Masonic Cancer Center
University of Minnesota

PTCy + Sirolimus/VIC-1911 as GVHD prophylaxis in myeloablative PBSC transplantation

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Revision History

Revision #	Version Date	Summary of Changes	Consent Revision
	08/09/2021	Original version to FDA	n/a
	10/05/2021	Response to FDA potential hold and non-hold comments: Major changes: Synopsis, Section 1.1, Section 2.5, Section 3.0, section 12, Section 13, Section 14 – updated statistics to change threshold and include definition of biologic efficacy Synopsis, Section 1.3 – updated and expanded correlative objectives Synopsis, Section 4.0 – updated inclusion/exclusion criteria Section 2.5 – expanded rationale for dose Section 3.0 – clarified definitions of DLT Section 6.5 – added dose reduction table for sirolimus Section 6.6 – added VIC-1911 dose adjustments for concurrent CYP3A inhibitors; clarified dose Modifications for Non-Hematological Toxicities Related to VIC-1911 Section 8.0, Section 9.1 – added lipase levels for expected toxicity monitoring Section 10.2 – editing AE documentation guidelines Section 14.4 – Added TRM, relapse, GVHD, graft failure to early stopping rules Minor Edits: Synopsis, Section 2.4, Section 3.0 – removed references to multi center Section 9.1, Section 11.1 – minor edits to study calendar timing; edited that blood tests will be processed at Dr. Betts' lab and not TTL, removed references to TTL	Y – removed assent, updated consent to adult only, edited typo in calendar
	10/13/21	Response to FDA Clinical Information Request: clarification of "unexpected" adverse event definition, update dosing per clinical pharmacology inquiry	N
	10/22/21	Synopsis – Clarified design/objectives of Phase II trial Synopsis, Section 1.2, Section 13 - added secondary objectives for QOL and CMV monitoring Synopsis, Section 14.3 - revised phase II enrollment goal to 57 total subjects Section 9.1 – Added QOL to study calendar Section 14 – Updated statistical considerations in response to FDA comments	N

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		Added references New Appendix III – FACT-QOL survey	
	11/29/2021	In response to CPRC Stipulations: Synopsis, Section 1, Section 3, Section 12, Section 13 – Phase II updated to estimate grade II –IV (changed from grade III-IV) aGVHD as a measure of long term efficacy; clarified secondary objective is estimate of grade III-IV aGVHD at 100 days; Synopsis - enrollment plan clarified that 3-9 patients will be treated at recommended phase II dose, and up to 58 patients to be enrolled in phase II Section 1.1 – fixed typographical error reference to aGVHD endpoint Section 2 – updated results and analysis of local experience with PTCy/TAC/MMF; clarified rationale for study treatment Section 4.0 – clarified lower age eligibility inconsistencies Section 7.2.3 and 7.3.3 – clarified that SOC drugs will be billed to patient insurance Section 14 – Updated statistics to clarify model with historical control; updated stopping rules to new enrollment plan	N
	1/04/2022	Synopsis, Section 4.2 – exclusion criteria – clarification of timing of post transplant maintenance therapy Section 7.1 – updated packaging information	
	5/19/2022	Update to collaborators, biostatistician Synopsis, Section 4.2 – exclusion criteria – added active smoking as exclusion criterion, included HCT-CI guidance Section 5.5 - replacement guidelines for nonevaluable Synopsis - corrected error in PK schedule Section 9.1 - clarified PKs are for phase 1 subjects only Section 10.5 - updated “MCC SAE report form” to “University of MN SAE report” in expedited reporting guidance	
	10/12/2022	Synopsis, Schema, Section 6.2 – change in sirolimus taper (start at d+100) Synopsis, Schema, Section 1.2 – added secondary objective to investigate peripheral blood transcriptomics Section 6.6 – revised VIC-1911 doses with coadministration of CYP 3A inhibitors Section 14.2 Bioinformatics plan clarified	Y – changed date for for sirolimus dosing to d100

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		Section 14.4 minor clarification in sample size for stopping rule calculation Minor corrections for readability/consistency of sample collection dates.	
	8/16/2023	Synopsis, schema, section 6.2, section 9.1, Appendix II – added busulfan/fludarabine alternative myeloablative conditioning regimen, updated dates of TBI treatment plan to move allopurinol to day -4 to reflect new admission guideline Synopsis, Schema, section 6.4 – updated dosing for post-transplant cyclophosphamide (PTCy) to reflect updated pharmacy guidelines Synopsis, section 4.2 – updated exclusion criterion re: smoking from any history of smoking within 6 months of protocol-directed activities, to daily smokers/users of e-cigarettes or vaping within 1 month, and removed exclusion for subjects unable to receive TBI Synopsis, schema, section 1, section 2.3, section 3, section 6, section 10, section 13 and section 14 – updated study phase language from “phase I/II” or “phase II” to “phase I dose finding/phase I extension” at request of pharmaceutical partner Vitrac Section 2.4 – clarifying the study structure, part 1 a dose escalation to identify MTD, and then part 2 an expansion at MTD for preliminary safety and efficacy data. Section 2.3, 2.4, 6.1 and 6.2 – removed references to a proposed additionl 90 mg dose level that PI and Vitrac decided was not required Section 9.1 – updated location of Brian Betts Lab Section 13 – added specific definition of relapse/progression Section 14 – edited to include Phase I extension objectives	Y – new conditioning regimen risks to be updated
	11/15/2023	Synopsis, section 1.3, section 9.1, section 13, section 14.2: pharmacokinetics studies completed on subjects in phase I dose finding cohort; sufficient data has obtained that they will not be required in phase I extension and have been removed to spare patients unnecessary blood draw/possibly lengthy outpatient observations Section 6.3 – corrected error in footnote in table re: busulfan dosng	Y

Revision #	Version Date	Summary of Changes	Consent Revision
		Section 9 – updated study calendar to reflect that radiation therapy consult only required for subjects receiving TBI Section 10.4 – corrected erroneous reference to phase II to phase I extension	
	01/08/2024	Updated to change UMN Site PI to Punita Grover, MBBS	Y

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Key Abbreviations

ABBREVIATION	DEFINITION
ABW	ACTUAL BODY WEIGHT
AdjBW	ADJUSTED BODY WEIGHT
AE	ADVERSE EVENT
aGVHD	ACUTE GRAFT VERSUS HOST DISEASE
AHC	ACADEMIC HEALTH CENTER
alloHCT	ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION
ALT	ALANINE AMINOTRANSFERASE
ANC	ABSOLUTE NEUTROPHIL COUNT
AST	ASPARTATE AMINOTRANSFERASE
CBC	COMPLETE BLOOD COUNT
CFR	CODE OF FEDERAL REGULATIONS
CMV	CYTOMEGALOVIRUS
CPRC	CANCER PROTOCOL REVIEW COMMITTEE
CR	COMPLETE REMISSION
CR/PR	COMPLETE RESPONSE OR PARTIAL RESPONSE
CRF	CASE REPORT FORM
CTCAE	COMMON TOXICITY CRITERIA ADVERSE EVENT
CTEP	CANCER THERAPY EVALUATION PROGRAM
CTO	CLINICAL TRIALS OFFICE
CTSI	CLINICAL AND TRANSLATIONAL SCIENCE INSTITUTE
DLCO	DIFFUSING CAPACITY OF THE LUNGS FOR CARBON MONOXIDE
DLT	DOSE LIMITING TOXICITY
DSMP	DATA AND SAFETY MONITORING PLAN
FDA	FOOD AND DRUG ADMINISTRATION
FEV	FORCED EXPIRATORY VOLUME
FVC	FORCED VITAL CAPACITY
GRFS	GRAFT-VERSUS-HOST DISEASE-FREE, RELAPSE-FREE SURVIVAL
GVHD	GRAFT VERSUS HOST DISEASE
GVL	GRAFT VERSUS LEUKEMIA
HBV	HEPATITIS B VIRUS
HCT-CI	HEMATOPOIETIC CELL TRANSPLANTATION-SPECIFIC COMORBIDITY INDEX
HCV	HEPATITIS C VIRUS
HIV	HUMAN IMMUNODEFICIENCY VIRUS
IB	INVESTIGATOR'S BROCHURE
IBW	IDEAL BODY WEIGHT
IRB	INSTITUTIONAL REVIEW BOARD
IV	INTRAVENOUS
MAC	MYELOABLATIVE CONDITIONING WITH
MCC	MASONIC CANCER CENTER
MCC-CISS	MASONIC CANCER CENTER - CLINICAL INFORMATICS SHARES SERVICES
MCT	MOLECULAR CELL THERAPY FACILITY
MMF	MYCOPHENOLATE MOFETIL
MR	MIXED RESPONSE

ABBREVIATION	DEFINITION
mTOR	MECHANISTIC TARGET OF RAPAMYCIN
MTX	METHOTREXATE
NCI	NATIONAL CANCER INSTITUTE
NIH	NATIONAL INSTITUTES OF HEALTH
NK	NATURAL KILLER
NR	NO RESPONSE
ONCORE	ONLINE ENTERPRISE RESEARCH MANAGEMENT ENVIRONMENT
OS	OVERALL SURVIVAL
PBSC	PERIPHERAL BLOOD STEM CELLS
PCRC	PRIMARY CLINICAL RESEARCH COORDINATOR
PHI	PROTECTED HEALTH INFORMATION
PT	PROTHROMBIN TIME
PTCY	POSTTRANSPLANTATION CYCLOPHOSPHAMIDE
PTT	PARTIAL THROMBOPLASTIN TIME
SAE	SERIOUS ADVERSE EVENT
SIR	SIROLIMUS
SOP	STANDARD OPERATING PROCEDURE
TBI	TOTAL BODY IRRADIATION
TCR	T-CELL RECEPTOR
TREGS	REGULATORY T CELLS
ULN	UPPER LIMIT OF NORMAL
USP	UNITED STATES PHARMACOPEIA
WOCBP	WOMEN OF CHILDBEARING POTENTIAL

Protocol Synopsis

PTCy + Sirolimus/VIC-1911 as GVHD prophylaxis in myeloablative PBSC transplantation

CPRC #2021LS006

Study Design:	This is a single-arm, phase I/extension study of PTCy/sirolimus plus VIC-1911 to prevent GVHD and relapse after alloHCT. Determination of the optimal dose during the Phase I trial is based on Dose Limiting Toxicity for safety and reduction of $CD4^+$, $pH3ser10^+$ T cells (phosphorylated histone 3 serine 10 is a biomarker of Aurora kinase A activity) for efficacy. Phase I extension cohort will be designed to obtain estimates of grade II-IV acute graft-versus-host disease and relapse and powered to independently test these endpoints for the improvement over historical estimates at the University of Minnesota. Patients will receive myeloablative conditioning (MAC) with total body irradiation (TBI), or an alternative busulfan/fludarabine regimen (BU/FLU) followed by infusion of HLA-matched related or unrelated peripheral blood stem cells (PBSC) on day 0 (Table 1). Cyclophosphamide will be administered on days +3 and +4. Sirolimus targeting 8-12ng/ml will begin on day +5 until day +100 with dose adjustment per protocol section 6.5-6.7 as needed. VIC-1911 will be administered as 25 mg, 50 mg, or 75 mg orally BID from day +5 to day +45 according to the rules of our phase I study (Table 2). The lowest biologically active and safe dose of VIC-1911 will be identified as the recommended phase I extension cohort dose. Dose Limiting Toxicity for the Phase 1 component of the study is defined as (CTCAE v5): 1. More than 48 hours of the following ocular disorders: a. Grade 2 or higher vitreous hemorrhage b. Grade 3 or higher visual acuity decreased c. Grade 3 or higher watery eyes d. Grade 3 or higher keratitis e. Grade 3 or higher floaters f. Grade 3 or higher corneal microcysts g. Grade 3 or higher other eye disorders 2. Any grade 3 or above adverse event considered at least possibly related to VIC-1911, excluding nausea, vomiting, constipation, pain, diarrhea or rash that is adequately controlled with supportive care and resolves to ≤ Grade 2 within 48 hours Biologic efficacy is defined as: 1. The proportion of patients with an average $CD4^+$, $pH3ser10^+$ T cell of <54%. The minimum desired biologic efficacy is 65% of patients by day 21 (- 3 to +7 days) having <54% of $CD4^+$ $pH3ser10^+$ T cells with no more than 30% of patients having a DLT. This threshold is based on the lower confidence interval of the normal, pretransplant frequency of $\%pH3ser10^+$, $CD4^+$ T cells (Note: pH3ser10 is the phosphoprotein target of Aurora kinase A). The optimal dose will be identified using the EffTox design. After completion of the dose finding trial, the final dose will be carried forward into a phase I extension trial to confirm safety and obtain an estimate of long-term efficacy as measured by Grade II-IV acute GVHD (aGVHD) by 100 days and relapse by 12 months.

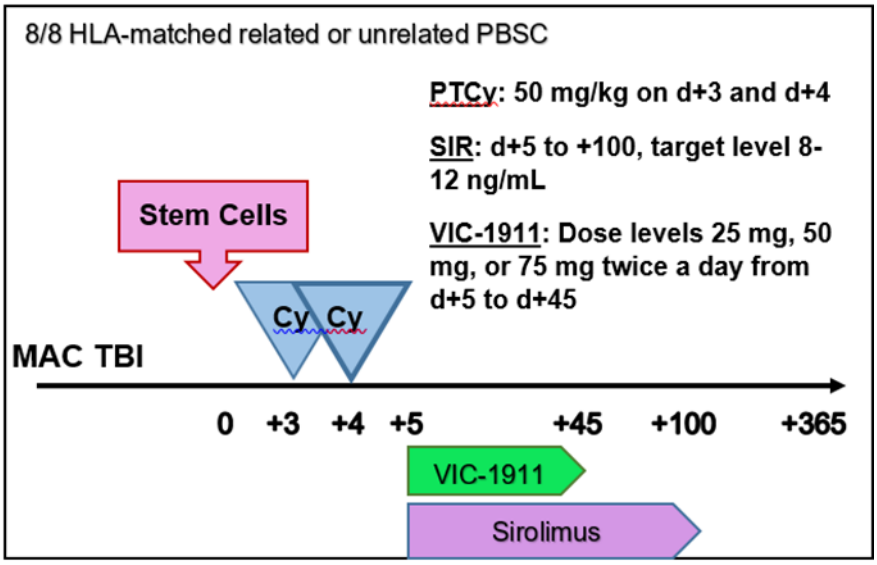
Primary Objective:	**Phase I:** To determine the safety and optimal dose of VIC-1911 when given in combination with standard immunosuppressive therapy in adult patients undergoing myeloablative stem cell transplantation. The lowest biologically active dose will be defined as the proportion of patients with an average $CD4^+$, $pH3ser10^+$ T cell of <54%. The minimum desired biologic efficacy is 65% of patients by day 21 (- 3 to +7 days) with <30% of patients experiencing a DLT. **Phase I extension cohort:** To confirm safety and obtain an estimate of long-term efficacy as measured by grade II-IV aGVHD assessed by 100 days and relapse assessed by 1 year
Secondary Objectives:	**Phase I dose-finding and extension cohort** • To analyze the frequency of $CD4^+$, $pS6^+$ [marker of mTOR activity], CD4+, pSTAT3+ [marker of IL-6/JAK2 activity] and $CD4^+$, $pSTAT5^+$ [marker of IL-2 activity] cells at pre-conditioning, +21, and +100. • To investigate whether peripheral blood transcriptomics correlate with GVHD and/or relapse. Transcriptomics analyses will focus on GVL (*LCK*, *PDCD1*, and *INFG)* versus GVHD (*AURKA* and *STAT3)* gene assessments at d+21, +60, and +100. • To determine the cumulative incidences of grade III-IV acute (day +100) and chronic GVHD (day +365). • To compare GRFS (defined as grade II-IV and III-IV acute GVHD by day +100, chronic GVHD (NIH consensus criteria) by day +365, and relapse by day +365) to the standard PTCY plus tacrolimus/mycophenolate mofetil regimen from MT2015-29 • To compare duration of initial transplant hospitalization to patients age 18+ who received treatment on MT2015-29 • To analyze the frequency of CMV reactivation and disease through day +180 • To measure Quality of life through day +100
Correlative Objectives:	Phase I - Pharmacokinetic (PK) parameters: For the first 3 patients enrolled at each dose level in the phase I dose finding portion of this study, pharmacokinetic sampling of plasma VIC levels will be drawn on +5 and 15 at the following timepoints: pre-dose, +30 minutes, +1 hours, +2 hours,+ 6 hours, and +24 hours (pre-morning dose). These studies will be batched and performed by collaborators at VITRAC. • Phase I - Extended CD28, JAK2, and pSTAT5 signal transduction studies: While the frequency of CD4+, pH3ser10+ T cell will be used to assess biologic activity at day +21, we will also measure the number and frequency of CD4+ T cell expressing the following phosphoproteins at pre-conditioning, +21, +60, and +100: pH3ser10, pS6, pSTAT3, and pSTAT5. The day +60 timepoint will allow us to observe if Aurora kinase A signal transduction flares or rebounds after discontinuing VIC on day +45. Treatment of acute GVHD will be at the discretion of the attending physician. However, we will monitor use of tacrolimus, glucocorticoids, and ruxolitinib to see how these medications may impact T cell phosphoproteins. • Phase I - Immune reconstitution: Immunophenotyping by flow cytometry will be conducted on pre-conditioning, +21, +60, and +100 for effectors of allotolerance - Tregs (CD4+, CD25+, CD127neg, Foxp3+); effectors of alloreactivity - allo-conventional T cell (Tconv) (CD4+, CD25+, CD127+) and CD4+ T helper 1/2/17 cells based on expression of T-bet, GATA3, and RORγt, respectively; effectors of chronic GVHD will be evaluated on day +60 and +100 including T follicular helper cells (Tfh:CD4+, CXCR5+, CD45RAneg), transitional (CD19+, IgD+, CD38Hi, CD27+) B cells, and pregerminal (CD19+, CD21Lo, CD27neg); and effectors of GVL including CD8+, perforin+, granzyme B+ T cells on day +60 and +100. Total B cells, CD4/CD8 T cells, and

	natural killer (NK) cells will be acquired from clinical immune reconstitution panels on Pre-conditioning, +21, +60, and +100. • Phase I - Functional Assays: Treg suppression assays will be performed using magnetic bead isolated peripheral Tregs at days +21 and +60 from peripheral blood (Treg:T effector ratios ranging from 0:1, 1:30, 1:10, 1:3, and 1:1). Non-Treg T cells from the patient will serve as responders against CD3/CD28 bead- or pre-transplant host dendritic cell-stimulation. Given that TAC can also limit GVL mediated by NK cells, we will evaluate the cytolytic activity of isolated NK cells (day +21, +60, and +100) against K562 target cells as well as proliferation with IL-2/IL-15 stimulation. • Phase I - CD3+ T cell transcriptomics: While we have designed PTCy/SIR/VIC to comprehensively limit CD28 signal transduction, we will seek out and identify other possible immune escape mechanisms using single cell RNA-seq on purified CD3+ T cells and then validate these findings with NanoString. Samples from patients (myeloablative conditioning) treated with PTCy/SIR/MMF from our UMN biobank, acquired on pre-conditioning, +21, +60, and +100 (+/- 3 days) will serve as a comparison group for these studies. Phase I extension • Phase I extension - Extended CD28, JAK2, and pSTAT5 signal transduction studies: While the frequency of CD4+, pH3ser10+ T cell will be used to assess biologic activity at day +21, we will also measure the number and frequency of CD4+ T cell expressing the following phosphoproteins at pre-conditioning, +21, +60, and +100: pH3ser10, pS6, pSTAT3, and pSTAT5. The day +60 timepoint will allow us to observe if Aurora kinase A signal transduction flares or rebounds after discontinuing VIC on day +45. Treatment of acute GVHD will be at the discretion of the attending physician. However, we will monitor use of tacrolimus, glucocorticoids, and ruxolitinib to see how these medications may impact T cell phosphoproteins. • Phase I extension - Immune reconstitution: Immunophenotyping by flow cytometry will be conducted on pre-conditioning, +21, +60, and +100 for effectors of allotolerance - Tregs (CD4+, CD25+, CD127neg, Foxp3+); effectors of alloreactivity - allo-conventional T cell (Tconv) (CD4+, CD25+, CD127+) and CD4+ T helper 1/2/17 cells based on expression of T-bet, GATA3, and RORγt, respectively; effectors of chronic GVHD will be evaluated on day +60 and +100 including T follicular helper cells (Tfh:CD4+, CXCR5+, CD45RAneg), transitional (CD19+, IgD+, CD38Hi, CD27+) B cells, and pregerminal (CD19+, CD21Lo, CD27neg); and effectors of GVL including CD8+, perforin+, granzyme B+ T cells on day +60 and +100. Total B cells, CD4/CD8 T cells, and natural killer (NK) cells will be acquired from clinical immune reconstitution panels on Pre-conditioning, +21, +60, and +100.
Patient Population:	HCT recipients 18 to 60 years of age with an 8/8 HLA-matched related or unrelated peripheral blood allograft donor

Inclusion Criteria:	• diagnosis of
	  ○ acute leukemia in complete remission, or
	  ○ myelodysplasia with <5% blasts, or
	  ○ myeloproliferative neoplasm/myelofibrosis with <5% marrow or circulating blasts, or
	  ○ chemosensitive Hodgkin or non-Hodgkin lymphoma,
	• left ventricular ejection fraction ≥ 45%,
	• pulmonary function with FEV1, FVC, and DLCO ≥ 50% predicted,
	• AST and ALT < 2 times upper limit of normal

	• total bilirubin <1.5 times the upper limit of normal. If the patient is suspected of having Gilbert syndrome, they require prior approval of the medical monitor • estimated creatinine clearance ≥ 50cc/min, • no active/uncontrolled infection, • negative HIV, HBV and HCV, • ferritin < 2000 ng/ml, • Karnofsky Performance Status Score ≥ 80% • Patients able to tolerate oral medication
Exclusion Criteria:	• HCT-CI > 4 • Patients with a history of hypersensitivity to any of the investigational products • Planned post-transplant maintenance therapy to begin prior to day +75. Patients may receive standard of care maintenance therapies starting at day +75 or later • Pregnancy or breastfeeding • Women or men of childbearing potential unwilling to take adequate precautions to avoid unintended pregnancy from the start of protocol treatment through 60 days after the last treatment of VIC-1911 or sirolimus • Active/recent daily smoker of tobacco or marijuana/user of e-cigarette or vaping within 1 months of protocol-directed therapy – intermittent (less than daily) use permitted.
Enrollment Plan:	Phase I dose finding cohort: up to 21 patients, with 3-9 treated at optimal dose as defined by E*ff*tox. Phase I extension cohort: up to 58 additional patients at optimal dose

Protocol Schema



- Cyclophosphamide will be administered on days +3 and +4. Cyclophosphamide to be dosed at ideal body weight (IBW), unless patient weight is less than IBW, in which case actual body weight (ABW) should be used.
- Sirolimus targeting 8-12ng/ml will begin on day +5 until day +100
- [Phase I] 25 mg, 50 mg, or 75 mg of VIC-1911 administered orally BID from day +5 to day +45; [Phase I extension cohort] The lowest biologically active and safe dose of VIC-1911 will be identified as the recommended phase I extension dose.

Conditioning Regimens:

MAC TBI:

Day	Drug/ Procedure	Dose and Route
-4	start allopurinol 300 mg/day PO	
-4	TBI AM, PM	165 cGy each dose
-3	TBI AM, PM	165 cGy each dose
-2	TBI AM, PM	165 cGy each dose
-1	TBI AM, PM	165 cGy each dose
0	HCT	

OR MAC BUSULFAN/FLUDARABINE (NO TBI)

Day	Drug/ Procedure	Dose and Route
-6	-start allopurinol 300 mg/day PO -begin levetiracetam per institutional guidelines (through day-1)	
-5	Busulfan	130 mg/m2 IV QD over 3 hours
	Fludarabine	40 mg/m2 IV QD
-4	Busulfan	130 mg/m2 IV QD over 3 hours
	Fludarabine	40 mg/m2 IV QD
-3	Busulfan	130 mg/m2 IV QD over 3 hours
	Fludarabine	40 mg/m2 IV QD
-2	Busulfan	130 mg/m2 IV QD over 3 hours
	Fludarabine	40 mg/m2 IV QD
-1	Rest	
0	HCT	

Research Samples:

- Blood (8 green top tubes and 1 pax gene tube): pre-conditioning, +21, day +60, and +100
- VIC-1911 Pharmacokinetics PK Studies: Plasma samples will be collected pre-dose, 30 minutes, 1 hours, 2 hours, 6 hours, 24 hours (pre-morning dose) in K2 EDTA tubes, collected at day +5 and day +15 post-transplant. If those day fall on weekend days, the samples should be collected on the next earliest weekday, no later than 3 days after the target date.

1 Objectives

1.1 Primary Objective

Phase I: The primary objective of this study is to determine the safety and optimal dose of VIC-1911 when given in combination with standard immunosuppressive therapy in adult patients undergoing myeloablative stem cell transplantation.

The lowest biologically active dose will be defined as the proportion of patients with an average $CD4^+$, $pH3ser10^+$ T cell of <54%. The minimum desired biologic efficacy is 65% of patients by day 21 (- 3 to +7 days) having <54% of $CD4^+$ $pH3ser10^+$ T cells, with no more than 30% of patients having a DLT. This threshold is based on the lower confidence interval of the normal, pretransplant frequency of %pH3ser10+, CD4+ T cells (Note: pH3ser10 is the phosphoprotein target of Aurora kinase A).

Phase I extension: The primary objective of this study is to confirm safety and obtain preliminary estimates of long-term efficacy as measured by grade II-IV aGVHD by 100 days and relapse by 1 year.

1.2 Secondary Objectives

In both Phase I and extension cohort, the secondary objectives of this study are:

- To analyze the frequency of $CD4^+$, $pS6^+$ [marker of mTOR activity], CD4+, pSTAT3+ [marker of IL-6/JAK2 activity] and $CD4^+$, $pSTAT5^+$ [marker of IL-2 activity] cells at pre-conditioning, +21, and +100.
- To investigate whether peripheral blood transcriptomics correlate with GVHD and/or relapse. Transcriptomics analyses will focus on GVL (LCK, PDCD1, and INFG) versus GVHD (AURKA and STAT3) gene assessments at d+21, +60, and +100.
- To determine the cumulative incidences of grade III-IV acute (day +100) and chronic GVHD (day +365).
- To compare GRFS (defined as grade II-IV and III-IV acute GVHD by day +100, chronic GVHD [NIH consensus criteria] by day +365, and relapse by day +365) to the standard PTCY plus tacrolimus/mycophenolate mofetil regimen from MT2015-29
- To compare duration of initial transplant hospitalization to patients age 18+ who received treatment on MT2015-29
- To analyze the frequency of CMV reactivation and disease through day +180
- To measure Quality of life through day +100

1.3 Correlative (or Exploratory) Objectives

Phase I dose finding cohort:

- Phase I - Pharmacokinetic (PK) parameters: For all patients enrolled in the phase I portion of this study, pharmacokinetic sampling of plasma VIC levels will be drawn on day +5 and +15 at the following time points: pre-dose, +30 min, +1, +2, +6- and 24-hours post-dose, for up to 3 subjects at each dose level until MTD reached. These studies will be batched and performed by collaborators at VITRAC.
    - November 10, 2023: 3 subjects have been treated at MTD of 75 mg BID. Sufficient data has been obtained from subjects to date, pharmacokinetics will not be obtained from subjects on phase I extension.
- Phase I - Extended CD28, JAK2, and pSTAT5 signal transduction studies: While the frequency of CD4+, pH3ser10+ T cell will be used to assess biologic activity at day +21, we will also measure the number and frequency of CD4+ T cell expressing the following phosphoproteins at pre-conditioning, +21, +60, and +100: pH3ser10, pS6, pSTAT3, and pSTAT5. The day +60 timepoint will allow us to observe if Aurora kinase A signal transduction flares or rebounds after discontinuing VIC on day +45. Treatment of acute GVHD will be at the discretion of the attending physician. However, we will monitor use of tacrolimus, glucocorticoids, and ruxolitinib to see how these medications may impact T cell phosphoproteins.
- Phase I - Immune reconstitution: Immunophenotyping by flow cytometry will be conducted on pre-conditioning, +21, +60, and +100 for effectors of allotolerance - Tregs (CD4+, CD25+, CD127neg, Foxp3+); effectors of alloreactivity - allo-conventional T cell (Tconv) (CD4+, CD25+, CD127+) and CD4+ T helper 1/2/17 cells based on expression of T-bet, GATA3, and RORγt, respectively; effectors of chronic GVHD will be evaluated on day +60 and +100 including T follicular helper cells (Tfh:CD4+, CXCR5+, CD45RAneg), transitional (CD19+, IgD+, CD38Hi, CD27+) B cells, and pregerminal (CD19+, CD21Lo, CD27neg); and effectors of GVL including CD8+, perforin+, granzyme B+ T cells on day +60 and +100. Total B cells, CD4/CD8 T cells, and natural killer (NK) cells will be acquired from clinical immune reconstitution panels on Pre-conditioning, +21, +60, and +100.
- Phase I - Functional Assays: Treg suppression assays will be performed using magnetic bead isolated peripheral Tregs at days +21 and +60 from peripheral blood (Treg:T effector ratios ranging from 0:1, 1:30, 1:10, 1:3, and 1:1). Non-Treg T cells from the patient will serve as responders against CD3/CD28 bead- or pre-transplant host dendritic cell-stimulation. Given that TAC can also limit GVL mediated by NK cells, we will evaluate the cytolytic activity of isolated NK cells (day +21, +60, and +100) against K562 target cells as well as proliferation with IL-2/IL-15 stimulation.

- Phase I - CD3+ T cell transcriptomics: While we have designed PTCy/SIR/VIC to comprehensively limit CD28 signal transduction, we will seek out and identify other possible immune escape mechanisms using single cell RNA-seq on purified CD3+ T cells and then validate these findings with NanoString. A prospective cohort of patients treated with standard PTCY/SIR/MMF will serve as a control for the correlative experiments, with samples collected acquired on pre-conditioning, +21, +60, and +100 (+/- 3 days).
- Phase I extension cohort
- Phase I extension- Extended CD28, JAK2, and pSTAT5 signal transduction studies: While the frequency of CD4+, pH3ser10+ T cell will be used to assess biologic activity at day +21, we will also measure the number and frequency of CD4+ T cell expressing the following phosphoproteins at pre-conditioning, +21, +60, and +100: pH3ser10, pS6, pSTAT3, and pSTAT5. The day +60 timepoint will allow us to observe if Aurora kinase A signal transduction flares or rebounds after discontinuing VIC on day +45. Treatment of acute GVHD will be at the discretion of the attending physician. However, we will monitor use of tacrolimus, glucocorticoids, and ruxolitinib to see how these medications may impact T cell phosphoproteins.
- Phase I extension - Immune reconstitution: Immunophenotyping by flow cytometry will be conducted on pre-conditioning, +21, +60, and +100 for effectors of allotolerance - Tregs (CD4+, CD25+, CD127neg, Foxp3+); effectors of alloreactivity - allo-conventional T cell (Tconv) (CD4+, CD25+, CD127+) and CD4+ T helper 1/2/17 cells based on expression of T-bet, GATA3, and RORγt, respectively; effectors of chronic GVHD will be evaluated on day +60 and +100 including T follicular helper cells (Tfh:CD4+, CXCR5+, CD45RAneg), transitional (CD19+, IgD+, CD38Hi, CD27+) B cells, and pregerminal (CD19+, CD21Lo, CD27neg); and effectors of GVL including CD8+, perforin+, granzyme B+ T cells on day +60 and +100. Total B cells, CD4/CD8 T cells, and natural killer (NK) cells will be acquired from clinical immune reconstitution panels on Pre-conditioning, +21, +60, and +100.

2 Background and Rationale

2.1 Graft-versus-Host Disease and Current Standard of Care

Allogeneic hematopoietic cell transplantation (HCT) is the only potentially curative treatment for many high-risk or relapsed/refractory hematologic malignancies. HCT with myeloablative conditioning (i.e., of sufficient intensity that autologous recovery of hematopoiesis is extremely unlikely) is currently the standard of care for young, fit

patients suitable for HCT. However, GVHD continues to impair survival and contribute to post transplant morbidity, with 35-50% of patients diagnosed with this complication post-transplant.

Acute GVHD occurs when donor T cells respond to genetically defined proteins on normal host cells. The attack on the host cells can cause an array of symptoms from skin rash, nausea, vomiting, diarrhea, hepatitis, jaundice as well as increase the risk for infection. This typically occurs within the first 6 months post-HCT. Chronic GVHD occurs later in most patients (average of 9-12 months post-HCT) and can lead to scarring and fibrosis of many organs, including the skin and subcutaneous tissues, mucous membranes, lungs, liver, and other organs. The challenge is to design current strategies that reduce the incidence and severity of GVHD, without sacrificing graft-versus-tumor effects.

Myeloablative Transplant at the University of Minnesota

The University of Minnesota Blood and Marrow Transplant (BMT) program has extensive experience in performing myeloablative HCT procedures in children and adults with lethal hematologic diseases. Over three hundred patients have undergone HCT under protocol MT2001-02, our standard of care myeloablative HCT protocol that began accruing patients in 2001 with the use of cyclophosphamide and TBI conditioning and cyclosporine/methotrexate prophylaxis. One year survival for the cohort was 62% (95% CI 62-73%). 40 percent of patients (95% CI 34-46%) treated on MT2001-02 developed grade II-IV acute GVHD by day +180 post-HCT. 16 percent of patients (95% CI 12-21%) had severe, grade III-IV acute GVHD. The majority of patients who developed acute GVHD did so prior to day +60 post-HCT. Thirty-three percent of patients (95% CI 27-39%) treated on MT2001-02 developed chronic GVHD by year one[1] post-HCT despite GVHD prophylaxis with cyclosporine A (CSA) and methotrexate (MTX). By 2 years, the cumulative incidence of chronic GVHD increased to 41%. Approximately one quarter (24%, 95% CI 18-29%) of patients treated under MT2001-02 experienced relapse of their underlying hematologic malignancy at one-year post-HCT. The 1-year graft-versus-host disease-free, relapse-free survival (GRFS) was just 21% for myeloablative transplants[1].

In 2018, our program updated our myeloablative preparative regimen approach to TBI alone followed by post-transplant cyclophosphamide (PTCy), tacrolimus (TAC), and mycophenolate mofetil (MMF) under MT2015-29. Matched unrelated donors remain the major stem cell source for our transplant patients. Interim results demonstrate the incidence of grade II-IV acute GVHD is 25% for matched unrelated

donors and 16% for those receiving a matched related allograft with PTCy/TAC/MMF. Overall, the incidence of disease relapse is 24% at 1 year with PTCy/TAC/MMF. While these outcomes with PTCy/TAC/MMF are a substantial improvement from the prior use of CSA/MTX, our patients remain at risk of developing acute GVHD and/or relapse. In part continued use of TAC broadly blunts donor T cell function, impairing both T effectors required for graft-versus-leukemia and regulatory T cells that mediate durable immune tolerance. Further, our supporting data provide evidence that concurrent inhibition of mTOR (via SIR) and Aurora kinase A (via VIC) will effectively and selectively block alloreactive donor T cell co-stimulation to optimize GVHD prevention. We hypothesize that our current, TAC-free trial of PTCy/SIR/VIC will reduce grade II-IV acute GVHD to <10% and relapse to <12%.

2.2 PTCY/Sirolimus/MMF

To improve GVHD outcomes while sparing the toxicities of calcineurin inhibitors, the Moffitt group pioneered a PTCy platform using sirolimus instead of TAC as the immunosuppressant backbone for haploidentical peripheral blood transplantation. In a phase II study of 32 patients, the GVHD rates were low (18.8% for both grade II-IV acute GVHD and NIH moderate/severe chronic GVHD), with a relapse rate of 22.2% and GRFS of 49.6%[2]. A large study of 249 alloHCT recipients from the IRCCS San Raffaele Scientific Institute in Italy evaluated the efficacy of PTCy/SIR/MMF or PTCy/SIR in several donor sources and match grades (Greco R. et al. TCT. 2021). This study demonstrated a grade II-IV acute GVHD incidence of 23% at day +100 and a 1 year relapse rate of ~25%. Essentially, PTCy/SIR/MMF eliminates the toxicities associated with calcineurin inhibitors, but provides the same level of immune suppression and similar rates of disease control as PTCy/TAC/MMF. However, investigations to further improve post alloHCT immune tolerance and enhanced GVL are clearly warranted.

2.3 VIC-1911, an Aurora Kinase A Inhibitor

An opportunity to use T cell signal transduction to improve PTCy

Importantly, there is interest in wider use of mobilized PBSC with PTCy-based regimens, but this requires the addition of TAC to maintain effective GVHD prevention. TAC impairs the TCR with broad and detrimental effects against alloreactive T cells as well as beneficial Tregs and T effectors needed for allotolerance and GVL, alike[4,5,6]. Thus, replacing TAC with effective, but selective, immune suppression is critical. An alternative approach is to fully neutralize T-cell costimulation via CD28, rather than impairing TCR function with TAC. SIR inhibits mTOR, partially suppressing CD28 signal transduction. SIR also has beneficial effects

toward Tregs, supporting their function and reconstitution after alloHCT. TAC can be replaced with SIR when using PTCy and achieve similar rates of acute GVHD but carries an unresolved 35% incidence of relapse[7]. However, even when SIR is present, CD28 can escape the suppressive influence of SIR by utilizing Aurora kinase A in donor T cells[8,9]. Thus, Aurora kinase A is an important resistance mechanism for SIR efficacy in GVHD prevention[8,9].

Effective blockade of CD28 activity is essential for optimal GVHD prevention. In preclinical studies, blocking ligand interactions between CD28 and B7 with neutralizing antibody significantly reduces GVHD mortality in transplanted mice[10]. Further, molecular deletion of CD28 in donor, murine T-cells similarly decreases GVHD severity[11]. Recently, abatacept, an Ig-CTLA4 fusion protein that blocks CD28 activity, reduced severe grade III-IV acute GVHD to 6.8% after unrelated donor alloHCT, albeit still paired with a calcineurin-inhibitor and MTX by design[12]. This data earned abatacept a Breakthrough Therapy Designation from the FDA for GVHD prevention in this setting. Further, our preliminary data shows concurrent mTOR/ Aurora kinase A inhibition synergistically increases the ratio of Tregs to pathogenic Th1 and Th17 cells in a xenogeneic GVHD model.

We now propose a first-in-human, **entirely TAC-free**, phase I/phase 1 extension lGVHD prevention trial, testing the safety and efficacy of PTCy plus SIR and VIC-1911, a selective Aurora kinase A inhibitor (PTCy/SIR/VIC). We hypothesize PTCy/SIR/VIC will leverage complementary effects on Tregs, ablate CD28 signal transduction, and permit the successful omission of TAC from GVHD prophylaxis among recipients of 8/8 HLA-matched related or unrelated PBSC allografts after myeloablative conditioning (MAC). PTCy/SIR/VIC is specifically designed to substantially reduce GVHD, facilitate the full potential of GVL without TAC, and maximize GRFS while using contemporary PBSC allografts and effective conditioning.

2.4 Rationale for the Study Treatment

To simultaneously reduce the competing risks of GVHD and relapse, we will combine comprehensive CD28 signal transduction blockade with PTCy in a phase I GVHD prevention trial in two parts, the first a dose finding study with 3 levels, and the second an extension at dose identified in part 1 to determine safety and efficacy. The dose finding portion of the trial will be conducted entirely at the University of Minnesota. We hypothesize that the TAC-free regimen, PTCy/SIR/VIC, will support Treg-mediated allotolerance and permit unconstrained GVL, effectively reducing grade II-IV acute GVHD (day +100) and relapse (day +365). Correlative studies will investigate mechanisms of immune suppression mediated by PTCy/SIR/VIC, in terms

of signal transduction, immune reconstitution, $CD3^+$ T cell gene dysregulation via transcriptomics, and Treg potency. A prospective cohort of patients treated with standard PTCY/SIR/MMF will serve as a control for the correlative experiments.

2.5 Rationale for Dose

We propose to combine the selective Aurora kinase A inhibitor, VIC-1911, with SIR to ablate CD28 signal transduction, using a PTCy immunosuppressive backbone. Importantly, our phase I trial will test VIC doses well below 250 mg (25 mg, 50 mg, or 75 mg), and the dose escalation will stop once we identify the lowest biologically active and safe dose of VIC. PTCy is well-suited for investigating TAC-free GVHD prophylaxis with concurrent mTOR and Aurora kinase A inhibition to fully control aberrant CD28 activity in alloreactive T cells. Like mTOR and Aurora kinase A blockade, PTCy favors Treg reconstitution and potency while suppressing alloreactive donor T cells[13,14,15]. We propose to combine SIR plus VIC with PTCy to spare Tregs, prevent GVHD with durable immune tolerance, and maximize GVL.

VIC-1911 will be administered orally at 25 mg, 50 mg, or 75 mg BID from day +5 to day +45 according to the rules of our phase I study. The justification to administer VIC-1911 from days +5 to +45 is to ensure comprehensive CD28 blockade very early after transplant to suppress effectors of GVHD. However, prolonged deprivation of CD28 signals in Tregs can paradoxically impair their function[16,17,18]. Thus, by day +45, we expect single agent SIR maintenance will carry the allotolerance established by PTCy-allodepletion and deep CD28 blockade early post-transplant. The lowest biologically active and safe dose of VIC-1911 will be identified as the recommended phase I extension dose. The biologic activity of VIC-1911 will be informed by adequate reduction in $pH3ser10^+$, $CD4^+$ T cells (E.g., <54% at day 21). This threshold is based on the lower confidence interval of the normal, pretransplant frequency of %pH3ser10+, CD4+ T cells (Note: pH3ser10 is the phosphoprotein target of Aurora kinase A).[9]. Importantly, all patients with grade II-IV acute GVHD on the PAC/SIR/TAC trial had pH3ser10+ CD4+ T cells >54%[9]. Notably, the single patient with grade IV acute GVHD on the PAC/SIR/TAC trial had a 16-fold increase in $pH3ser10^+$, $CD4^+$ T cells at day +21, compared to pretransplant levels, yet the number of $pS6^+$, $CD4^+$ T at day +21 was negligible in the presence of SIR[9]. Unpublished data from patients with acute GVHD that failed standard SIR/TAC alone also averaged 84.3% pH3ser10+ CD4+ T cells at time of GVHD diagnosis. Therefore, we will assess VIC-1911 biologic activity by measuring the frequency of $pH3ser10^+$, $CD4^+$ T cells at day +21 and safety will be informed by DLT assessments.

3 Overview

This is a single-arm, phase I dose finding study of PTCY/sirolimus plus VIC-1911 to prevent grade II-IV acute GVHD and reduce relapse after alloHCT. The trial is powered to determine if Aurora kinase A inhibition with VIC-1911 reduces the frequency CD4+, pH3ser10+ T cells (phosphorylated histone 3 serine 10 is a biomarker of Aurora kinase A activity) and improves aGVHD and relapse after alloHCT, compared to historic data at the University of Minnesota.

Patients will receive myeloablative conditioning (MAC) with total body irradiation (TBI) followed by infusion of HLA-matched related or unrelated peripheral blood stem cells (PBSC) on day 0. Cyclophosphamide will be administered on days +3 and +4. Sirolimus targeting 8-12ng/ml will begin on day +5 until day +100, dose adjustment or taper if needed per section 6.5. VIC-1911 will be administered as 25 mg, 50 mg, or 75 mg orally BID from day +5 to day +45 according to the rules of our phase I study. The lowest biologically active and safe dose of VIC-1911 will be identified as the recommended phase I extension dose.

Dose Limiting Toxicity for the Phase 1 dose finding component is defined as (CTCAE v5):

1. The following ocular disorders:
    a. Grade 2 or higher vitreous hemorrhage not explained by thrombocytopenia
    b. Grade 3 or higher visual acuity decrease
    c. Grade 3 or higher watery eyes
    d. Grade 3 or higher keratitis
    e. Grade 3 or higher floaters
    f. Grade 3 or higher corneal microcyst
    g. Grade 3 or higher other eye disorders
2. Any grade 3 or above unexpected adverse event considered at least possibly related to VIC-1911. “Unexpected” is defined as a suspected adverse reaction is that is not listed in protocol-related documents (e.g. protocol, consent documents, investigator brochure), or is not listed at the specificity or severity that has been observed or given the characteristics of the subject population being studied. Included in this definition is higher than expected rates of adverse events than would be expected in the setting of transplant at the University of Minnesota as reflected in our stopping rules for excess toxicity (Section 14.4).

Biologic efficacy is defined as:

The proportion of patients with an average CD4+, pH3ser10+ T cell of <54%.

The maximum desired toxicity is 30% of patients having a DLT by day 28 and the minimum desired efficacy is 65% of patients with an average CD4+, pH3ser10+ T cell of <54% by day 21 (- 3 to +7 days).

The optimal dose will be identified using the EffTox design. Three dose levels of VIC-1911 will be tested (25 mg, 50 mg, or 75 mg BID). EffTox is an adaptive Bayesian design to facilitate seamless phase I dose-finding. In this trial, the measure for efficacy in the Phase I dose finding component (CD4+, pH3ser10+ T cell <54% by day 21) differs from the Phase I extension component our co-primary endpoints. Two parameters are required in the Phase I dose finding trial in addition to the desired toxicity and efficacy. The first is the trade-off function, which has been calculated as 1.79 based on points that are of equal utility: (1) the maximum permissible probability of toxicity when efficacy is guaranteed, (2) the minimum required probability of efficacy when toxicity is impossible and (3) a point in between that is considered equally desirable. The 2nd is the mean effective sample size (ESS) calculated as 0.90 based on the expected toxicity and efficacy at each dose, which is well within the advised range of 0.5 to 1.5. This framework combines experience from patients in the earlier part of the trial with clinicians' initial estimates of DLT's, efficacy and trade-off at each dose.

As the study progresses, updated probabilities of DLT and efficacy are computed before each new cohort of three patients is enrolled and the last patient reaches Day 28 (end of the assessment period) prior to enrollment of a subsequent cohort. All patients in a cohort must also achieve neutrophil engraftment prior to day 28 before enrollment of a subsequent cohort. Each subsequent cohort will be assigned to the most appropriate dose based on these updated probabilities. To promote patient safety: 1) patients will be enrolled in cohorts of 3 patients starting at the 1st dose; and 2) dose levels will not be skipped when escalating. The optimal dose will be identified by one of the following criteria: (1) the sample size of 21 is exhausted, (2) 9 patients are sequentially enrolled at the same dose.

After completion of the dose finding trial, the final doses will be carried forward into a phase I extension trial to confirm safety and obtain preliminary estimates of long-term efficacy as measured by rates of aGVHD and relapse.

4 Patient Selection

Study entry is open to patients 18 years of age and older regardless of gender, race, or ethnic background. While there will be every effort to seek out and include minority patients, the patient population the patient population is dependent upon the transplant population at the University of Minnesota.

A potential participant must meet all of the inclusion and exclusion criteria to be considered eligible for study participation.

4.1 Inclusion Criteria

4.1.1 Diagnosis of
- acute leukemia in complete remission, or
- myelodysplasia with <5% blasts, or
- myeloproliferative neoplasm/myelofibrosis with <5% marrow or circulating blasts, or
- chemosensitive Hodgkin or non-Hodgkin lymphoma

4.1.2 Age 18 years or older

4.1.3 Performance status of ≥ 80% Karnofsky

4.1.4 Adequate organ function within 28 days of study registration defined as:
- left ventricular ejection fraction ≥ 45%
- pulmonary function with FEV1, FVC, and DLCO ≥ 50% predicted
- AST and ALT < 2 times upper limit of normal
- total bilirubin <1.5 times the upper limit of normal. If the patient is suspected of having Gilbert syndrome, they require prior approval of the medical monitor
- estimated creatinine clearance ≥ 50cc/min
- no active/uncontrolled infection
- negative HIV, HBV and HCV
- ferritin < 2000 ng/ml

4.1.5 Patients able to tolerate oral medication

4.1.6 Women of childbearing potential and men with partners of child-bearing potential must agree to use of contraception for the duration of treatment through 60 days after the last treatment of VIC-1911 or sirolimus

4.1.7 Able to provide written voluntary consent prior to the performance of any research related tests or procedures.

4.2 Exclusion Criteria

4.2.1 HCT-CI > 4. Physicians determining subject's hematopoietic cell transplant comorbidity index (HCT-CI) score for subjects enrolling on study should use Sorror's guidance to standardize the interpretation of this instrument across patients.

4.2.2 Use of planned post-transplant maintenance therapy to begin prior to day +75. Patients may receive standard of care maintenance therapies starting at day +75 or later

4.2.3 Patients with a history of hypersensitivity to any of the investigational products

4.2.4 Pregnant or breastfeeding as agents used in this study are Pregnancy Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations, and Pregnancy category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Females of childbearing potential must have a negative pregnancy test (serum or urine) within 28 days of study registration.

4.2.5 Women or men of childbearing potential unwilling to take adequate precautions to avoid unintended pregnancy from the start of protocol treatment through 60 days after the last treatment of VIC-1911 or sirolimus

4.2.6 Participants must not be daily smokers of tobacco, marijuana or daily users of e-cigarettes/vaporizer pens within 1 month of study enrollment. Intermittent use (less than once per day) permitted.

5 Participant Registration and Study Enrollment

To be eligible for this study, the patient must sign the treatment consent and meet each inclusion criteria listed and none of the exclusion on the eligibility checklist based on the eligibility assessment documented in the patient's medical record. A copy of the eligibility checklist is under attachments within the study in OnCore.

Written consent must be obtained prior to the performance of any research related tests or procedures. Consent is usually obtained before final eligibility is determined.

5.1 Registration with the Masonic Cancer Center Clinical Trials Office

Any patient who has been consented is to be registered in OnCore by the Primary Clinical Research Coordinator (PCRC) or designee. If a patient is consented, but not enrolled, the patient's record is updated in OnCore as a screen failure and reason for exclusion recorded.

5.2 Study Enrollment with the Masonic Cancer Center Clinical Trials Office

Study enrollment occurs after final eligibility is determined.

5.3 Dose Level Assignment

Up to 3 dose levels of VIC-1911 will be tested in this study. The Primary Clinical Research Coordinator (PCRC) or designee will assign the patient's dose level in

OnCore. The dose level of VIC-1911 will be assigned based on the currently enrolling dose for that phase of the trial.

5.4 Patients Who Do Not Begin Study Treatment

If a patient is enrolled in the study and is later found not able to begin study treatment (beginning with the conditioning regimen), the patient will be removed from study and treated at the physician's discretion. The study staff will update OnCore of the patient's non-treatment status (off study). The reason for removal from study prior to starting study treatment will be clearly indicated in OnCore. The patient will be replaced to complete enrollment.

5.5 Patients Who Do Not Complete Study Treatment

A patient must receive scheduled VIC-1911 through day +21 without confounding medical complications (including but not limited to those requiring high-dose corticosteroids or other immune modulators) to be assessed for response. If a patient does not qualify for response assessment, they will be considered not evaluable and can be replaced with another study participant.

6 Study Treatment Plan

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, antimicrobials, etc.

6.1 Pre-transplant conditioning regimen: TBI

Table 2: Treatment Plan - Myeloablative Conditioning (MAC) with TBI		
Day	**Drug/Procedure**	**Dose and Route**
-4	start allopurinol 300 mg/day PO	
-4	TBI AM, PM	165 cGy each dose
-3	TBI AM, PM	165 cGy each dose
-2	TBI AM, PM	165 cGy each dose
-1	TBI AM, PM	165 cGy each dose
0	HCT	Per Institutional practice
+3	Cyclophosphamide	50 mg/kg
+4	Cyclophosphamide	50 mg/kg
+5	Begin VIC-1911 Begin Sirolimus	Per dose level cohort: 25 mg, 50 mg, or 75 mg targeting 8-12ng/ml

TBI will be given on days -4 through day -1 using the following institutional guidelines:

- 1320 cGy administered in 8 fractions of 165 cGy each with 2 fractions being given each day

- Each fraction will be 165 cGy prescribed to the mid-plane at the level of the umbilicus
- The dose rate will be 10 to 19 cGy/minute
- The two daily fractions are given at least 6 hours apart.

Testicular boosts should be used for all males with ALL (and according to institutional practice for other diseases).

Refer to Appendix II for risks associated with TBI.

6.2 Pre-transplant alternative conditioning regimen for participants with Busulfan/Fludarabine

Table 3:Treatment Plan - Myeloablative Conditioning (MAC) With Busulfan/Fludarabine		
Day	**Drug**	**Dose and Route**
-6	-start allopurinol 300 mg/day PO -begin levetiracetam per institutional guidelines through day-1	
-5	Busulfan[1]	130 mg/m^2 IV once daily over 3 hours
	Fludarabine	40 mg/m2 IV
-4	Busulfan	IV once daily over 3 hours
	Fludarabine	40 mg/m2 IV
-3	Busulfan	IV once daily over 3 hours
	Fludarabine	40 mg/m2 IV
-2	Busulfan	IV once daily over 3 hours.
	Fludarabine	40 mg/m2 IV
-1	Rest	
0	HCT[2]	Per institutional practice
+3	Cyclophosphamide	50 mg/kg
+4	Cyclophosphamide	50 mg/kg
+5	Begin VIC-1911 Begin Sirolimus	Per dose level cohort: 25 mg, 50 mg, or 75 mg targeting 8-12ng/ml

1 Busulfan: Initial dosing 130 mg/m2/dose for patients age 18 years or older. Therapeutic drug monitoring per Institutional Standard of Care. if available model-based dosing utilizing Bayesian methodology.
2 Refer to section 6.2.1 for note on timing of infusion if donor requires additional apheresis

Patients should not take azole anti-fungal drugs for one week prior to beginning conditioning chemotherapy.

Fludarabine (day -5, -4, -3 and -2)

Fludarabine will be given at a dose of 40 mg/m2 IV, administered as a 1 hour infusion per institutional guidelines on day -5 through day -2. Dose adjustments will be made for patients with renal impairment defined as CrCL < 70mL/minute. Fludarabine dose MAY also be

reduced if there is prior malignancy involvement of the central nervous system with intrathecal chemotherapy and/or cranio-spinal irradiation.

Busulfan (day -5, -4, -3 and -2)

Dosing Guidelines based on Therapeutic Drug Monitoring (TDM):

Busulfan dosing and administration and therapeutic drug monitoring (TDM) per institutional guidelines. Initial busulfan dosing will be determined by model-based dosing utilizing Bayesian pharmacokinetic software with a cumulative area under the curve (cAUC) of 82.1 mg*hr/L. For patients age 18 or older, initial dose of 130 mg/m2/dose will be utilized.

Busulfan area under the curve (AUC) analyses will be calculated per University of Minnesota BMT SOC guidelines for all BMT patients. Busulfan therapeutic drug monitoring (TDM) will be used to target a cumulative exposure for the entire course cAUC= 78 -86.2 mg*h/L (with a target of 82.1 mg*h/L) . Results of TDM performed with the first dose will inform subsequent busulfan dosing. Refer to Busulfan SOC Guidelines for blood sample collection process, busulfan results reporting and TDM procedures. If this method of pharmacokinetic monitoring is not available at other sites, blood samples will be sent to the Fairview Hospital Laboratory (Lab Code LAB6416) and analyzed by pharmacists at the University of Minnesota.

Levetiracetam (Keppra)

As seizures have occurred following high dose busulfan, all patients will be treated with Keppra beginning day -6 and continuing until day -1 per institutional guidelines.

Refer to Appendix II for risks associated with this treatment plan.

6.3 Stem Cell Selection and Infusion

The stem cells will be infused per cell source specific institutional guidelines.

6.3.1 Related Donor Peripheral Blood

Related donors will be selected, evaluated and collected according to institutional guidelines (MT2012-14C: Procedure Guidelines For Related Hematopoietic Stem Cell Donors). A target collection of 5 x 10^6 CD34+ cells/kg will be requested in the case of peripheral blood stem cells as the graft source. Note that if a related donor undergoes a second apheresis session to collect the target number of peripheral blood stem cells, the product should be held at MCT until both collections have been completed. The entire collection yield should be infused on the same day, the patient

in effect has two "Day 0s" (a rest day, then an infusion day) and the days of post-transplant cyclophosphamide should be adjusted accordingly to be days +3 and +4 post-stem cell infusion. The post-transplant sirolimus and VIC-1911 should be adjusted accordingly to be days +5 post-stem cell infusion.

6.3.2 Unrelated Donor Peripheral Blood

Unrelated donor PBSC will be collected in the usual manner using established techniques determined by the National Marrow Donor Program. Collection of the products will follow registry practice and guidelines. A target collection of 5 x 10^6 CD34+ cells/kg will be requested in the case of peripheral blood stem cells as the graft source with a minimum of 2 million CD34+ cells/kg.

6.3.3 Infusion

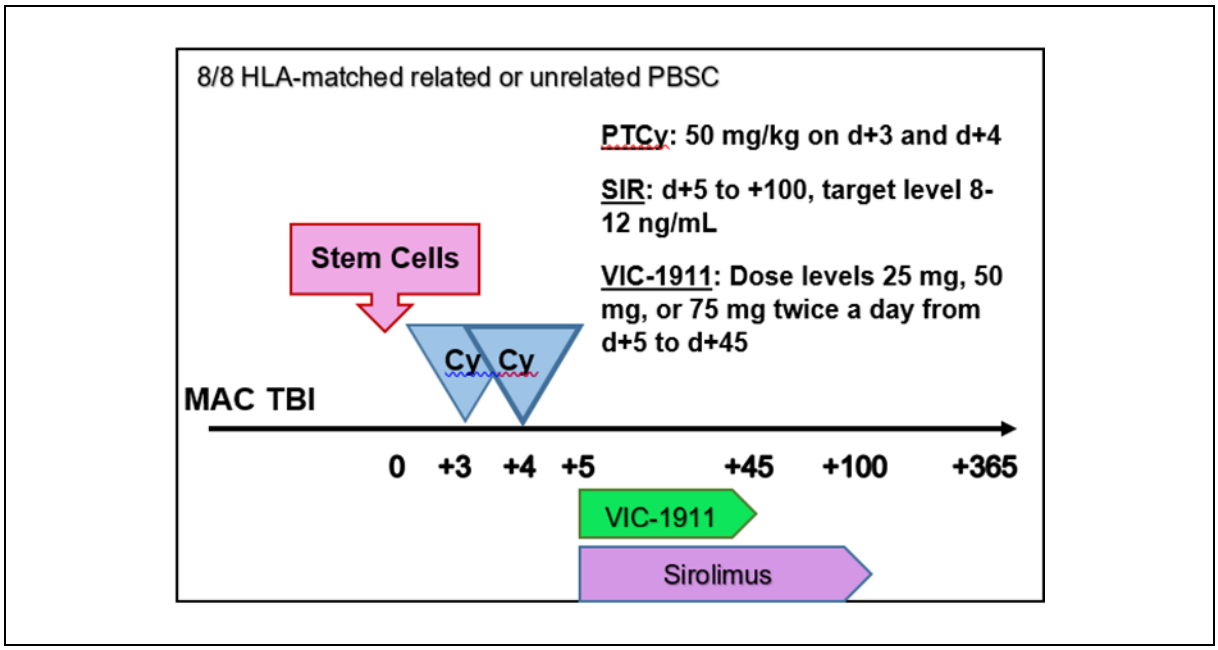
Recommended Pre-medication: acetaminophen 15 mg/kg (max 650 mg) PO and diphenhydramine 0.5 mg/kg (25 mg) PO/IV

Extra hydration is recommended per institutional guidelines for ABO mismatched and cryopreserved grafts.

Vital signs will be checked before and after the infusion, and one hour post infusion per University of Minnesota transplant guidelines. More frequent vital signs may be required as clinically indicated.

Refer to Appendix II for risks associated with stem cell infusion.

Table 3: Phase I dose finding/phase 1 extension GVHD Prevention Trial Schema



6.4 Post-Transplant Cyclophosphamide (days +3 and +4)

Cyclophosphamide will be administered on days +3 and +4. Cyclophosphamide will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs less than IBW, in which case the drug will be dosed according to their actual body weight (ABW)

Hydration and uroprotection with mesna will be given according to institutional standards. Cyclophosphamide 50mg/kg will be given as an IV infusion over 1-2 hours (depending on volume) on Days +3 post-transplant (between 60 and 72 hours after stem cell infusion) and on Day +4 post-transplant (approximately 24 hours after Day +3 cyclophosphamide).

Refer to Table 7 for toxicities associated with Cyclophosphamide

6.5 VIC-1911 starting Day +5

6.5.1 Phase 1: 25 mg, 50 mg, or 75 mg of VIC-1911 administered orally BID from day +5 to day +45. The Primary Clinical Research Coordinator (PCRC) or designee will assign the patient's dose level in OnCore. All VIC-1911 doses will be given in the fasting state (ie, for at least 1 hour before or 2 hours after the morning and evening meals).

6.5.2 Phase I extension: The lowest biologically active and safe dose of VIC-1911 will be identified as the recommended phase I extension dose. All VIC-1911

doses will be given in the fasting state (ie, for at least 1 hour before or 2 hours after the morning and evening meals).

6.5.3 Recommended supportive care for the duration of VIC-1911 treatment (day +4 to +45) to reduce the risk of ocular toxicity:

6.5.3.1 Prednisolone acetate ophthalmic solution 1% twice daily

6.5.3.2 Brimonidine tartrate ophthalmic solution 0.2% twice daily

6.6 Sirolimus starting Day +5

Sirolimus targeting 8-12ng/ml will begin on day +5 until day +100

- Loading Dose on Day +5: Sirolimus 5 mg/m2/day PO ONCE (max of 8 mg/day)
- Maintenance Dose starting Day +6: Sirolimus 2.5 mg/m2/day PO DAILY

Sirolimus dose should be reduced according to institutional guidelines for concomitant voriconazole or other drugs with strong interactions. Refer to Table 6 for toxicities associated with sirolimus.

Dose reductions for sirolimus when using concurrent voriconazole or Posaconazole are as follows:

Table 6A: Dose reductions for sirolimus when using concurrent voriconazole or posaconazole	
Sirolimus	Reduce sirolimus dose by 66-90%

In the case of persistent, otherwise unexplained cytopenias (hemoglobin <8 g/dL, ANC <1.0 e^3/µL, OR platelets <50,000 e^3/µL), sirolimus may be tapered per institutional guidelines.

6.7 Dose Delays/Dose Modification for VIC-1911

A maximum of two dose reductions are allowed per patient. Dose Reductions for VIC-1911 should be made according to the dose levels outlined in Section 6.4.

- Dose reductions are not permitted in Dose Level 1.
- Only one dose reduction is permitted in Dose Level 2.
- A maximum of 2 dose reductions are allowed per patient in Dose Level 3 across the entire duration of their treatment.

Should the toxicities that require further dose reduction recur after the maximum dose reductions or dose reduction is not permitted based on the patient's current dose level, the affected patient should be discontinued from treatment.

Patients requiring a dose reduction will not be allowed to re-escalate the dose throughout the rest of treatment. If during any cycle a patient experiences a drug-related toxicity that results in the patient receiving less than 80% of the intended dose, then the patient requires a dose reduction by 1 level when resuming therapy. Patients experiencing study drug-related toxicities that require a delay in schedule VIC-1911 dosing for > 14 days will require a dose reduction when resuming therapy. Patients experiencing study drug-related toxicities that require a delay in scheduled VIC-1911 dosing for > 28 days will be discontinued from further treatment in this study. Details of procedures and criteria for dose reduction are shown as follows:

- Table 3 provides the criteria and procedure for making VIC-1911 dose modifications for hematologic toxicity considered related to VIC-1911 within a cycle.
- Table 4 provides the criteria and procedure for making VIC-1911 dose modifications for non-hematologic toxicity considered related to VIC-1911 within a cycle.
- Table 5 provides common toxicities for VIC-1911

Table 3:Dose Modifications for Hematologic Toxicity.

*Note these modifications take effect only in the setting of secondary cytopenias **AFTER** engraftment (defined as the 3rd consecutive day of ANC ≥ 1000 for neutrophils and the 3rd consecutive day of ≥75,000 for platelets).*

ANC ≥ 1000/mm^3 and Platelets ≥ 75,000/mm^3	No dose reduction (treat on time)
ANC < 1000/mm^3 or Platelets < 75,000/mm^3	Hold
Febrile Neutropenia **or** Any Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with bleeding **or** Any Grade 4 neutropenia lasting > 7 days	Hold Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment.

Table 4: Dose Modifications for Non-Hematological Toxicities Related to VIC-1911

CTCAE Grade[a] of Non-Hematologic Toxicity	Dose Hold/Resumption	Resumption dose
Grade 1 or 2	Maintain treatment at the same dose level	No dose adjustment
Grade 3 or higher unexpected AE	Hold until AE is Grade 0 or 1	Reduce VIC-1911 by 1 dose level

[a] At the discretion of the Investigator, patients may continue on study medication at the same dose without a reduction or an interruption for AEs (irrespective of grade) considered unlikely to become serious or life-threatening (including, but not limited to, fatigue and dry skin).

6.8 Dose Delays/Dose Modification for Sirolimus

Dose adjustments and withholding of sirolimus for elevated blood levels will occur based upon institutional guidelines for dosing and monitoring sirolimus

In the case of persistent, otherwise unexplained cytopenias (hemoglobin <8 g/dL, ANC <1.0 e^3/µL, OR platelets <50,000 e^3/µL), sirolimus may be tapered per institutional guidelines.

6.9 General Concomitant Medication Guidelines

All immune-modulating medications and therapies that are administered during the study must be recorded in the patient's CRF and in the source documents. Concomitant medications for other medical conditions are permitted as clinically indicated, subject to specific protocol requirements outlined below. Additional concomitant medications administered to manage reportable adverse events (AEs) per section 10.2 should be recorded in the patient CRF, with the AE being treated with the medication listed as the indication for use.

- Administer hematologic support as medically indicated (blood transfusions, G-CSF, etc) according to the institutional site standards. If there are no standard procedures for the use of growth factors, follow American Society of Clinical Oncology (ASCO) "Guidelines for Use of Hematopoietic Colony-Stimulating Factors" available at www.asco.org.

The primary route of elimination of VIC-1911 is glucuronidation. The major metabolite is the acyl glucuronide conjugate (M1), representing 31% of the total radioactivity peak after 4 hours in a human hepatocyte study. The only other metabolite identified (M2) represented < 1% of the total peak area and was not conclusively shown as a separate component.

An *in vitro* study with human liver microsomes demonstrated that VIC-1911 has the potential to inhibit CYP2C8 and CYP3A4/5, including metabolism-dependent inhibition. However, for CYP2C8, the inhibition seen upon pre-incubation with NADPH was reversible, indicating that it may be mediated by metabolites of VIC-1911. The IC_{50} of metabolism-dependent inhibition for CYP2C8 (14 µM, equivalent to 7080 ng/mL, well above the C_{max} that will be achieved in this study) was less than 2-fold lower than that of the direct IC_{50}, and occurred at a relatively high concentration, which indicates that the clinical impact may be low. For CYP3A4/5, the inhibition seen upon pre-incubation with NADPH was only partially reversible, and a K_i of 37 µM (for midazolam 1'-hydroxylation) was determined. The K_i for the other CYP3A4/5 substrate (testosterone 6β-hydroxylation; 200 µM) was substantially higher. The lower K_i value of 37 µM (equivalent to 18700 ng/mL) was also a relatively high concentration, again, well above the C_{max} that will be achieved in this study. Therefore, the clinical impact should be low.

An *in vitro* human hepatocyte study indicated that at a concentration of 10 µM, VIC-1911 may induce CYP3A4, although the concentration of VIC-1911 which showed *in vitro* induction was relatively high (10 µM, equivalent to 5060 ng/mL, again, well above the Cmax that will be achieved in this study. Therefore, the clinical impact should be low.

In this study, VIC-1911 was administered once daily to 2 patients taking fluconazole, a moderate inhibitor of CYP3A4, with no impact on the pharmacokinetics of VIC-1911. C_{max} was similar between patients given VIC-1911 once or twice daily. The AUC_{last} was approximately half for patients on fluconazole when VIC-1911 was given once daily vs. twice daily administration for patients not on fluconazole, with no sustained elevated plasma concentrations after a single daily dose. By 24 hours post-first dose (24 hours after the dose for patients given VIC-1911 once daily), the AUC was not elevated post-dose after fluconazole administration. Dose-normalizing these data to VIC-1911 once or twice daily administration from other VIC-1911 studies in which CYP3A4 inhibitors were not routinely administered concomitantly, there is no evidence of a drug-drug interaction with CYP3A4 inhibitors in this study.

Additionally, the following information is based on results from *in vitro* studies. Caution is advised if these drugs are given concomitantly.

- P-gp inhibitors/inducers: VIC-1911 is a substrate of P-gp. P-gp inhibitors/inducers may alter the PK and activity of VIC-1911.
- OATP1B1/1B3 substrates: VIC-1911 is a potential inhibitor of OATP1B1/1B3. VIC-1911 may alter the PK and activity of OATP1/1B3 substrates.
- OATP1B1/1B3 inhibitors: VIC-1911 is a substrate of OATP1B1/1B3. OATP1B1/1B3 inhibitors may alter the PK and activity of VIC-1911.

6.10 Duration of Study Treatment

Treatment continues until one year unless any of the following occurs:

- Patient develops GVHD requiring systemic investigational intervention
- Patient develops relapse requiring systemic intervention
- Unacceptable toxicity
- One of the study drugs must be permanently discontinued
- Patient requests or patient is non-compliant

6.11 Duration of Study Participation

Patients will be followed for GVHD and standard BMT survival data to a maximum of 12 months from the start of study treatment unless one of the following occurs:

- Consent is withdrawn
- The patient is unevaluable

7 Study Agent Information

7.1 VIC-1911

7.1.1 Other Names

Previously called TAS-119

7.1.2 Product Description

Molecular Formula	$C_{23}H_{22}Cl_2FN_5O_3$ HCl		
Molecular Weight	542.82		
Appearance	White to off-white solid		
pH-Solubility Profile	Solvent (20° C)	mg/mL	USP Definition
	Water	0.169	Very slightly soluble
	Methanol	344.1	Freely soluble
	Ethanol (absolute)	32.84	Sparingly soluble
	0.1 mol/L HCl	1.298	Slightly soluble
	0.1 mol/L NaOH	1.679	Slightly soluble

VIC-1911 drug products are immediate release, film coated tablets. The tablets are packaged in 50 mL High Density Polyethylene (HDPE) bottles. The bottles are sealed with a solid medicinal safe cap. Each bottle contains 60 tablets. There are 2 strengths: 10 mg and 25 mg. The different strengths are clearly differentiated by shape and color as follows:

- VIC-1911 Tablet (10 mg): round shape, white to off-white tablet
- VIC-1911 Tablet (25 mg): caplet shape, white to off-white tablet

7.1.3 Procurement

VITRAC Therapeutics, LLC (VITRAC) will supply VIC-1911 at no charge to patients participating in this clinical trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

7.1.4 Storage Requirements

Store in bottles between 15° and 25° C, and protect from light.

7.1.5 Preparation and Administration

- Store VIC-1911 at room temperature (15°C – 25 °C).
- Only remove the amount of VIC-1911 needed at the time of dosing.
- Do not remove doses in advance of the next scheduled dosing.
- Bring all used and unused bottles to the site at each visit.
- Keep VIC-1911 bottles in a safe place and out of sight or reach of children.
- VIC-1911 should be taken in the fasting state (ie, at least 1 hour before or 2 hours after the morning or evening meal) with a glass of water.
- Doses are not to be replaced if the patient misses a dose or vomits a dose.
- Patients should make every effort to take doses on schedule.
- Record all doses taken or missed in the Patient Diary.

7.1.6 Drug Accountability and Destruction

VIC-1911 must be dispensed only from official study sites and to eligible patients under the supervision of the site investigator. VIC-1911 should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to patients. After final drug reconciliation, unused VIC-1911 will be disposed at the site following procedures for the disposal of anticancer drugs.

7.1.7 Warnings and Precautions

At the present time, there is limited clinical experience with VIC-1911 in monotherapy in humans. Therefore, investigators should be observant for any signs of toxicity.

Refer to the Investigator Brochure for additional information

7.1.8 Expected Toxicities

Below (Table 5) is a cumulative list of serious related adverse events reported from any VIC-1911 (TAS-119) clinical trials through 01 May 2017.

Table 5: SAEs

Common (≥ 10%)	Less Common (≥ 5%)	Rare (≤ 2% or less)
Anemia	Corneal changes (microepithelial cysts, keratitis, punctate keratitis)	Blepharitis
Vision blurred	Chest pain	Cataract
Abdominal pain/discomfort	Pain in extremity	Conjunctival hemorrhage
Constipation	Pyrexia	Eye irritation
Diarrhea	Upper respiratory tract infection	Eye pain
Nausea	Blood bilirubin increased	Dry eye
Vomiting	Blood glucose increased	Conjunctivitis
Fatigue	Blood albumin increased	Lacrimation increased
Decreased appetite	Blood potassium decreased	Ulcerative keratitis
Pain (general, back, flank, musculoskeletal)	Blood sodium decreased	Visual acuity reduced
Urinary tract infection	Blood calcium decreased	Intraocular pressure increased
ALT increased	Blood phosphorus decreased	Vitreal hemorrhage
AST increased	Hematuria (blood in urine)	Retinopathy
ALP increased	Hemoptysis	Colitis (including ulcerative)
Blood creatinine increased	Alopecia	Dry mouth/throat
Gamma-glutamyltransferase increased	Pruritis	Dyspepsia
Lipase increased	Hypertension	Hemorrhoids (including hemorrhagic hemorrhoids)
Weight decreased	Abdominal distention	Esophageal obstruction
Headache	Dysgeusia (altered taste)	Oral pain
Cough	Arthralgia	Mucosal inflammation
Dyspnea (difficulty breathing)	Weight increased	Stomatitis
Rash (including maculo-papular, pustular)	Edema peripheral	Dysphonia (difficulty speaking)
Pruritis (itching)	*Candida* infection	Chills
Hypotension	WBC count decreased	Pancreatitis
	Flushing (skin)	Jaundice
		Cholangitis
		Lung infection/pneumonia

Table 5: SAEs

Common (≥ 10%)	Less Common (≥ 5%)	Rare (≤ 2% or less)
		Neutrophil count decreased
		Febrile neutropenia
		Dizziness
		Somnolence
		Anxiety
		Insomnia
		Paresthesia
		Peripheral neuropathy
		Hydronephrosis
		Urinary retention

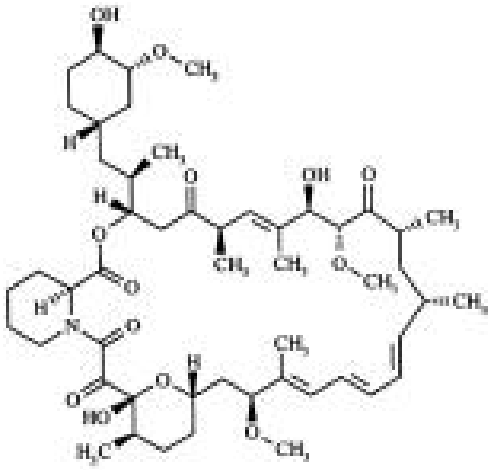
7.2 Sirolimus

7.2.1 Other Names

Rapamune, rapamycin

7.2.2 Product Description

Rapamune (sirolimus) is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by Streptomyces hygroscopicus. The chemical name of sirolimus (also known as rapamycin) is (3S,6R,7E,9R,10R,12R,14S,15E,17E,19E, 21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S, 3R,4R)-4-hydroxy-3-methoxycyclohexyl] -1-methylethyl]-10,21-dimethoxy-6,8,12, 14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4H,6H,31H)-pentone. Its molecular formula is C51H79NO13 and its molecular weight is 914.2. The structural formula of sirolimus is illustrated as follows.



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

7.2.3 Procurement

This drug is commercially available by prescription. It will be dispensed by the outpatient pharmacy and billed to the patient's insurance.

7.2.4 Storage Requirements

Rapamune Oral Solution bottles should be stored protected from light and refrigerated at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, the contents should be used within one month. If necessary, the patient may store the bottles at room temperatures up to 25°C (77°F) for a short period of time (e.g., not more than 15 days for the bottles).

Refer to package insert for additional information.

7.2.5 Preparation and Administration

Per package insert

7.2.6 Stability

Per package insert

7.2.7 Drug Accountability and Destruction

Sirolimus must be dispensed only from the pharmacy and to eligible patients under the supervision of the study team. Sirolimus should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to patients on this study.

The drug will be destroyed per hospital pharmacy SOPs.

7.2.8 Warnings and Precautions

Refer to the current package insert for the most up to date information.

Increased Susceptibility to Infection and the Possible Development of Lymphoma
Hypersensitivity Reactions
Angioedema
Fluid accumulation and wound healing
Hyperlipidemia
Renal function
Proteinuria
Latent viral infections

Interstitial lung disease
Skin cancer
Interaction with Strong Inhibitors and Inducers of P-gp
Pregnancy Category C

7.2.9 Expected Toxicities

Refer to the current package insert for the most up to date information.

Table 6: Sirolimus

Common	Less Common	Rare
Nausea, Vomiting Diarrhea Hypertension Increased Creatinine Hypercholesteremia, Hypertriglyceridemia	Rash Infections (e.g. nasopharyngitis); Edema; Weight Gain, Arthralgia; Tremor; Acne; Myelosuppression; Abdominal Pain; Fatigue; Myalgia; Chest Pain; Dizziness; Hypokalemia; Hypophosphatemia; Hyperglycemia (diabetes mellitus) Stomatitis, Wound Complications	Angioedema Hepatotoxicity Hirsutism, Secondary Lymphoma, PulmonaryHemorrhage Interstitial Lung Disease

7.3 Cyclophosphamide

7.3.1 Other Names

Cytoxan

7.3.2 Product Description

Antineoplastic Agent, Immunosuppressant

7.3.3 Procurement

This drug is commercially available by prescription. It will be dispensed by the outpatient pharmacy and billed to the patient's insurance.

7.3.4 Storage Requirements

Refer to package insert for additional information.

7.3.5 Preparation and Administration

Refer to package insert for additional information.

7.3.6 Stability

Refer to package insert for additional information.

7.3.7 Drug Accountability and Destruction

Cyclophosphamide must be dispensed only from the pharmacy and to eligible patients under the supervision of the study team. Cyclophosphamide should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to patients on this study.

The drug will be destroyed per hospital pharmacy SOPs.

7.3.8 Warnings and Precautions

- To reduce the risk of hemorrhagic cystitis, Mesna and adequate hydration will be administered per institutional guidelines

- Pregnancy Category D

)Refer to the Investigator Brochure (if investigational) or Package Insert (if commercially available) for additional information

7.3.9 Expected Toxicities

Table 7: Cyclophosphamide

Common	Less Common	Rare
nausea/vomiting mucositis sterility severe suppression of blood counts diarrhea fluid weight gain/edema alopecia	hemorrhagic cystitis	Cardiomyopathy skin rash SIADH (Syndrome of Inappropriate Anti-diuretic Hormone)

8 Dose Delays/Dose Modifications or Management of Selected Toxicities

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used to grade adverse events. A copy of the CTCAE v 5.0 can be downloaded: (https:// ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

Study product (VIC-1911) dose modifications are listed in Section 6.6.

As increased lipase is a commonly observed toxicity of VIC-1911, weekly surveillance of lipase levels will be performed from day +5 to day +45 or while taking VIC-1911.

Cyclophosphamide and Sirolimus

Management of toxicities from cyclophosphamide and sirolimus will be per the package insert and standard institutional guidelines.

9 Study Calendar

All clinical and research evaluations are listed in Table 9. Scheduled evaluations up to Day 28 may be performed - 3 to +7 days from the targeted date; assessments to be performed after Day 28 may be done +/-7 days of the targeted date. In addition, targeted days may be altered as clinically appropriate.

9.1 Required Evaluations

All clinical evaluations are standard of care and will be done according to current institutional guidelines. Post-transplant and some pre-transplant monitoring are suggested guidelines and should be tailored for each patient's clinical case. Minor modifications to the patient's care made for increased patient convenience and/or safety are not considered deviations.

Patients should undergo a standard eye examination to assess their vision prior to initiating dosing and at intervals during the study. The standardized eye examination consists of the following evaluations: visual acuity, pupil shape and pupillary reflexes, extraocular motility and alignment, tonometry, visual field, external examination, slit-lamp examination, and fundoscopy. Every attempt should be made to have the same ophthalmologist perform all of the vision assessments for a given patient.

Table 9: Study Calendar	Pre-transplant work-up	Conditioning Regimen	Day 0	Days in Reference to the transplant		
				Day 1 to engraftment	Follow-up Days 31-100	6 months, 1 year
Informed consent	X					
Medical history	X			Daily	Weekly	X
Physical exam	X			Daily	Weekly	X
Radiation Therapy consult[1]	X					
Performance status	X			Day 28	X (Day 100)	X
Height/Weight	X					
GVHD evaluation				Weekly	Weekly	Prn

Table 9: Study Calendar	Pre-transplant work-up	Conditioning Regimen	Day 0	Days in Reference to the transplant		
				Day 1 to engraftment	Follow-up Days 31-100	6 months, 1 year
CMV Surveillance	X			Weekly	Weekly	Prn
Toxicity Assessment				Weekly	Weekly	X
Monitoring for Stopping Rule Events and Reportable Events per Section 10.2 Section 10.3 and Section 10.4				Weekly	Weekly	Prn
FACT-BMT Quality of LIfe Survey[21] (Appendix III)	X			Day 21	Day 100	
Routine Laboratory						
CBC, diff, platelet	X			Daily	Weekly	X
PT/PTT	X			As clinically indicated		
Full metabolic panel	X			2x/weekly	Weekly	X
Basic metabolic panel				Daily		
Urine or serum pregnancy test for females of childbearing potential	X					
Chimerism – CD3/CD33	X			Day 21 - 3 to +7 days	Day 100 +/- 7 days	Prn
Lipase levels				Weekly from day +5 through day +45*		
Intervention						
TBI[1]		Days -4, -3, -2, -1				
Busulfan[2]		Days -5, -4, -3, -2				
Fludarabine[2]		Days -5, -4, -3, -2				
Stem Cell Infusion			X			
Cyclophosphamide				Days +3, +4		
Eye Drops				Prednisolone acetate ophthalmic solution 1% BID and		

Table 9: Study Calendar	Pre-transplant work-up	Conditioning Regimen	Day 0	Days in Reference to the transplant		
				Day 1 to engraftment	Follow-up Days 31-100	6 months, 1 year
				11.1.1 Brimonidine tartrate ophthalmic solution 0.2% BID Days +4 to +45		
VIC-1911				Day +5 through +45		
Sirolimus				Day +5 through +100		
Research Blood Draw						
VIC-1911 Pharmacokinetics				Day 5, Day 15*		
Research samples (8 green top tubes, 1 pax gene tube)	Pre-transplant			Day 21 - 3 to +7 days	Day 60 +/- 7 days	Day 100 +/- 7 days
Procedures						
Ophthalmologic Evaluation	Pre-transplant			Day 28 +/- 3 days	Day 100 +/- 7 days	Prn
EKG	X			As clinically indicated	As clinically indicated	As clinically indicated
TTE	X			As clinically indicated		
Chest x-ray	X			As clinically indicated		
Bone Marrow Biopsy/Aspirate with specific studies (e.g. morphology, immunophenotyping, FISH, cytogenetics, PCR, etc.) as clinically indicated	X			X (Day 28 - 3 to +7 days	X (Day 100 +/- 7 days)	X
PFT	X					

* for subjects on Phase I (N=up to 9) while taking VIC-1911

[1]for subjects on TBI conditioning regimen

[2]for subjects on alternative busulfan/fludarabine regimen

If day 5 or 15 falls on a weekend or holiday, PK samples can be obtained on the closest weekday occurring after the post-transplant day, no more than 3 days later. Plasma samples will be collected pre-dose, +30 minutes, +1 hours, +2 hours, +6 hours, and +24 hours (pre-morning dose) for the first 3 subjects at each dose level. Pharmacokinetics will not be obtained for the 6 subjects in the phase 1 expansion cohort.

Research Related Tests and Procedures

Research sample collection is tied to the clinical care schedule of events and their associated window for performance. Therefore, if a clinical time point does not occur or is altered, the research related time point will be adjusted (or eliminated) as appropriate.

It is recognized that with novel therapies as used in this study, the timing of protocol directed research samples may miss important patient specific events. For this reason, up to 3 extra samples for a total of 180 ml of blood may be drawn at additional time points that are not specified above.

Translational Therapy Lab will receive the required blood draws on pre-conditioning, +21, +60, and +100 and complete preliminary processing. De-identified samples without PHI will be batch shipped to:

Roswell Park Comprehensive Cancer Center
Brian C. Betts MD Lab
665 Elm Street
Buffalo, New York 14203
c/o Clinical Practice Plan

Betts Lab will run laboratory and correlative studies related to the clinical trial.

10 Event Monitoring, Documentation, and Reporting

Toxicity and adverse events will be classified and graded according to NCI's Common Terminology Criteria for Adverse Events V 5.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from the CTEP home page. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

The following definitions of adverse events (AEs) and serious adverse events (SAEs) will determine whether the event requires expedited reporting via the SAE Report Form in addition to routine documentation in the OnCore AE case report form (CRF).

Note: for the purposes of this study, the study related treatment of VIC-1911 is considered the investigational product, “study drug.”

10.1 Event Terminology

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Event: An adverse event is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death

- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Event: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in protocol-related documents (e.g. protocol, consent documents, investigator brochure), or is not listed at the specificity or severity that has been observed or given the characteristics of the subject population being studied.

Attribution: is the relationship between an adverse event or serious adverse event and the study drug. Attribution is assigned as follows:

- Definite – The AE is clearly related to the study drug
- Probable – the AE is likely related to the study drug
- Possible – the AE may be related to the study drug
- Unlikely – the AE is doubtfully related to the study drug
- Unrelated – the AE is clearly not related to the study drug

Attribution must be assigned by the treating physician or the PI.

The following definitions are from the Masonic Cancer Center's Data and Safety Monitoring Plan (https://z.umn.edu/dsmp)

Major Deviation: A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

Minor Deviation: A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

10.2 AE Monitoring and Documentation Requirements

Adverse event collection for the purposes of this study will focus on events felt to be related to VIC-1911 or events that cannot be attributed to other causes (i.e. transplant-related, co-morbidities).

Monitoring for adverse events will begin with the first dose of VIC-1911 through the 30 days after the last dose of VIC-1911.

Adverse event documentation for the purposes of this study will focus on:

- unexpected grade 4 or greater events
- expected toxicities felt to be related to the VIC-1911
  - Grade 2 or higher vitreous haemorrhage unrelated to thrombocytopenia
  - Grade 3 or higher visual acuity decrease
  - Grade 3 or higher watery eyes
  - Grade 3 or higher keratitis
  - Grade 3 or higher floaters
  - Grade 3 or higher corneal microcyst, or other eye disorders
  - Any grade 3 or above unexpected adverse event considered at least possibly related to VIC-1911.
- unexpected adverse events that cannot be attributed to the transplant procedure or other causes (i.e. underlying disease, co-morbidities)

After the End of Treatment visit, monitoring for adverse events will become less frequent based on the schedule in Table 9 and only events that are unexpected and at least possibly related to VIC-1911 will be documented upon knowledge.

10.3 SAE and Death Documentation

Any event meeting the definition of a serious adverse event (SAE) requires documentation using the MCC SAE Report Form in OnCore.

Deaths, including due to disease, within the follow-up period will be recorded as an SAE. Deaths due to disease should be recorded as a Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease).

In addition, upon knowledge, the death date and cause must be reported in the patient follow-up tab in OnCore using the comment field in the survival status section to record the cause.

10.4 Dose Limiting Toxicity Event/Early Stopping Rule Documentation and Reporting

All patients enrolled in Phase I dose-finding cohort are monitored for dose limiting toxicity (DLT) and excessive toxicity (early stopping events) specific to the Component. Refer to Section 3 and Section 14.4 for definitions.

In addition to documenting the event in the study's CRF's, all DLTand SR events are to be documented on the Event Form found in OnCore per Masonic Cancer Center procedures.

An event that counts as a DLT does not necessarily constitute a SAE and should be reported as such only if they meet the criteria for reporting as defined in Section 10.5.

DLTs do not apply to the Phase I extension portion of the study. All toxicities will be graded and determined to be an SAE as appropriate.

10.5 Expedited Reporting Requirements (MCC)

As the study sponsor, the Masonic Cancer Center has the following expedited reporting responsibilities (Table 10) for events documented in Section 10.2, Section 10.3 and Section 10.4:

Table 10: Reporting Requirements

Agency reporting to	Criteria for reporting	Timeframe	Form to Use	Submission address/email address
U of MN IRB	Unanticipated death of a locally enrolled subject(s); New or increased risk; Any adverse event that require a change to the protocol or consent form – refer to the IRB website for complete details	5 Business Days	RIN	Ethos
	Deviation reporting per current IRB requirements			
FDA	Unexpected and fatal or unexpected and life threatening suspected adverse reaction	no later than 7 Calendar Days	University of Minnesota SAE Report	Submit to FDA as an amendment to IND
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	no later than 15 Calendar-Days		

Masonic Cancer Center **SAE Coordinator**	Events that meet the definition of dose limiting toxicity or an early study stopping rule	At time of reporting	Event Form	mccsaes@umn.edu

11 Study Data Collection and Study Monitoring

11.1 Data Management

This study will collect regulatory and clinical data using University of Minnesota CTSI's instance of OnCore® (Online Enterprise Research Management Environment).

The Oncore database resides on dedicated secure and PHI compliant hardware consisting of 3 physical servers: dev, DR, and production. The dev server is located in the University of Minnesota (UMN) datacenter (WBOB) and houses six database instances (test, train, sandbox, mcc reports, oncdm, and vendor) that are backed up locally because the data is refreshed from Oncore production data. The production server is located in the UMN datacenter (WBOB). All the data servers are managed by the Academic Health Center – Information Systems (AHC-IS) virtual servers which utilize clustered infrastructure to provide real-time failover of virtual servers. This real-time clustering is physically limited to the UMN data center. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to Oncore databases.

The integrated data will be stored in PHI compliant servers managed by AHC IS with access given to those authorized users in the Clinical and Translation Science Institute Informatics team (CTSI BPIC and MCC CISS). The data will be integrated and extracted to researchers through the CTSI Informatics team and will be delivered through secure and compliant mechanisms (e.g. AHC IE data shelter, BOX, sftp, etc). If data de-identification is needed, then compliant AHC IE data de-identification tools will be used. The informatics team will grant the IRB approved study team members access to data.

Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore.

11.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRF) developed within OnCore based on its library of standardized forms. The e-

CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRF based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

11.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at https://z.umn.edu/dsmp

For the purposes of data and safety monitoring, this study is classified as high risk (investigator initiated). Therefore, the following requirements will be fulfilled:

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the study's progress at least quarterly.
- The PI will comply with at least twice-yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in Section 10.5 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB, and the FDA.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the Sponsor-Investigator will submit a progress report annually. The report will be submitted within 60 days of the anniversary date that the IND went into effect.

11.4 Study Related Monitoring

The IND sponsor/investigator will permit study-related monitoring, audits, and inspections by the Masonic Cancer Center or their designee, IRB, government regulatory bodies, and University of Minnesota compliance groups. All study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.) will be made available. The S/I will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

11.5 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB and FDA.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

12 Measurement of Effect

Phase I:

- Safety of VIC-1911 with PTCy and SIR after alloHCT
- Identify the recommended phase I extension dose of VIC-1911

Phase I extension:

- Time-to-event grade II-IV acute GVHD by 100 days
- Relapse by 1 year
- Safety

13 Study Design and Endpoints

This is a Phase I dose-finding study with extension at MTD of VIC-1911 combined with PTCY and sirolimus for the prevention of acute GVHD after matched related or unrelated peripheral blood stem cell allografts. The primary endpoint of the phase I trial is to determine the safety of VIC-1911 with PTCy and SIR as GVHD prophylaxis after allo HCT. Once the optimal dose is identified along with estimates of safety, the objective will be to confirm safety and obtain preliminary estimates of longer-term efficacy as measured by the co-primary endpoints of grade II-IV acute graft-versus-host disease (aGVHD) by 100 days and relapse by 1 year in the phase I extension trial.

The definition of relapse will be the same used in BMT CTN 1703: “Relapse is defined by either morphological or cytogenetic evidence of acute leukemia or MDS consistent with pre-transplant features, or radiologic evidence of lymphoma, documented or not by biopsy. Progression of disease applies to patients with lymphoproliferative diseases (lymphoma or chronic lymphocytic leukemia) not in remission prior to transplantation. The event is defined as increase in size of prior sites of disease or evidence of new sites

of disease, documented or not by biopsy. 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 regardless of whether the criteria described above were met." The presence of mutations by molecular techniques will not fulfill the criteria of relapse/progression if systemic therapy, immunosuppression withdrawal, or DLI is not given to treat it. However, in this event, the presence of measurable disease by molecular techniques will be noted.

The primary analysis for Phase I and Phase I extension will be a full analysis set in that all patients receiving any treatment with VIC-1911 will be evaluable for DLTs and efficacy.

Secondary trial endpoints will include pre-conditioning, +28, and +100 Treg (CD4+, CD25+, CD127neg, Foxp3+), allo-conventional T cell (Tconv) (CD4+, CD25+, CD127+), and T helper 1/2/17 cells values by flow cytometry. Day +100 T follicular helper cells (Tfh:CD4+, CXCR5+, CD45RAneg), CD8+ T cells, NK cells, total CD19+ B cells, transitional (CD19+, IgD+, CD38Hi, CD27+) B cells, and pre-germinal B cells (CD19+, CD21Lo, CD27neg) will be measured by flow cytometry. Treg suppression assays will be performed using purified Tregs at day +21 and day +100. The cumulative incidences of acute (day +100) and chronic GVHD (day +365) as well as relapse (day +365) will be monitored. While the frequency of CD4+ T cell pHistone 3 serine 10 (pH3ser10) [marker of Aurora kinase A activity (10)] will be followed as part of the identification of the recommended phase I extension dose, we will also analyze the frequency of CD4+ T cell pS6 [marker of mTOR activity (20)] at pre-conditioning, +21, and +100. In the phase I, VIC-1911 pharmacokinetics will be measured as well for the first 3 patients in each dose level. Clinical secondary endpoints will include GRFS as measured by GVHD relapse-free survival by 1 year, grade III-IV acute GVHD by day +100, chronic GVHD (NIH consensus criteria) by day +365, CMV reactivation and disease through day +180, and Quality of life through day +100.

14 Statistical Considerations

14.1 Study Design

This single-arm Phase I dose finding with extension study of PTCY/sirolimus plus VIC-1911 will test up to 3 dose levels of VIC-1911 for safety and short and long-term efficacy. Once the optimal dose is identified in Phase I, the objective will be to confirm safety and obtain estimates of long-term efficacy as measured by the two co-primary endpoints of grade II-IV aGVHD by day 100 and relapse by 1 year.

Phase I dose finding component: Find the optimal dose of VIC-1911:

The first phase is a dose finding study with the aim of establishing the optimal dose of VIC-1911 based on aggregate data along with the investigator's prior beliefs of rates of efficacy and toxicity at each dose as well as their input for the expected and maximum/minimum toxicity/efficacy desired. DLTs are defined in section 3 and short-term efficacy is defined as the proportion of patients with an average $CD4^+$, $pH3ser10^+$ T cell of <54%. The maximum desired toxicity is 30% of patients having a DLT by day 28 and the minimum desired efficacy is 65% of patients having $CD4^+$, $pH3ser10^+$ T cell of <54% by day 21 (- 3 to +7 days) . The optimal dose will be identified using the E*ff*Tox design[19].

Three dose levels of VIC-1911 will be tested (25 mg, 50 mg, or 75 mg) starting with a dose of 25 mg. E*ff*tox is an adaptive Bayesian design to facilitate seamless safety/efficacy dose-finding. In this trial, the measure for efficacy in the Phase I component ($CD4^+$, $pH3ser10^+$ T cell <54% by day 21) differs from the Phase I extension component (aGVHD by 100 days and relapse by 1 year). In the design, two parameters are required in addition to the desired toxicity and efficacy. The first is the trade-off function, which has been calculated as 1.79 based on points that are of equal utility: (1) the maximum permissible probability of toxicity when efficacy is guaranteed, (2) the minimum required probability of efficacy when toxicity is impossible and (3) a point in between that is considered equally desirable. The 2nd is the mean effective sample size (ESS) calculated as 0.9 based on the expected toxicity and efficacy at each dose, which is well within the advised range of 0.5 to 1.5. This framework combines experience from patients in the earlier part of the trial with clinicians' initial estimates of DLT's, efficacy and trade-off at each dose.

As the study progresses, updated probabilities of DLT and efficacy are computed before each new cohort of three patients is enrolled and the last patient reaches Day 28 (end of the assessment period) prior to enrollment of a subsequent cohort. Each subsequent cohort will be assigned to the most appropriate dose based on these updated probabilities. To promote patient safety: 1) we will enroll cohorts of 3 patients starting at the 1st dose and 2) dose levels will not be skipped when escalating. The optimal dose will be identified by one of the minimum of the following criteria: (1) the sample size of 21 is exhausted and (2) 9 patients are sequentially enrolled at the same dose. Implementation of E*ff*tox will be carried out by software published by the MD Anderson Cancer Center at https://biostatistics.mdanderson.org/SoftwareDownload/.

Phase I Expansion: Studying efficacy of VIC-1911 using aGVHD and relapse as the primary endpoints in addition to safety:

This 1-stage trial is designed to show a 15% improvement over an historical estimate of aGVHD and a 12% improvement over an historical estimate of relapse. Trial enrollment will only stop early for safety. The null hypothesis rate for grade II-IV aGVHD is ≥25% by 100 days and the null hypothesis rate for relapse is ≥24% by 1 year. These will be tested against a one-sided alternative that aGVHD ≤10% by 100 days and relapse ≤12% by 1 year using a type-I error of 2.5% to control for the multiple comparisons. We will potentially enroll 58 patients in the extension phase after completion of Phase I.

14.2 Statistical Analysis and Bioinformatics

The proportion of patients with an average CD4+, pH3ser10+ T cell <54% and safety endpoints will be assessed with descriptive statistics such as medians, ranges, frequencies and proportions as well as plots at baseline, day +21 and day +100. Other immune measures will be similarly estimated. The optimal dose will be determined by design. GVHD and relapse curves along with their competing risk will be estimated with cumulative incidence along with 95% confidence intervals treating non-event mortality as a competing risk. GVHD will be compared to a null value using a one-sided exact test and relapse be tested using a one-sample one-sided log-rank test. Kaplan-Meier curves and 95% confidence intervals will be used to estimate GRFS. Duration of hospitalization will be measured using median, range and interquartile range. CMV reactivation and CMV disease will be estimated using cumulative incidence treating non-CMV mortality as a competing risk. FACT quality of life measures along with its subscales will be measured through day +100, descriptively analyzed and possibly assessed with general linear mixed models. Pharmacokinetics and other correlative measure will be descriptive.

For comparison to historical controls where VIC-1911 was not part of the conditioning, we may perform regression analyses on the secondary endpoint of GFRS. This will include patients from our current study as well as a set of control patients age 18+ from MT2015-29 at our center. The historical cohort used similar conditioning. Given the use of historical controls, we will adjust for potential confounding using Fine and Gray regression by including the pre-specified factors of age (continuous), donor type (matched sibling versus haploidentical versus unrelated donor), disease-risk index (low risk versus intermediate risk versus high/very high risk) and comorbidity (HCT-CI: low risk versus intermediate versus high risk) . These pre-specified factors were determined in collaboration with investigators. No p-values will be listed. Only confidence intervals will be cited around the hazard ratios.

Bioinformatics Plan: To investigate genes associated with GVHD versus GVL, transcriptome profiling of 79 PBMC samples will be done following standard RNAseq protocols using PBMCs from patients on PTCy/SIR/VIC versus PTCy/SIR/MMF. We expect to have 50 million pair-end reads (2x100bp) per sample. RNA-seq sequencing reads in FASTQ files will be QCed, trimmed, and aligned to the reference genome and transcriptome. Gene counts matrix will be generated and used for downstream gene differential analysis, expression pattern clustering and for select gene set/pathway analysis. Limma model will be used for differential analyses between groups with a <5% false discovery rate after controlling for multiple comparisons, for assessments of GVL genes: LCK, PDCD1, and INFG and GVHD genes: AURKA and STAT3. We will further focus on modeling gene expression levels of LCK, PDCD1, and INFG (for GVL) plus AURKA and STAT3 (for GVHD), compared at d+21, between patients treated on PTCy/SIR/VIC or PTCy/SIR/MMF (n=79 for each), also collecting clinical data regarding relapse by day +365 and grade II-IV acute GVHD by day +100. In exploratory analyses, d+60 and +100 gene expression changes will be modeled and evaluated between the two groups using a type I error level of 0.05 without adjustment for multiple comparisons. We will also perform pathway analysis using both Enrichr and gene set enrichment analysis using GSEA with the Molecular Signatures Database (MSigDB) hallmark pathways collection. Logistic regression modeling and calculation of the area under the ROC curve for each analyte will be used to determine associations with outcome. Protein phosphorylation, immune reconstitution, and functional assays will be evaluated with descriptive statistics such as medians, ranges, proportions, and plots at baseline, d+21, +60, +100.

14.3 Sample Size and Power Considerations

14.3.1 Phase I

We will enroll a maximum of 21 patient during Phase I. Operating characteristics for various 'true' and 'excessive' probabilities are listed in Tables 1 and 2.

Table 1. Operating characteristics for E*ff*Tox with **expected** DLTs

Dose (mg)	Expected Efficacy/DLT			Excessive Efficacy/Expected DLT		
	Efficacy/DLT	Probability of selecting dose	Patient Number	Efficacy/DLT	Probability of selecting dose	Patient Number
25	30%/5%	0%	3	50%/5%	0%	3
50	65%/10%	0%	3	80%/10%	40%	9
75	95%/15%	100%	9	99%/15%	60%	9

Table 2. Operating characteristics for E*ff*Tox with **excessive** DLT

	Expected Efficacy/Excessive DLT	Excessive Efficacy/Excessive DLT

Dose (mg)	Efficacy/DLT	Probability of selecting dose	Patient Number	Efficacy/DLT	Probability of selecting dose	Patient Number
25	30%/15%	0%	3	50%/15%	20%	6
50	65%/25%	50%	9	80%/25%	50%	9
75	95%/45%	40	9	99%/45%	30%	6
None		10%				

Based on these simulations, 21 patients should be sufficient and safe to define the optimal dose in phase I. All patients treated at the optimal dose will be carried forward into the Phase I extension trial.

14.3.2 Phase I extension

The null hypotheses for the Phase I extension trial are that grade II-IV aGVHD is $\geq$ 25% by 100 days and relapse is $\geq$ 24% by 1 year. There will be 2 tests against one-sided alternatives that aGVHD ≤10% by 100 days and relapse ≤12% by 1 year. Similar rates for these null hypotheses are taken from unpublished data for adult matched unrelated donor PBSC patients enrolled on protocol MT2015-29. We expect most if not all patients on the current trial to have a donor source of adult matched unrelated donor PBSC. For power calculations, Bonferroni was used to adjust the type I error to maintain the experiment-wise type I error at the 0.05 level (0.05/2 = 0.025). A sample size of 58 patients achieves 81% power to detect an improvement to a 12% relapse rate using a one-sided one-sample log-rank test. This assumes that the last patient has follow-up of 6 months and patients are enrolled over a 30-month period. Distribution of relapse time is approximated by an exponential distribution. For the endpoint of grade II-IV aGVHD, 58 patients achieves 84% power to detect an improvement to at least 10% using a one-sided exact test.

Assuming 5% or less loss to follow-up, we will increase the overall sample size for phase I extension to 61 (an increase of 3 patients).

Overall, we expect that approximately 52-58 patients will be required during the extension (3-9 patients from the Phase I trial who are treated at the optimal dose may also be used during Phase I extension).

There will be no interim analysis for futility due to a short enrollment period and a reasonable assumption that the treatment will be at least as efficacious as the prior standard of care. Monitoring will be for safety only.

14.4 Monitoring Guidelines (Early Stopping Rules for Excess Toxicity)

Phase I

Posterior probabilities for DLT and efficacy will be calculated after each cohort of 3 patients using e*ff*tox. If after calculating these probabilities, e*ff*tox advocates that (i) no doses are tolerable and (ii) no doses are efficacious, the design will suggest stopping the trial.

Phase I extension

Monitoring for adverse events will begin with the first dose of VIC-1911 through day 75 post-transplant[20].

Unexpected grade 4 or greater events

The goal is to construct a boundary based on unexpected grade 4+ events such that the probability of early stopping is at most 10% if the rate is equal to 5% and our sample size is at most 58 (the maximum of patients enrolled in Phase I extension stage, which does not include the minimum of 3 patients treated at the recommended phase I extension dose during phase I). With these stipulations, the trial will be stopped and reviewed if 2/6, 3/14, 4/25, 5/37, 6/49 or 7 patients have events by Day 75. If the true probability of an event is 20%, there is a 98% chance of triggering the monitoring boundary.

Expected toxicities felt to be related to the VIC-1911:

a. Grade 2 or higher vitreous haemorrhage
b. Grade 3 or higher visual acuity decreased
c. Grade 3 or higher watery eyes
d. Grade 3 or higher keratitis
e. Grade 3 or higher floaters
f. Grade 3 or higher corneal microcysts,
g. Grade 3 or higher other eye disorders

The goal is to construct a boundary based on events such that the probability of early stopping is at most 10% if the rate is equal to 10% and our sample size is at most 58. With these stipulations, the trial will be stopped and reviewed if 2/2, 3/7, 4/12, 5/17, 6/24, 7/30, 8/37, 9/43, 10/51 or 11 patients have events by Day 75. If the true probability of toxicity is 20%, there is a 73% chance of triggering the monitoring boundary.

Treatment related mortality (TRM) by day 100

The goal is to construct a boundary based on TRM such that the probability of early stopping is at most 10% if the rate is equal to 5% and our sample size is at most 58.

With these stipulations, the trial will be stopped and reviewed if 2/6, 3/14, 4/25, 5/37, 6/49 or 7 patients have events by Day 75. If the true probability of an event is 20%, there is a 98% chance of triggering the monitoring boundary.

Relapse by day 100

The goal is to construct a boundary based on relapse such that the probability of early stopping is at most 10% if the rate is equal to 5% and our sample size is at most 58. With these stipulations, the trial will be stopped and reviewed if 2/6, 3/14, 4/25, 5/37, 6/49 or 7 patients have events by Day 75. If the true probability of an event is 20%, there is a 98% chance of triggering the monitoring boundary.

Grade III-IV acute GVHD by day 100

The goal is to construct a boundary based on GVHD such that the probability of early stopping is at most 10% if the rate is equal to 5% and our sample size is at most 58. With these stipulations, the trial will be stopped and reviewed if 2/6, 3/14, 4/25, 5/37, 6/49 or 7 patients have events by Day 75. If the true probability of an event is 20%, there is a 98% chance of triggering the monitoring boundary.

Primary Graft Failure by day 42

The goal is to construct a boundary based on graft failure such that the probability of early stopping is at most 10% if the rate is equal to 5% and our sample size is at most 58. With these stipulations, the trial will be stopped and reviewed if 2/6, 3/14, 4/25, 5/37, 6/49 or 7 patients have events by Day 75. If the true probability of an event is 20%, there is a 98% chance of triggering the monitoring boundary.

15 Ethical and Regulatory Considerations

15.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

15.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only

be conducted at sites where IRB approval has been obtained. The protocol, informed consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

15.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved Consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

16 References

1. Holtan SG, DeFor TE, Lazaryan A, Bejanyan N, Arora M, Brunstein CG, Blazar BR, MacMillan ML, Weisdorf DJ. Composite end point of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. Blood. 2015;125(8):1333-8. Epub 2015/01/17. doi: 10.1182/blood-2014-10-609032. PubMed PMID: 25593335; PMCID: PMC4335084.

2. Bejanyan N, Pidala JA, Wang X, Thapa R, Nishihori T, Elmariah H, Lazaryan A, Khimani F, Davila ML, Mishra A, Faramand R, Jain MD, Ochoa L, Perez LE, Liu H, Alsina M, Kharfan-Dabaja MA, Fernandez H, Nieder ML, Locke FL, Anasetti C, Ayala E. A phase 2 trial of GVHD prophylaxis with PTCy, sirolimus, and MMF after peripheral blood haploidentical transplantation. Blood Adv. 2021;5(5):1154-63. Epub 2021/02/27. doi: 10.1182/bloodadvances.2020003779. PubMed PMID: 33635333; PMCID: PMC7948297.

3. Greco R, Lorentino F, Morelli M, Giglio F, Mannina D, Assanelli A, Mastaglio S, Dalto S, Perini T, Lazzari L, Piemontese S, Corti C, Marcatti M, Bernardi M, Lupo Stanghellini MT, Ciceri F, Peccatori J. Posttransplantation cyclophosphamide and sirolimus for prevention of GVHD after HLA-matched PBSC transplantation. Blood. 2016;128(11):1528-31. Epub 2016/08/09. doi: 10.1182/blood-2016-06-723205. PubMed PMID: 27495140.

4. Vaeth M, Bauerlein CA, Pusch T, Findeis J, Chopra M, Mottok A, Rosenwald A, Beilhack A, Berberich-Siebelt F. Selective NFAT targeting in T cells ameliorates GvHD while maintaining antitumor activity. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(4):1125-30. doi: 10.1073/pnas.1409290112. PubMed PMID: 25583478; PMCID: 4313840.

5. Singh K, Stempora L, Harvey RD, Kirk AD, Larsen CP, Blazar BR, Kean LS. Superiority of rapamycin over tacrolimus in preserving nonhuman primate Treg half-life and phenotype after adoptive transfer. Am J Transplant. 2014;14(12):2691-703. Epub 2014/11/02. doi: 10.1111/ajt.12934. PubMed PMID: 25359003; PMCID: PMC4236286.

6. Zeiser R, Nguyen VH, Beilhack A, Buess M, Schulz S, Baker J, Contag CH, Negrin RS. Inhibition of CD4+CD25+ regulatory T-cell function by calcineurin-dependent interleukin-2 production. Blood. 2006;108(1):390-9. doi: 10.1182/blood-2006-01-0329. PubMed PMID: 16522809; PMCID: 1895845.

7. Cieri N, Greco R, Crucitti L, Morelli M, Giglio F, Levati G, Assanelli A, Carrabba MG, Bellio L, Milani R, Lorentino F, Stanghellini MT, De Freitas T, Marktel S, Bernardi M, Corti C, Vago L, Bonini C, Ciceri F, Peccatori J. Post-transplantation Cyclophosphamide and Sirolimus after Haploidentical Hematopoietic Stem Cell Transplantation Using a Treosulfan-based

Myeloablative Conditioning and Peripheral Blood Stem Cells. Biol Blood Marrow Transplant. 2015;21(8):1506-14. Epub 2015/05/24. doi: 10.1016/j.bbmt.2015.04.025. PubMed PMID: 26001696.

8. Furlan SN, Watkins B, Tkachev V, Flynn R, Cooley S, Ramakrishnan S, Singh K, Giver C, Hamby K, Stempora L, Garrett A, Chen J, Betz KM, Ziegler CG, Tharp GK, Bosinger SE, Promislow DE, Miller JS, Waller EK, Blazar BR, Kean LS. Transcriptome analysis of GVHD reveals aurora kinase A as a targetable pathway for disease prevention. Sci Transl Med. 2015;7(315):315ra191. Epub 2015/11/27. doi: 10.1126/scitranslmed.aad3231. PubMed PMID: 26606970; PMCID: PMC4876606.

9. Pidala J, Walton K, Elmariah H, Kim J, Mishra A, Bejanyan N, Nishihori T, Khimani F, Perez L, Faramand R, Davila ML, Nieder M, Lawrence N, Lawrence H, Anasetti C, Sebti S, Betts BC. Biological and Clinical Impact of JAK2/mTOR Blockade in Gvhd Prevention: Preclinical and Phase I Trial Results. Blood. 2020;136(Supplement 1):48-9. doi: 10.1182/blood-2020-133874.

10. Yu XZ, Bidwell SJ, Martin PJ, Anasetti C. CD28-specific antibody prevents graft-versus-host disease in mice. Journal of immunology. 2000;164(9):4564-8. Epub 2000/04/26. doi: 10.4049/jimmunol.164.9.4564. PubMed PMID: 10779758.

11. Yu XZ, Martin PJ, Anasetti C. Role of CD28 in acute graft-versus-host disease. Blood. 1998;92(8):2963-70. Epub 1998/10/09. PubMed PMID: 9763584.

12. Watkins B, Qayed M, McCracken C, Bratrude B, Betz K, Suessmuth Y, Yu A, Sinclair S, Furlan S, Bosinger S, Tkachev V, Rhodes J, Tumlin AG, Narayan A, Cribbin K, Gillespie S, Gooley TA, Pasquini MC, Hebert K, Kapoor U, Rogatko A, Tighiouart M, Kim S, Bresee C, Choi SW, Davis J, Duncan C, Giller R, Grimley M, Harris AC, Jacobsohn D, Lalefar N, Norkin M, Farhadfar N, Pulsipher MA, Shenoy S, Petrovic A, Schultz KR, Yanik GA, Waller EK, Levine JE, Ferrara JL, Blazar BR, Langston A, Horan JT, Kean LS. Phase II Trial of Costimulation Blockade With Abatacept for Prevention of Acute GVHD. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2021:JCO2001086. Epub 2021/01/16. doi: 10.1200/JCO.20.01086. PubMed PMID: 33449816.

13. Betts BC, Veerapathran A, Pidala J, Yang H, Horna P, Walton K, Cubitt CL, Gunawan S, Lawrence HR, Lawrence NJ, Sebti SM, Anasetti C. Targeting Aurora kinase A and JAK2 prevents GVHD while maintaining Treg and antitumor CTL function. Sci Transl Med. 2017;9(372). Epub 2017/01/13. doi: 10.1126/scitranslmed.aai8269. PubMed PMID: 28077684; PMCID: PMC6368389.

14. Kanakry CG, Ganguly S, Zahurak M, Bolanos-Meade J, Thoburn C, Perkins B, Fuchs EJ, Jones RJ, Hess AD, Luznik L. Aldehyde dehydrogenase expression drives human regulatory T cell resistance to posttransplantation cyclophosphamide. Sci Transl Med. 2013;5(211):211ra157. Epub 2013/11/15. doi: 10.1126/scitranslmed.3006960. PubMed PMID: 24225944; PMCID: PMC4155575.

15. Pidala J, Kim J, Jim H, Kharfan-Dabaja MA, Nishihori T, Fernandez HF, Tomblyn M, Perez L, Perkins J, Xu M, Janssen WE, Veerapathran A, Betts BC, Locke FL, Ayala E, Field T, Ochoa L, Alsina M, Anasetti C. A randomized phase II study to evaluate tacrolimus in combination with sirolimus or methotrexate after allogeneic hematopoietic cell transplantation. Haematologica. 2012;97(12):1882-9. Epub 2012/06/13. doi: 10.3324/haematol.2012.067140. PubMed PMID: 22689677; PMCID: PMC3590095.

16. Zhang R, Borges CM, Fan MY, Harris JE, Turka LA. Requirement for CD28 in Effector Regulatory T Cell Differentiation, CCR6 Induction, and Skin Homing. Journal of immunology. 2015;195(9):4154-61. Epub 2015/09/27. doi: 10.4049/jimmunol.1500945. PubMed PMID: 26408668; PMCID: PMC4610862.

17. Zhang R, Huynh A, Whitcher G, Chang J, Maltzman JS, Turka LA. An obligate cell-intrinsic function for CD28 in Tregs. J Clin Invest. 2013;123(2):580-93. Epub 2013/01/03. doi: 10.1172/JCI65013. PubMed PMID: 23281398; PMCID: PMC3561819.

18. Zhang R, Sage PT, Finn K, Huynh A, Blazar BR, Marangoni F, Mempel TR, Sharpe AH, Turka LA. B Cells Drive Autoimmunity in Mice with CD28-Deficient Regulatory T Cells. Journal of immunology. 2017;199(12):3972-80. Epub 2017/11/03. doi: 10.4049/jimmunol.1700409. PubMed PMID: 29093061; PMCID: PMC5716898.

19. Thall PF, Cook JD. Dose-finding based on efficacy-toxicity trade-offs. Biometrics. 2004;60(3):684-93. Epub 2004/09/02. doi: 10.1111/j.0006-341X.2004.00218.x. PubMed PM

20. Ivanova, A., Qaqish, B.F., and Schell, M.J. (2005). Continuous toxicity monitoring in phase II trials in oncology. Biometrics 61: 540-545ID: 15339291.

21. Sorror ML. How I assess comorbidities before hematopoietic cell transplantation. Blood. 2013;121(15):2854-2863. doi:10.1182/blood-2012-09-455063

22. McQuellon RP, Russell GB, Cella DF, et al. Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale., Bone Marrow Transplant, 1997, vol. 19 4(pg. 357-368)

Appendix I – Performance Status

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
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.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

Appendix II – Risks of Stem Cell Transplant, TBI, Busulfan and Fludarabine

Risks of Stem Cell Transplant

Risks associated with the cell infusion
nausea and vomiting
possible allergic reaction (including itching, hives, flushing [red face], shortness of breath, wheezing, chest tightness, skin rash, fever, chills, stiff muscles, or trouble breathing)

Risks associated with transplant
slow recovery of blood counts
graft failure
Graft-Versus-Host Disease (GVHD)
other complications including:
damage to the vital organs
serious infections
relapse of disease or a new blood cancer
risk to the unborn
changes in vital signs (commonly tachycardia, hypotension or hypertension)

Total Body Irradiation
Risks of TBI are listed in Table 12

Table 12: TBI		
Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
nausea and vomiting diarrhea cataracts sterility endocrinopathies growth failure intestinal cramps mucositis pancytopenia electrolyte disturbances neutropenic fever infections dry eyes	parotitis interstitial pneumonitis generalized erythema veno-occlusive disease	Dysphagia vertebral deformities nephropathy risk of 2nd malignancy years later cholestasis

Busulfan

Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
● low white blood cell count with increased risk of infection ● low platelet count with increased risk of bleeding ● low red blood cell count (anemia) which may cause tiredness, headache, dizziness ● hair loss or thinning, including face and body hair (usually grows back after treatment) ● long-term or short-term infertility (inability to have children) in men and women	• tiredness (fatigue) • sores in mouth or on lips • fever • nausea • vomiting • rash • loss of appetite • diarrhea • serious infection due to low white blood cell count	● abnormal blood tests results which suggest that the drug is affecting the liver ● allergic reaction with hives, itching, headache, coughing, shortness of breath, or swelling of the face, tongue, or throat ● scarring of lung tissue, with cough, difficulty breathing, and shortness of breath that may occur after prolonged use, or even months or years after stopping the drug ● secondary cancers ● darkened skin ● heart problems with high-dose treatment, most often in people with thalassemia or others with iron overload ● hormone deficiency ● death due lung damage, bone marrow failure, or other causes

Fludarabine		
Common	**Less Common**	**Rare**
● severe suppression of blood counts ● diarrhea ● anorexia ● mucositis ● nausea/vomiting ● stomatitis ● osteoporosis ● dysuria	● chills ● fever ● GI bleeding ● peripheral edema	● neurotoxicity - agitation and confusion - blurred vision - peripheral neuropathy - hearing loss - headache - cerebellar syndrome - blindness - coma - weakness ● depression ● insomnia ● hemorrhagic cystitis (except in FA)

Fludarabine		
Common	**Less Common**	**Rare**
		● abnormal renal function test ● autoimmune hemolytic anemia ● deep venous thrombosis ● aneurysms ● pruritic skin rash ● abnormal liver function/liver failure ● constipation ● transient ischemic attack ● dysphagia ● myalgia ● arthralgia ● renal failure

Appendix III – FACT-BMT Quality of Life Survey[21]

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.* ☐					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The side effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate	0	1	2	3	4
BMT11	I have frequent colds/infections	0	1	2	3	4
BMT12	My eyesight is blurry	0	1	2	3	4
BMT13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4

BMT15	I am bothered by skin problems	0	1	2	3	4
BMT16	I have trouble with my bowels	0	1	2	3	4
BMT17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

Translated versions of survey may be downloaded here: https://www.facit.org/measure-languages/FACT-BMT-Languages