINUATION, AND WITHDRAWAL

MCW must follow all MCW IRB requirements and policies regarding subject participation, found here:

https://www.mcw.edu/HRPP/Policies-Procedures.htm

4.1 Subject Status

Subject statuses throughout the trial are defined as follows:

- Prescreening: preconsent (subject considering trial or study staff considering patient for the trial per institutional recruitment methods).
- Screening: period after consent, but prior to eligibility confirmation.
- Consented: consented, prior to eligibility confirmation.
- Eligible: the local investigator confirms all eligibly criteria apply.
- On study/enrolled: date eligibility is confirmed.
- On arm: date of enrollment.
- On treatment: first day treatment was given to the last day treatment was given.
- Off treatment: the last day treatment was given.
- On follow-up: from last day of treatment to the end of follow-up period.
- Off study: follow-up period completed, with no additional data gathered.
- Withdrawn: subject fully withdraws consent (i.e., refuses ALL follow-up, even survival) or is taken off study by the local PI.

4.2 Prescreening and Screening Log

The MCW study principal investigator regularly reviews screen failure reasons to understand barriers to accrual and consider amending eligibility criteria. Screen failures are defined as participants who were considered for the trial to participate in the clinical trial with or without consent but are not subsequently assigned to the study intervention or enrolled in the study.

MCWCC CTO will follow its SOPs regarding prescreening and screening tracking.

4.3 Consent

Investigators or their appropriate designees will identify potentially eligible subjects from their clinics, subject self-referrals, referrals from other clinicians and/or other IRB-approved recruitment methods. No study conduct, including subject prescreening, can occur until after IRB approval.

A written, signed informed consent form (ICF) must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record (per local IRB policies and SOPs). The original will be kept on file with the study records.

4.4 Screening Procedures

Refer to study calendar of events.

Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count towards screening tests and eligibility if they are within the screening window.

4.5 Eligibility Confirmation

Study staff must adhere to MCWCC CTO SOPs regarding eligibility review/confirmation.

Patients must have baseline evaluations performed prior to the first study drug dose and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all study aspects, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study, unless otherwise specified.

In the unlikely event that a patient meets criteria during the pretransplant period but is no longer eligible at time of first administration of tildrakizumab, they will be removed and replaced on study.

No waivers of protocol eligibility will be granted, but when clinical factors relating to an eligibility item are unclear or questionable, the study principal investigator (Lyndsey Runaas, MD lrunaas@mcw.edu) can only provide guidance or clarification on eligibility.

Inclusion Criteria

1. Age ≥18 years.
2. Patients with any hematologic malignancy for which alloHCT is indicated. Patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) must be in complete remission at the time of alloHCT (<5% blasts in the bone marrow, normal maturation of all cellular components in the bone marrow and absence of extramedullary disease). Patients with myelodysplastic syndrome (MDS) must have <10% blasts in the bone marrow, no circulating blasts.
3. Myeloablative conditioning (MAC) regimen, based on CIBMTR criteria (total body irradiation [TBI] ≥5 Gy single dose or ≥8 Gy fractionated or busulfan [Bu] dose >8 mg/kg oral or >6.4 mg/kg intravenous).[39]
4. T cell-replete peripheral blood graft.
5. Patients must have a matched related or unrelated donor (at least 6/6 match at HLA-A, -B and -C for related donors and at least 8/8 match at HLA-A, -B, -C and -DRB1 for unrelated donors).
6. Cardiac function: Left ventricular ejection fraction ≥45% for myeloablative conditioning.
7. Estimated creatinine clearance ≥40 mL/minute (using the Cockcroft-Gault formula and actual body weight).
8. Pulmonary function: DLCO ≥40% (adjusted for hemoglobin) and FEV1 ≥50%.
9. Liver function: total bilirubin <3 x upper limit of normal and ALT/AST <5 x upper normal limit.
10. Female subjects must meet one of the following:
    Postmenopausal for at least one year before enrollment, **OR**
    a. Surgically sterile (i.e., undergone a hysterectomy or bilateral oophorectomy), **OR**

CRC Initials:_____ Date:_____

Investigator/Enrolling Physician Initials:_____ Date:_____

   b. If subject is of childbearing potential (defined as not satisfying either of the above two criteria), she must agree to practice two acceptable methods of contraception (combination methods require use of two of the following: diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge, male or female condom, hormonal contraceptive) from the time of signing of the informed consent form through 90 days after the last dose of study agent, **OR**
   c. Agrees to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable contraception methods.)
11. Male subjects, even if surgically sterilized (i.e., status postvasectomy), must agree to one of the following:
   a. Practice effective barrier contraception during the entire study period and through 60 calendar days after the last dose of study agent, **OR**
   b. Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception.)
12. Signed informed consent: Voluntary written consent must be given before patient registration and performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
13. Planned post-transplant maintenance therapy is allowed.
14. Prior autologous transplant is allowed.

Exclusion Criteria

1. Prior allogeneic HCT.
2. Active CNS involvement with malignancy.
3. Patients receiving cord blood or haploidentical allograft.
4. Patients undergoing *in vivo* or *ex vivo* T cell-depleted alloHCT.
5. Karnofsky performance score <60% or ECOG > or = 2.
6. Patients with uncontrolled bacterial, viral or fungal infections (currently on treatment and with progression of infectious disease or no clinical improvement) at time of enrollment.
7. Active hepatitis B or C virus infection or known human immunodeficiency virus (HIV) positive.
8. Use of rituximab, alemtuzumab, anti-thymocyte globulin (ATG), or other monoclonal antibody planned as part of conditioning regimen for GVHD prophylaxis.
9. Participation in another GVHD prophylaxis clinical trial.

CRC Initials:_____ Date:_____

Investigator/Enrolling Physician Initials:_____ Date:_____

10. Any current uncontrolled cardiovascular conditions, including uncontrolled ventricular arrhythmias, NYHA class III or IV congestive heart failure, uncontrolled angina, or electrocardiographic evidence of active ischemia or active conduction system abnormalities.
11. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

"I have reviewed all inclusion and exclusion criteria and confirm the subject is eligible."

_____ _____

(CRC Signature) (Date)

_____ _____

(Investigator/Enrolling Physician Signature) (Date)

4.6 Discontinuation of Study Treatment, Withdrawal, and Compliance

Discontinuation from the study treatment does not mean discontinuation from the study. Subject will be considered in follow-up, study procedures should still be completed as indicated by the study protocol and AEs/SAEs will continue to be reported according to this protocol.

In the absence of treatment delays due to adverse events, study treatment/intervention may continue until:

- Disease (relapse or progression of the primary malignancy) for which treatment is indicated.
- Donor leukocyte infusion (DLI) prior to planned redose of tildrakizumab for any indication: infection, disease control or to address mixed chimerism.
- Grade III–IV acute GVHD. Patients with grade I–II acute GVHD and on topical or systemic corticosteroids therapy (equivalent to prednisone ≤20 mg/d) can receive further doses of tildrakizumab.
- Active chronic GVHD requiring systemic therapy.
- General or specific changes in the subject's condition renders the subject unacceptable for further treatment in the investigator's judgment.
- Inter-current illness that prevents further treatment administration.
- Subject decides to withdraw from the study.
- The subject has significant noncompliance with the protocol (see below).
- Unacceptable adverse event(s) beyond requirements as detailed in this protocol.

Subjects who sign the informed consent form, and are enrolled and receive the study intervention, but subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

Consent Withdrawal

A subject may decide to withdraw from the study at any time. MCWCC CTO will follow its IRB of record's SOPs regarding consent withdrawal.

If a subject intends on withdrawing consent, staff should confirm which of the following options the subject chooses and document the discussion:

- Full consent withdrawal, with no study follow-up.
- Selective consent withdrawal from interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information.

Investigator-initiated Withdrawal

The investigator will withdraw a subject whenever continued participation is no longer in the subject's best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance or simply significant uncertainty on the part of the investigator that continued participation is prudent. The reason for study withdrawal and the date the subject was removed from the study must be documented.

4.7 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

- The investigator or designee must make every effort to regain contact and/or reschedule a missed visit with the participant.
- A participant is deemed lost to follow-up if his/her status cannot be obtained after *all* of the following occurs at two consecutive scheduled protocol calendar timepoints:
    - Three telephone calls (at least one day apart) from the study team are unanswered.
      AND
    - A letter to the participant's last known mailing address goes unanswered.
      AND
    - These contact attempts must be documented in the participant's medical record or study file.
- Update OnCore® (follow-up tab and eCRF) when a participant is officially considered lost to follow-up.
- If a subject is considered lost to follow-up, but subsequently contacts the study team, the subject should be considered in follow-up again.

4.8 Accrual Suspension and Closure

The MCW PI facilitates the suspension and closing of accrual in the following manner:

- OnCore® tracks accrual throughout the study.
- If the study must be suspended, OnCore® is updated to a 'suspended' status.
- When the accrual number is reached, OnCore® notifies staff of study closure.

4.9 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW Study PI, DSMC, sponsor, and/or IRB). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the MCW Principal Investigator (PI) will promptly inform the MCW Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

5 STUDY ENTRY AND WITHDRAWAL; STUDY PROCEDURES

5.1 Required Preregistration Screening Tests and Procedures

The study-specific assessments are detailed in this section and outlined in the Study Calendar.

A written, signed informed consent form (ICF) must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the MCW Cancer Center Clinical Trial Management System. The system is password protected and meets HIPAA requirements.

5.2 Registration Process

Patients will be approached for this study after the decision to proceed with transplant is made and a suitable HLA-matched donor is identified. Transplant physicians will evaluate the patient eligibility into this study. All source documents that support eligibility include a signed informed consent/HIPAA and signed eligibility checklist. These must be available for review and verification.

At the point of registration, the study staff will register the patient in the electronic database (where applicable), including demographic, consent and on-study information. The patient will be assigned a unique sequence number for the study.

Patients will be enrolled on this trial within 30 days preceding the conditioning regimen for alloHCT.

5.3 Pretreatment Period

Pretransplant Evaluations

The following observations must be completed within 30 days before the initiation of the conditioning regimen.

- History, physical examination, height, and weight.
- CBC with differential will be performed as appropriate during hospitalization for alloHCT on clinic visits and at minimum performed on days indicated on the schedule of events.
- Comprehensive metabolic panel will be performed as appropriate during hospitalization for alloHCT, on clinic visits and at minimum performed on days indicated on the schedule of events.
- HLA typing (donor and recipient).
- Adverse events assessments.
- Karnofsky Performance Status Scale and HCT-Specific Comorbidity Index score.
- Infectious disease markers: CMV antibody, hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), HIV and HTLV I/II antibody.
- EKG and LVEF (may be performed <30 days prior to patient enrollment).
- Pulmonary function tests, including DLCO and FEV1 (may be performed <30 days prior to patient enrollment).
- Disease evaluation of the malignant disease: For acute leukemia, CML and MDS, this includes a bone marrow aspirate and biopsy for pathology and cytogenetics.

- Pregnancy test per institutional practices for females of childbearing potential. NOTE: pregnancy test must be performed <30 days before initiation of the conditioning regimen.

- Pretransplant blood samples for future research.

  Research (stool) sample will be collected pretransplant after admission to the hospital during the (pretransplant) conditioning period. Samples will be collected from each patient as a baseline and then at weekly intervals through the period of engraftment. In addition, stool samples will be obtained at the time of GVHD onset in any affected patients. Fresh fecal samples will be collected and immediately preserved in RNAlater solution, to facilitate optimal sample preservation, consistency of sample quality and ease of sample transport. Genomic DNA will be isolated from 200 mg of fecal sample using the Qiagen Powerlyzer Powersoil kit as described.[40] Bacterial composition and abundance will be validated by quantitative PCR analysis. Composition of the microbiota will be determined through sequencing of the 16S rRNA gene V4 region (Diversigen, Baylor College of Medicine, Waco, TX). PCR products will be generated using a dual-indexing amplification strategy, then sequenced on the MiSeq platform (Illumina, San Diego, CA).

5.4 Study Procedures during Treatment

Patients must meet eligibility criteria eligible on day -1 to be treated.

5.5 GVHD Assessment

Patients will be monitored for development of acute and chronic GVHD, per standard operating procedures at the MCW BMT Program, but at minimum on days +28 (+/-7), +56 (+/-7), +100 (+/-14), +180 (+14), +365 (+/-28) post-HCT. Diagnosis of acute GVHD may not necessitate biopsy confirmation in at least one involved organ but would be preferred. When more than one organ is involved, biopsy confirmation of all involved organs is recommended but not necessary. With liver-only GVHD, biopsy confirmation is strongly recommended. Acute GVHD will be assessed by consensus criteria (Appendix 2), and chronic GVHD diagnosis and grading will be according to NIH Criteria (please see Appendix 2).

Independent GVHD adjudication is mandated in the study. Acute and chronic GVHD will be adjudicated by an independent Faculty Research Committee (FRC)-appointed review panel. Protocol PIs will be blinded to the adjudication panel and will not be permitted to grade or modify GVHD assessments. GVHD case report forms (CRFs) will be completed by treating MDs/NPs/APPs in real time, as indicated in study calendar. FRC adjudication panel will grade GVHD, using a calendar-driven approach (days +100 and +180 for aGVHD and days +180 and +365 for chronic GvHD).

6 TREATMENT PLAN

6.1 Investigational Agent Administration

Treatment will be administered on an inpatient or outpatient basis depending on patient status. Treatment cannot be self-administered. Allow prefilled syringe in original carton to sit and reach room temperature (30 minutes) before injecting subcutaneously. Inject a site with clear skin and easy access (e.g., abdomen, thighs, or upper arm); do not administer two inches around navel or where skin is tender, bruised, erythematous, indurated, or affected by psoriasis; do not inject into scars, stretch marks, or blood vessels.

Study Drug	Premedication; precautions	Dose	Route	Schedule (Day pre or post-transplant)
Tildrakizumab	None	100 mg	Subcutaneously	Day -1, Day 28 ± 3, Day 112 ± 7, Day 196 ± 14, and Day 280 ± 14.

The following are contraindications for tildrakizumab dosing beyond the first dose:

1) Grade 4 (according to CTCAE version 5 hematologic or nonhematologic events (which have life-threatening consequences and require urgent treatment). Dosing will be allowed upon recovery to grade ≤3. Transfusion to increase platelet and hemoglobin is allowed.
2) Disease (relapse or progression of the primary malignancy) for which treatment is indicated.
3) Donor leukocyte infusion (DLI) prior to planned redose of tildrakizumab for any indication: infection, disease control or to address mixed chimerism.
4) Grade III–IV acute GVHD. Patients with grade I–II acute GVHD and on topical or systemic corticosteroids therapy (equivalent to prednisone ≤20 mg/d) can receive a second dose of tildrakizumab.
5) Active chronic GVHD requiring systemic therapy.

6.2 Standard GVHD Prophylaxis Administration

6.2.1 Tacrolimus

Tacrolimus will be given per standard operating procedures from the MCW BMT program, intravenously at a dose of 0.03 mg/kg/day starting day –3. Subsequent dosing will be based on blood levels. The dose should be adjusted accordingly to maintain a suggested level of 5–10 ng/mL. The dose of tacrolimus may be switched to oral at a 1:3 dose equivalence and rounded to the nearest 0.5 mg at the discretion of the treating physician. If patients are on medications which alter the metabolism of tacrolimus (e.g., azoles), the initial starting dose and subsequent doses should be altered, as per institutional practices. Tacrolimus taper can be initiated at a minimum of 90 days post-HSCT, if there is no evidence of active GVHD. The rate of tapering will be done according institutional practices, but patients should be off tacrolimus by day 180 post-HSCT.

6.2.2 Methotrexate

Methotrexate will be administered, per institutional practices, at the doses of 15 mg/m^2 IV bolus on day +1, and 10 mg/m^2 IV bolus on days +3, +6 and +11 after hematopoietic cell infusion. Dose reduction of MTX due to worsening creatinine clearance after initiation of conditioning regimen, high serum levels or development of oral mucositis is allowed, according to institutional practices.

6.3 General Concomitant Medication and Supportive Care Guidelines

There are no restricted concomitant medications.

Patients should avoid live vaccines until at least two years post-transplant as per institutional protocol.

6.4 Dietary Restrictions

There are no dietary restrictions for this study.

6.5 Supportive Care Guidelines

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on source documents as concomitant medication.

Concurrent or concomitant use of medication is not restricted during protocol therapy. However, subjects are not permitted to take any anti-cancer medications or supplements during study treatment.

6.6 Follow-up Period

Patients will be followed for a total 12 months or until death, whichever occurs first. All patients who receive at least one dose of the study drug will be followed.

7 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

7.1 DEFINITIONS

7.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (International Conference on Harmonisation [ICH], E2A, E6). This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

7.1.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

- **Death.** Results in death.

- **Life-threatening.** Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- **Hospitalization.** Requires inpatient hospitalization or prolongation of an existing hospitalization.

- **Disability/incapacity.** Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- **Pregnancy.**

- **Medically important event.** This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

7.1.3 Attribution of an Adverse Event

An assessment of the relationship between the adverse event and the medical intervention, using the following categories:

Definitely Related: The AE is clearly related to the intervention. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Probably Related: The AE is likely related to the intervention. There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Possibly Related: The AE may be related to the intervention. There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

Unlikely: The AE is doubtfully related to the intervention. A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration

of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

Unrelated: The AE is clearly NOT related to the intervention. The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology.

7.1.4 Expectedness of an Adverse Event

Study investigator or treating physician will be responsible for determining whether an AE is expected or unexpected, as indicated in the protocol, informed consent form and/or drug information brochure. An AE will be considered unexpected if the nature, severity, or frequency of the event is NOT consistent with the risk information previously described for the study intervention.

7.2 Collection and Reporting Requirements for Adverse Events and Serious Adverse Events

Only grade 3,4 and 5 adverse events (including SAEs) must be recorded in OnCore® and/or an adverse event log. All AEs required to be collected must be graded according to the CTCAE v5. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Investigator's or treating physician's assessment of AE attributions must also be documented.

AEs will be collected from the time the subject signs the consent form through 30 days post last dose of study drug(s). AEs will be tracked and followed until resolution, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early). All adverse events collected per the protocol will be followed with appropriate medical management until they are resolved, if they are related to the study treatment, or until the investigator deems the event to be chronic. Please see section 7.2.2 and Table 1 to identify the adverse events that need to be reported.

7.2.1 Reporting of Adverse Events and Serious Adverse Events

Please refer to Table 1 below to identify adverse events that meet reporting requirements.

All serious adverse events (SAEs) that occur after the subject has signed the consent form through 30 days post last dose of study drug(s) will be reported. All SAEs will be followed until satisfactory resolution, or until the investigator deems the event to be chronic. All serious adverse events (SAEs) must also be documented in OnCore®.

Table 1

Attribution	SAE				AE		
	Grade 1, 2 & 3		Grade 4 and 5		Grade 3	Grade 4	
	Expected	Unexpected	Expected	Unexpected	Unexpected	Expected	Unexpected

Unrelated Unlikely	**IRB[1] and DSMC[2]-Routine Review[3]**	**IRB[1] and DSMC[2]-Routine Review[3]**	**IRB[1]-Routine Review[3]** **DSMC[2]-Within 5 calendar days**	**IRB[1]-Routine Review[3]** **DSMC[2]-Within 5 calendar days**	**DSMC[2]-Routine Review[3]**	**DSMC[2]-<u>Heme</u>: Routine review** **<u>Non-Heme</u>: Within 5 calendar days**	**DSMC[2]-Within 5 calendar days**
Possible Probable Definite		**IRB[1] and DSMC[2]-Within 5 calendar days** **FDA[4]** **Sun Pharma[5]**	**IRB[1] and DSMC[2]-Within 5 calendar days** **FDA[4]** **Sun Pharma[5]**				

1. Guidance on adverse event reporting to the IRB is available online at MCW IRB Policies and Procedures.
2. For expedited DSMC reporting, study coordinator/research nurse must notify the DSMC via email including the subject ID, date of event, grade, relatedness, expectedness, and a short narrative. DSMC will review data entered into OnCore®. Non-hematological grade 4, unexpected hematological grade 4 and all grade 5 events must be reported to the DSMC within five calendar days of study staff's knowledge. Expected hematological grade 4 adverse events will be routine reported.
3. For routine reporting, the events will be reported to IRB as part of the annual continuing progress report and the DSMC will review data entered into OnCore® at the time of scheduled monitoring.
4. Fatal or life-threatening SAEs meeting the criteria indicated in the above table will be reported to FDA no later than seven calendar days after study staff's initial awareness of the event. If the SAE is not fatal or life-threatening and meets the above criteria, the timeline for submitting an IND safety report to FDA is no later than 15 calendar days after study staff's initial awareness of the event. See section 7.2.2 for detailed reporting instructions.
5. *Sun Pharmaceutical Industries Ltd. reporting requirements will be same as FDA (see footnote 4 above). For the purpose of reporting to Sun Pharmaceutical Industries Ltd, study staff should submit the MedWatch form and a deidentified OnCore® SAE report.*

7.2.2 Reporting Instructions

- **Food and Drug Administration**

  An IND safety report will be submitted for any adverse event that meets all three definitions: possibly related to the study drug, unexpected and serious. If the adverse event does not meet one of the above definitions, it should not be submitted as an expedited IND safety report.

  Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Suggested Reporting Form:

US FDA MedWatch 3500A:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

- **Sun Pharmaceutical Industries Ltd. (Sponsor)**

  Serious adverse events (SAEs) as per the table above must be reported to Sun Pharmaceutical Industries Ltd.'s local safety representative by FAX at 609-720-8505 (preferred) or by email: drug.safetyUSA@sunpharma.com.

7.3 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others. This information may be found on *the Human Research Protection Program website*.

7.4 Reporting of Pregnancy

Female subjects who become pregnant during treatment and 30 days post the last dose of the study drug should discontinue the study treatment immediately. Study staff should report the pregnancy in OnCore® as a grade 3 SAE and email the PDF report to the study PI and DSMC coordinator within 24 hours of staff awareness.

If a male subject impregnates his partner during treatment and 30 days post last dose of the study drug, the study team should report the pregnancy in OnCore® as a grade 3 SAE and email the pdf report to the study PI and DSMC coordinator within 24 hours of staff awareness.

Whenever possible, a pregnancy (for either a subject or male subject's partner as described above and according to IRB policies regarding consent of this partner) should be followed to term, any premature termination reported, and the status of the mother and child should be reported. Data on fetal outcome and breastfeeding are to be collected for regulatory reporting and drug safety evaluation.

7.5 Subject Complaints

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

A product complaint is a verbal, written or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the drug manufacturer and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a drug manufacturer representative.

Product complaints in and of themselves are not reportable events. If a product complaint results in an SAE, an SAE form should be completed.

7.6 Known AEs List

Tildrakizumab

Tildrakizumab side effects include:

- Nasopharyngitis
- Diarrhea
- Injection site reaction

Tacrolimus

Tacrolimus side effects include:

- Neurologic: confusion, dizziness, insomnia, seizures, tremors, changes in how clearly one can think
- Cardiovascular: hypertension
- Gastrointestinal: nausea, vomiting
- Hematologic: microangiopathic hemolytic anemia, thrombocytopenia
- Endocrine and metabolic: hypomagnesemia, hypokalemia, hypocalcemia, hyperlipidemia
- Miscellaneous: unwanted hair growth, changes in vision, liver problems, reversible renal insufficiency, infections and posttransplant lymphoproliferative disorders

Methotrexate

The most frequently reported adverse reactions associated with methotrexate use as GVHD prophylaxis include:

- Neurologic: fever, dizziness, chills, undue fatigue
- Gastrointestinal: ulcerative stomatitis, nausea, abdominal distress, diarrhea
- Hematologic: leucopenia, anemia and suppressed hematopoiesis (leading to infection)

Miscellaneous

- Abnormal liver tests, kidney failure and pulmonary complications after transplantation

8 PHARMACEUTICAL INFORMATION

Tildrakizumab

8.1 Agent Description: Tildrakizumab is a high affinity (297 pM), humanized immunoglobulin G1/kappa (IgG1/κ) antibody that specifically binds and neutralizes human IL-23 (SN 08197 [Addendum 1]). This antibody has been shown in Phase 1, Phase 2, and Phase 3 studies to reduce the clinical signs and symptoms of psoriasis.

8.2 Absorption: Absolute bioavailability is 73–80% with slow absorption with time to reach maximum concentration at 6.2 days after SC injection. Tildrakizumab exposure increased

proportionally with dose and did not exhibit time-dependent PK. Steady-state is achieved by 16 weeks with the clinical regimen (dosing on Week 0 and Week 4 and Q12W thereafter) with 1.1-fold accumulation in C_{max}. Tildrakizumab has low to moderate PK variability (33-41% CV).

8.3 Distribution: Tildrakizumab has limited extravascular distribution with an apparent volume of distribution (Vd/F) of 10.8 L, which was found to depend on the body weight. Plasma protein binding is not expected to impact tildrakizumab exposure.

8.4 Metabolism: Tildrakizumab is catabolized by general protein degradation processes; typical small-molecule metabolic pathways (e.g., CYPs), glucuronosyltransferases) do not contribute to its clearance.

8.5 Elimination: Tildrakizumab is catabolized into component amino acids by general protein degradation processes and is not eliminated by renal or hepatic pathways. Apparent clearance is independent of dose. Apparent elimination half-life (%CV) is 23.4 days (23%).

8.6 Contraindications: As tildrakizumab is eliminated by protein catabolism, not affected by hepatic drug metabolizing enzymes and not eliminated by renal or hepatic pathways, no dose adjustments for tildrakizumab are necessary when co-administered with other therapies.

8.7 Side Effects: Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

8.8 Storage Requirements and Stability: Ongoing stability studies have shown that tildrakizumab solution DP in PFS is stable under refrigerated storage conditions (2ºC to 8°C). Please refer to the package insert for additional storage and stability information.

8.9 Agent Destruction and Return: Used, and any unused study drug will be destroyed and documented, as per institutional standards.

8.10 Availability

This drug is commercially available for the indication of psoriasis. For the purpose of this study, it will be paid for and supplied by the funding sponsor, Sun Pharmaceutical Industries Ltd. For drug ordering, fill out the drug supply form request form provided by Sun Pharmaceutical Industries Ltd.

9 CORRELATIVE STUDIES/SPECIAL STUDIES

9.1 DESCRIPTION

We intend to perform correlative studies to understand the impact of anti-IL-23 antibody treatment post allogeneic hematopoietic progenitor cell transplantation. This testing should help us better understand the changes that are happening within the immune system to inhibit graft-versus-host disease (GVHD).

We plan to perform the analysis of immune cells subsets from fresh or frozen peripheral blood mononuclear cells by flow cytometry, with the hypothesis that treatment with anti-IL-23 antibody will prevent alterations in circulating immune cell subsets and cytokines/biomarkers that are associated with development of GVHD.

Analysis of immune cell subsets from fresh or frozen peripheral blood mononuclear cells (PBMCs) by flow cytometry

As a measure of systemic immunity (using PBMCs), the relative percentage of circulating immune cells will be assessed by multiparametric flow cytometry. Multiparametric flow cytometry will allow for identification of immune cell subsets by recording the simultaneous expression of biomarkers unique to that cell subset. Flow cytometry will be performed on a MACS Quant flow cytometer in the Cell Therapy Laboratory at the Medical College of Wisconsin. We will use flow cytometry of antibody stained PBMCs to evaluate the relative percentage of cell types including T, B, NK and myeloid cells. Correlating changes in immune cell subsets upon anti-IL-23 therapy will facilitate the identification of a peripheral immune signature that correlates with absence or presence of GVHD. We will test for the expression of the following immune cell markers: T cell marker panel (includes regulatory T cell markers): CD3, CD4, CD8, CD25, CD44, CD62L, CD56, CD127, Foxp3 (intracellular), phospho-STAT3 (intracellular); NK cell marker panel: CD56, CD16, CD3; Myeloid cell marker panel: CD11b, CD33, CD14; B cell marker panel: CD19, CD20.

We also intend to perform the analysis of cytokines and biomarkers in blood plasma. Plasma, or serum, cytokine and biomarker signatures can provide important information regarding peripheral immune responses. Changes in serum cytokines and other biomarkers have been reported during GVHD and in cancer patients. However, currently, there are no defined cytokine signatures that are predictive of outcome following allogeneic hematopoietic progenitor cell transplantation.

Analysis of cytokines and biomarkers in blood plasma (Luminex® platform)

For this study, plasma cytokines and other biomarkers will be analyzed longitudinally before and after immune therapy with anti-IL-23 antibody. Serum cytokines will be quantified using customized Luminex® bioplex assays. For the **cytokine array**, we will analyze the following: IL-1, IL-2, IL-4, IL-6, IL-10, IL-17, IL-23, TNFα, GM-CSF, IFNγ. The **biomarker array** will analyze the following: ST2, REG3A, BAFF, CCL15, MMP3, CXCL9, CXCL10, osteopontin, soluble CD163.

9.2 Instructions Regarding Sample Collection for Correlatives:

For each time point, one 10 ml red top tube and one 10 ml purple top tube will be collected. Once the samples are collected, study coordinator will contact the BMT and Cell Therapy Laboratory (414-805-6143).

The samples will be transferred to Dr. Bryon Johnson's lab once collected (no spinning or other special handling). They can be at room temperature. If they were to be collected on weekends or holidays, the samples should be stored at 4°C until they are transferred to the lab.

10 STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

The endpoints are defined with more detail in Sections 2.3 through 2.5.

Primary endpoint
The primary endpoint is the 12-month probability of GVHD-free relapse-free survival (GRFS). An event for this outcome is defined as either grade III–IV acute GVHD, systemic therapy-requiring chronic GVHD, relapse, or death at 12 months.

Secondary endpoints

1. Cumulative incidence of mild, moderate and severe chronic GVHD according to the NIH criteria and limited or extensive GVHD by conventional criteria.
2. Cumulative incidence of grade II–IV acute GVHD at days 100 and 180.
3. Cumulative incidence of grade III–IV acute GVHD at days 100 and 180.
4. Incidence of primary and secondary graft failure.
5. Hematopoietic recovery will be assessed according to neutrophil and platelet counts recovery after HSCT.
6. Cumulative incidence of non-relapse mortality (NRM) post HSCT.
7. Cumulative incidence of relapse/progression of the primary malignancy.
8. Overall survival (OS) post HSCT.
9. Assess the pharmacokinetic (PK) profile of multi-dose tildrakizumab.
10. Probability of lower GI tract GVHD.

Exploratory endpoints

1. Longitudinal trajectory of serum cytokines.
2. Longitudinal trajectory of serum biomarkers.
3. Longitudinal trajectory of immune cell markers.

10.2 Study Design

10.2.1 Determination of Sample Size and Accrual Rate

Dr. Aniko Szabo will assist with the statistical analyses in the trial. The study will test the primary hypothesis that GRFS at 12 months exceeds the historical control value of 20% at a two-sided 10% significance level. The target sample size will be 55 patients with a known outcome (i.e., GVHD, relapse, or death status at 12 months). With this sample size the study will have 80% power to detect an increase in GRFS at 12 months to 35%, 94% power to detect an increase to 40%, and 54% power to detect an increase to 30%. Justification for the 15% increase in GRFS probability as a clinically meaningful endpoint derives from the recently published BMT Clinical Trials Network 1203 GVHD prevention trial which compared three different prophylaxis regimens to standard therapy with tacrolimus and methotrexate and was powered to detect a 15% increase in GRFS. To achieve the target sample size, we will enroll 55 patients to allow for a 10% loss to follow-up.

10.2.2 Accrual Estimates

It is estimated that 30 months of accrual will be adequate. This is based on our historical rate of approximately 50 myeloablative allogeneic stem cell transplants per year over the past three years. Assuming a conservative 40% enrollment rate, approximately 30 months should be sufficient to enroll our target of 55 patients.

10.3 Analysis Population

The **full analysis set** will include all patients enrolled in the study.

The **efficacy analysis set** will include all patients in the full analysis set who receive at least one dose of tildrakizumab.

The **biomarker analysis set** will include all patients in the efficacy analysis set who have at least one evaluable biomarker sample.

10.3.1 Primary Analysis (or Analysis of Primary Endpoints)

The primary endpoint will be evaluated in the efficacy analysis set. The GRFS will be estimated using the Kaplan-Meier estimator and plotted with a 90% confidence band. An event for this outcome is defined as grade III–IV acute GVHD, chronic GVHD requiring systemic therapy, relapse or death. Patients who are alive without GVHD or relapse will be censored at the last follow-up. The 12-month GRFS will be compared to the prespecified historical control value of 20% using a one-sided z-test at a 5% significance level.

10.3.2 Secondary Analysis (or Analysis of Secondary Endpoints)

The secondary endpoints will be evaluated in the efficacy analysis set. Time-to-event outcomes with and without competing risks will be analyzed using Kaplan-Meier and Nelson-Aalen estimates, respectively, and presented with 95% confidence intervals. Binary outcomes will be analyzed using proportions and presented with 95% confidence intervals.

Bacterial community composition will be characterized using OTU counts generated as described above. OTU counts will be converted to measures of relative abundance to account for variation in sequencing coverage between samples. Statistical analysis will be carried out using the statistical software package R (www.r-project.org). Alpha (α) diversity (richness and evenness of taxa within a population) will be reported using the Shannon Index[46] and Chao1 richness estimator.[47] Beta (β) diversity (overlap in taxa shared between populations) will be analyzed using the Bray-Curtis dissimilarity metric[48] in conjunction with multivariate statistical analysis methods that will include Principal Components Analysis (PCA) and Permutational Multivariate Analysis of Variance (PERMANOVA).[49] Changes in abundance of individual taxa will also be analyzed using traditional univariate statistical methods.

10.3.3 Other Analyses/Assessments

Demographic and other baseline data, such as disease characteristics, as well as outcome measures, will be presented for the full analysis set overall and separately for unrelated and matched related donor patients. Categorical data, such as gender, race, etc. will be presented by frequencies and percentages. Descriptive summary statistics (e.g., frequency, mean, median, range and standard deviation) will be used to present numeric data.

10.4 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v5. The frequency and proportion of patients experiencing an SAE will be reported with 95% confidence intervals overall, as well as classified by grade and organ system.

10.5 Stopping Rules

Formal statistical monitoring will be in place for 100-day overall mortality and 100-day grade 3–4 aGVHD rate. Based on program experience, a 100-day mortality rate <10% and a 100-day aGVHD rate of <15% are expected in the study population. Using a Bayesian approach to

toxicity monitoring as implemented by J. Jack Lee, Ying-Wei Kuo, Diane Liu and Nan Chen (http://www.trialdesign.org/one-page-shell.html#BTOX), we derived a stopping boundary that pauses the trial if we are 90% confident that the probability of the monitored event exceeds the historical value, i.e., 100-day mortality exceeds 10% or 100-day grade 3–4 aGVHD rate exceeds 15%. A Beta prior distribution with effective sample size of 1 and mean equal to the historical value was used with a maximum of 37 patients, and a continuous evaluation starting at two patients. The following tables show the number of 100-day mortality and grade 3–4 aGVHD events that would trigger a safety review depending on the number of evaluable patients. For the purposes of the safety monitoring patients in the safety set who are alive with at least 100 days of follow-up or have experienced the monitored event within 100 days are considered evaluable.

Number of Evaluable Patients	Boundary for excessive 100-day mortality
1	-
2–6	2+
7–12	3+
13–18	4+
19–25	5+
26–33	6+
34–37	7+
41–48	8+
49–54	9+

Number of Evaluable Patients	Boundary for excessive grade 3–4 aGVHD
1	-
2–4	2+
5–8	3+
9–13	4+
14–17	5+
18–22	6+
23–27	7+
28–33	8+
34–37	9+
39–43	10+

44–49	11+
50–54	12+

The following table shows the probability of finding excessive 100-day mortality and 100-day grade 3–4 aGVHD rate during the study for several underlying true values of the outcomes.

Underlying 100-day event rate	Probability of crossing mortality boundary	Probability of crossing aGVHD boundary
5%	4.8%	1.9%
10%	24%	9.8%
15%%	53%	28%
20%	78%	53%
25%	92%	76%
30%	98%	90%

If a stopping rule is triggered based on excessive 100-day mortality or 100-day grade III–IV aGVHD, the trial will be paused. The DSMC will meet and review all relevant data. They will determine the relevant next steps in terms of permanent discontinuation of the trial versus additional safety modifications needed to allow the trial to continue.

11 DATA AND SAFETY MONITORING PLAN (DSMP)

Data and Safety Management Overview

The Medical College of Wisconsin (MCW) Data and Safety Monitoring Committee (DSMC) and the MCW Institutional Review Board (IRB) will approve protocol-specific DSM plans. A local, investigator-initiated trial will be required to be continuously monitored by the principal investigator of the study with safety and progress reports submitted to the DSMC.

The DSMP for this study will involve the following entities:

11.1 Study Team

The study team minimally consists of the principal investigator, the clinical research coordinator, regulatory specialist and the study biostatistician. While subjects are on study, the principal investigator will meet regularly with the research coordinator and the study biostatistician to review study status. This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for a next subject enrollment is addressed. All meetings, including attendance, are documented.

11.2 Quality Assurance

This protocol was classified as high risk and will be reviewed internally by the MCW Cancer Center Clinical Trials Office Quality Assurance Staff according to the MCWCC Data and Safety Monitoring Plan and current version SOP, 6.5.2 Internal Quality Assurance Reviews.

11.3 Clinical Trials Office

The MCWCC Clinical Trials Office [CTO] provides administrative assistance and support to the DSMC.

11.4 DSMC

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW includes a plan for safety and data monitoring.

More information can be found related to the MCWCC Data and Safety Monitoring Plan at the MCWCC website (Data and Safety Monitoring Plan).

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety.
- Review all DSM reports.
- Submit a summary of any recommendations related to study conduct.
- Terminate the study if deemed unsafe for patients.

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination, as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

12 REGULATORY COMPLIANCE, ETHICS AND STUDY MANAGEMENT

12.1 Ethical Standard

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

12.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol.

- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and §312 (Investigational New Drug Application; and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

12.3 Prestudy Documentation

Prior to implementing this protocol at MCWCC, the protocol, informed consent form and any other information pertaining to participants must be approved by the MCW IRB.

12.4 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Prior to obtaining MCW approval, the protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Potential subjects will be told, and a statement will be included that this study is designed to determine both safety and effectiveness. The consent forms will include the approved MCW IRB template language.

Consent forms will be IRB-approved and the subject (and legally authorized representative, if necessary) will be asked to read and review the document. The treating physician or the investigator will explain the research study to the subject and answer any questions that may arise. The study coordinator may complete the consenting process. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, per FH/MCW IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the patient and why a witness signed. (For example, "Although not required, the subject's spouse was present during the consenting process and signed as the witness." Or "Although not required, hospital staff was present for consenting process and signed as a witness.")

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Patients that require reconsenting will be defined in the IRB approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. The MCWCC CTO will follow the MCW/FH IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject's visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject's satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject's study file, and a copy of the consent is sent to the OCRICC office, which will then submit to HIM a copy of the signed consent to be scanned into EPIC, the legal medical record.

12.5 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor-investigator, participating investigators, and any staff, and the sponsor. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

The conditions for maintaining confidentiality of the subjects' records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

One risk of taking part in a research study is that more people will handle the personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

While data are being collected and after all data have been collected but are still in the process of being analyzed, the subject's data/PHI are stored in the locked Clinical Research Office in the Clinical Trials Office. Databases in which the study subject information is stored and accessed are password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the Case Report Forms contain the study identifiers, subject initials, date of birth and date of service.

Personal identifiers, such as name and medical record number, will be removed from accompanying lab reports and test results. Any data/PHI that are not stored for the purposes of the study are shredded in the Clinical Trials Office.

After all study queries and analyses are completed, the data/PHI will not be destroyed but will be archived in a secure long-term storage site in order to keep an accurate record of screened and enrolled subjects for the sponsor and potential audit purposes only specific for this study.

12.6 Protection of Human Subjects

12.6.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

12.6.2 Protection of Privacy

As noted, patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document.

12.6.3 Changes in the Protocol

Once the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the investigator and approved by IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the investigator must then notify the IRB in writing within five working days after implementation.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

Any departures from the protocol must be fully documented in the source documents.

12.7 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

13 DATA HANDLING AND RECORD KEEPING

13.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection

protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

13.2 Data Management Responsibilities

13.2.1 Principal Investigator

The principal investigator oversees the management of patient records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) patient records are maintained to include history, prescribed medication and investigational product(s), measurements, exams, evaluations and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is correlation between the case report forms and the source documents**.**

13.2.2 Research Coordinator

A research coordinator creates, collects and organizes clinical trial documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol specified time points.

13.2.3 Research Nurse/Medical Staff

The research nurse and medical staff documents protocol-required care or assessment of the subject's outcomes, adverse events and compliance to study procedures.

13.2.4 Biostatistician

The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

13.3 Handling and Documentation of Clinical Supplies

The MCWCC Principal Investigator will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The principal investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the principal investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

13.4 Source Documents

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the patient's clinical file.

All source documents will be written following ALCOA standards:

ALCOA Attribute	Definition
Attributable	Clear who has documented the data.
Legible	Readable and signatures identifiable.
Contemporaneous	Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
Original	Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
Accurate	Accurate, consistent and real representation of facts.
Enduring	Long-lasting and durable.
Available and accessible	Easily available for review by treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
Complete	Complete until that point in time.
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

13.5 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. The Clinical Research Coordinator will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by MCWCC personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The principal investigator will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and data will be available for review/monitoring by the MCWCC DSMC and regulatory agencies.

13.6 Study Record Retention

The principal investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects, as well as written records of the disposition of the drug when the study ends.

The principal investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, sponsor-investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

APPENDIX 1. *PERFORMANCE STATUS CRITERIA*

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory 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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX 2. *GVHD ASSESSMENT*

ACUTE GVHD ASSESSMENT

Stage	Skin (active erythema only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	< 2 mg/dl	No or intermittent nausea, vomiting or anorexia	Adult: < 500 ml/day or <3 episodes/day Child: < 10 ml/kg/day or <4 episodes/day
1	Rash < 25% BSA	2–3 mg/dl	Persistent nausea, vomiting or anorexia	Adult: 500–999 ml/day or 3–4 episodes/day Child: 10 –19.9 ml/kg/day or 4–6 episodes/day
2	Rash 25 – 50% BSA	3.1–6 mg/dl	–	Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day
3	Rash > 50% BSA	6.1–15 mg/dl	–	Adult: >1500 ml/day or >7 episodes/day Child: > 30 ml/kg/day or >10 episodes/day
4	Generalized rash (>50% BSA) and bullous formation or desquamation > 5% BSA	>15 mg/dl	–	Severe abdominal pain with or without ileus, or grossly bloody stool (volume independent)

	Pathologic evidence	Clinician assessment	Treatment for acute GVHD	Comments
Confirmed	Unequivocal evidence of GVHD	GVHD is the etiology for symptoms	Not required	GVHD is clearly present even if other etiologies co-exist simultaneously
Probable	Not required (includes equivocal and non-diagnostic biopsies)	GVHD most likely etiology for symptoms	Yes	GVHD is most likely present but other etiologies may also explain the symptoms and there insufficient evidence to make a confirmed diagnosis
Possible		GVHD in differential diagnosis (but no treatment is being provided)	No	GVHD may be present, but other etiologies are favored
Negative	Unequivocal evidence of a diagnosis other than GVHD (e.g., drug rash)	GVHD is not considered as an explanation for the symptoms	No and the symptoms resolve without GVHD treatment	A "negative" biopsy (e.g., normal skin) is not unequivocal evidence of a diagnosis other than GVHD

Grade	Skin	GI	Liver
I	Stage 1-2	0	0
II	Stage 3 or	Stage 1 or	Stage 1
III	---	Stage 2-4	Stage 2-3
IV	Stage 4	---	Stage 4

Grading of Chronic GVHD (NIH Criteria)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS[†] **FEV1** ☐ **DLCO** ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none – 0,mild -1, moderate -2, severe – 3)

Esophageal stricture or web___	Pericardial Effusion___	Pleural Effusion(s)___
Ascites (serositis)___	Nephrotic syndrome___	Peripheral Neuropathy___
M yasthenia Gravis___	Cardiomyopathy___	Eosinophilia > 500µl___
Polymyositis___	Cardiac conduction defects___	Coronary artery involvement___
Platelets <100,000/µl ___	Progressive onset___	

OTHERS: Specify:_____

APPENDIX 3. *MEDICATION GUIDE*

ILUMYA™ - tildrakizumab-asmn injection, solution
Sun Pharmaceutical Industries, Inc.

Medication Guide

ILUMYA™ (“e-loom’-me-a”) (tildrakizumab-asmn)

injection, for subcutaneous use

What is the most important information I should know about ILUMYA™ ?
ILUMYA™ may cause serious side effects, including:

Serious allergic reactions. Get emergency medical help right away if you get any of the following symptoms of a serious allergic reaction:

- feel faint
- swelling of your face, eyelids, lips, mouth, tongue or throat
- skin rash
- trouble breathing or throat tightness
- chest tightness

Infections. ILUMYA™ is a medicine that may lower the ability of your immune system to fight infections and may increase your risk of infections. Your healthcare provider should check you for infections and tuberculosis (TB) before starting treatment with ILUMYA™ and may treat you for TB before you begin treatment with ILUMYA™ if you have a history of TB or have active TB. Your healthcare provider should watch you closely for signs and symptoms of TB during and after treatment with ILUMYA™ .

Tell your healthcare provider right away if you have an infection or have symptoms of an infection, including:

- fever, sweats, or chills
- cough
- shortness of breath
- blood in your phlegm (mucus)
- muscle aches
- warm, red or painful skin or sores on your body different from your psoriasis
- weight loss
- diarrhea or stomach pain
- burning when you urinate or urinating more often than normal

See **“What are the possible side effects of ILUMYA™ ?”** for more information about side effects.

What is ILUMYA™ ?
ILUMYA™ is a prescription medicine used to treat adults with moderate to severe plaque psoriasis who may benefit from taking injections, pills (systemic therapy) or treatment using ultraviolet or UV light (phototherapy).

It is not known if ILUMYA™ is safe and effective in children under 18 years of age.

Do not use ILUMYA™ if you have had a severe allergic reaction to tildrakizumab or any of the other ingredients in ILUMYA™ . See the end of this Medication Guide for a complete list of ingredients in ILUMYA™ .

Before receiving ILUMYA™ , tell your healthcare provider about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section **"What is the most important information I should know about ILUMYA™ ?"**
- have an infection that does not go away or that keeps coming back.
- have TB or have been in close contact with someone with TB.
- recently received or are scheduled to receive a vaccine (immunization). You should avoid receiving live vaccines during treatment with ILUMYA™.
- are pregnant or plan to become pregnant. It is not known if ILUMYA™ can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ILUMYA™ passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive ILUMYA™ ?
- ILUMYA™ should only be given to you by a healthcare provider.
- ILUMYA™ is given as an injection under your skin (subcutaneous injection) in areas of your body such as your thighs, stomach area (abdomen), or upper arm.
- If you miss a follow-up appointment and do not receive your dose of ILUMYA™ , schedule another appointment as soon as possible.

What are the possible side effects of ILUMYA™ ?
ILUMYA™ may cause serious side effects. See "What is the most important information I should know about ILUMYA™ ?"
The most common side effects of ILUMYA™ include:
- upper respiratory infections
- injection site reactions
- diarrhea

These are not all of the possible side effects of ILUMYA™ . Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

General information about the safe and effective use of ILUMYA™ .
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider for information about ILUMYA™ that is written for health professionals.

What are the ingredients in ILUMYA™ ?
Active ingredient: tildrakizumab-asmn
Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose, and water for Injection, USP.

Manufactured by: Sun Pharma Global FZE, Inc.
Sharjah, U.A.E.
U.S. License No. 2092
At: MSD Ireland (Carlow), County Carlow, Ireland
Tildrakizumab-asmn (active ingred.) Product of The Netherlands.
Distributed by: Sun Pharmaceutical Industries, Inc., Cranbury, NJ 08512
ILUMYA™ is a trademark of Sun Pharma Global FZE

usmg-tildrakizumab-pfs-00001

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 08/2018

REFERENCES

1. D'Souza A FC. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides. http://www.cibmtr.org: CIBMTR; 2017.

2. Markey KA, MacDonald KP, Hill GR. The biology of graft-versus-host disease: experimental systems instructing clinical practice. Blood 2014;124:354-62.

3. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet (London, England) 2009;373:1550-61.

4. Nash RA, Pineiro LA, Storb R, et al. FK506 in combination with methotrexate for the prevention of graft-versus-host disease after marrow transplantation from matched unrelated donors. Blood 1996;88:3634-41.

5. Deeg HJ. How I treat refractory acute GVHD. Blood 2007;109:4119-26.

6. Levine JE, Logan B, Wu J, et al. Graft-versus-host disease treatment: predictors of survival. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2010;16:1693-9.

7. MacMillan ML, DeFor TE, Weisdorf DJ. The best endpoint for acute GVHD treatment trials. Blood 2010;115:5412-7.

8. Zeiser R, Socie G, Blazar BR. Pathogenesis of acute graft-versus-host disease: from intestinal microbiota alterations to donor T cell activation. Br J Haematol 2016;175:191-207.

9. Vriesendorp HM, Heidt PJ. History of graft-versus-host disease. Exp Hematol 2016;44:674-88.

10. Socie G, Ritz J. Current issues in chronic graft-versus-host disease. Blood 2014;124:374-84.

11. Das R, Chen X, Komorowski R, Hessner MJ, Drobyski WR. Interleukin-23 secretion by donor antigen-presenting cells is critical for organ-specific pathology in graft-versus-host disease. Blood 2009;113:2352-62.

12. Hill GR, Ferrara JL. The primacy of the gastrointestinal tract as a target organ of acute graft-versus-host disease: rationale for the use of cytokine shields in allogeneic bone marrow transplantation. Blood 2000;95:2754-9.

13. Wilhelm K, Ganesan J, Muller T, et al. Graft-versus-host disease is enhanced by extracellular ATP activating P2X7R. Nat Med 2010;16:1434-8.

14. Apostolova P, Zeiser R. The Role of Purine Metabolites as DAMPs in Acute Graft-versus-Host Disease. Front Immunol 2016;7:439.

15. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. Nat Rev Immunol 2012;12:443-58.

16. Naymagon S, Naymagon L, Wong SY, et al. Acute graft-versus-host disease of the gut: considerations for the gastroenterologist. Nat Rev Gastroenterol Hepatol 2017;14:711-26.

17. Oppmann B, Lesley R, Blom B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity 2000;13:715-25.

18. Parham C, Chirica M, Timans J, et al. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R. Journal of immunology (Baltimore, Md : 1950) 2002;168:5699-708.

19. Cua DJ, Sherlock J, Chen Y, et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature 2003;421:744-8.

20. Murphy CA, Langrish CL, Chen Y, et al. Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. The Journal of experimental medicine 2003;198:1951-7.

21. Yen D, Cheung J, Scheerens H, et al. IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. J Clin Invest 2006;116:1310-6.

22. Zhou V, Agle K, Chen X, et al. A colitogenic memory CD4+ T cell population mediates gastrointestinal graft-versus-host disease. J Clin Invest 2016;126:3541-55.

23. Das R, Komorowski R, Hessner MJ, et al. Blockade of interleukin-23 signaling results in targeted protection of the colon and allows for separation of graft-versus-host and graft-versus-leukemia responses. Blood 2010;115:5249-58.

24. Elmaagacli AH, Koldehoff M, Landt O, Beelen DW. Relation of an interleukin-23 receptor gene polymorphism to graft-versus-host disease after hematopoietic-cell transplantation. Bone marrow transplantation 2008;41:821-6.

25. Kopp T, Riedl E, Bangert C, et al. Clinical improvement in psoriasis with specific targeting of interleukin-23. Nature 2015;521:222-6.

26. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet (London, England) 2017;390:276-88.

27. Teshima T, Reddy P, Zeiser R. Acute Graft-versus-Host Disease: Novel Biological Insights. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2016;22:11-6.

28. Andermann TM, Peled JU, Ho C, et al. The Microbiome and Hematopoietic Cell Transplantation: Past, Present, and Future. Biol Blood Marrow Transplant 2018;24:1322-40.

29. Holler E, Butzhammer P, Schmid K, et al. Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of

diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. Biol Blood Marrow Transplant 2014;20:640-5.

30. Weber D, Jenq RR, Peled JU, et al. Microbiota Disruption Induced by Early Use of Broad-Spectrum Antibiotics Is an Independent Risk Factor of Outcome after Allogeneic Stem Cell Transplantation. Biol Blood Marrow Transplant 2017;23:845-52.

31. Jenq RR, Taur Y, Devlin SM, et al. Intestinal Blautia Is Associated with Reduced Death from Graft-versus-Host Disease. Biol Blood Marrow Transplant 2015;21:1373-83.

32. Peled JU, Devlin SM, Staffas A, et al. Intestinal Microbiota and Relapse After Hematopoietic-Cell Transplantation. J Clin Oncol 2017;35:1650-9.

33. Shono Y, Docampo MD, Peled JU, Perobelli SM, Jenq RR. Intestinal microbiota-related effects on graft-versus-host disease. Int J Hematol 2015;101:428-37.

34. Kroemer G, Zitvogel L. Cancer immunotherapy in 2017: The breakthrough of the microbiota. Nat Rev Immunol 2018;18:87-8.

35. Wilkinson EM, Ilhan ZE, Herbst-Kralovetz MM. Microbiota-drug interactions: Impact on metabolism and efficacy of therapeutics. Maturitas 2018;112:53-63.

36. Walters W, Hyde ER, Berg-Lyons D, et al. Improved Bacterial 16S rRNA Gene (V4 and V4-5) and Fungal Internal Transcribed Spacer Marker Gene Primers for Microbial Community Surveys. mSystems 2016;1.

37. Kuczynski J, Stombaugh J, Walters WA, Gonzalez A, Caporaso JG, Knight R. Using QIIME to analyze 16S rRNA gene sequences from microbial communities. Curr Protoc Microbiol 2012;Chapter 1:Unit 1E 5.

38. Taur Y, Jenq RR, Perales MA, et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. Blood 2014;124:1174-82.

39. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 2009;15:1628-33.

40. Liu TC, Gurram B, Baldridge MT, Head R, Lam V, Luo C, Cao Y, Simpson P, Hayward M, Holtz ML, Bousonis P, Noe J, Lerner D, Cabrera J, Biank V, Stephens M, Huttenhower C, McGovern DP, Xavier RJ, Stappenbeck TS, Salzman NH. Paneth cell defects in Crohn's disease patients promote dysbiosis. JCI Insight 2016; 1: e86907.

41. Bolger AM, Lohse M, Usadel B, 2014. Trimmomatic: a flexible trimmer for Illumina sequence data. Bioinformatics. 2014; 30: 2114-2120.

42. Magoc T, Salzberg SL. FLASH: fast length adjustment of short reads to improve genome assemblies. Bioinformatics 2011; 27: 2957-2963.

43. Edgar RC, Haas BJ, Clemente JC, Quince C, Knight R. 2011 UCHIME improves sensitivity and speed of chimera detection. Bioinformatics 2011; 27: 2194-2200.

44. Edgar RC. UPARSE: highly accurate OTU sequences from microbial amplicon reads. Nature Methods 2013; 10: 996-998.

45. Wang Q, Garrity GM, Tiedje JM, Cole JR. Naïve Bayesian classifier for rapid assessment of rRNA sequences into the new bacterial taxonomy. Applied and Environmental Microbiology 2007; 73: 5261-5267.

46. Shannon CE. A mathematical theory of communication. The Bell System Technical Journal, 1948; 27: 379-423.

47. Chao. Nonparametric estimation of the number of classes in a population. Scandinavian Journal of Statistics 1984; 11: 265–270.

48. Bray JR, Curtis JT. An Ordination of the Upland Forest Communities of Southern Wisconsin. Ecological Monographs. 1957; 27: 325-349.

49. Anderson MJ. A new method for non-parametric multivariate analysis of variance. Austral Ecology 2001; 26: 32-4