

Abbreviated Title: HCT/Briquilimab/GATA2 Deficiency
Version Date: 06/10/2025

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Title: A Phase II Study of Allogeneic Hematopoietic Stem Cell Transplantation with Briquilimab-Based Conditioning in Participants with GATA2 Deficiency

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Drug Name:	Briquilimab; JSP191	Fludarabine	Cyclophosphamide	Tacrolimus	Mycophenolate mofetil	GATA2 assay (Sanger sequencing on the peripheral blood)
IND Number:	164877					NSR device
Sponsor:	CCR, NCI					
Manufacturer:	Jasper Therapeutics	Generic	Generic	Generic	Generic	Immunology service, NIH
Supplier:	Jasper Therapeutics	Clinical Center Pharmacy	Clinical Center Pharmacy	Clinical Center Pharmacy	Clinical Center Pharmacy	Immunology service, NIH

PRÉCIS

Background:

- GATA2 deficiency, an immunodeficiency and bone marrow failure disorder due to inherited or sporadic mutations in or loss of one allele of the GATA2 gene, is characterized by: 1) nontuberculous mycobacteria (NTM) and other opportunistic infections, 2) deficiency of monocytes, B lymphocytes, and Natural Killer (NK) cells in the peripheral blood, and 3) progression to myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), and acute myelogenous leukemia (AML).
- Allogeneic hematopoietic cell transplantation (HCT) appears to be curative, and interim results from protocol #13-C-0132, NCT01861106, demonstrated a 2-year event-free survival rate of 83% for 59 participants with GATA2 deficiency who underwent HCT with a busulfan-based conditioning regimen.
- However, traditional HCT approaches using alkylating agents such as busulfan continue to place recipients at risk for potentially life-threatening, transplant-related toxicities as well as late effects such as infertility and secondary malignancy.
- Briquilimab is a humanized, glycosylated IgG1 monoclonal antibody that targets CD117 (human c-Kit) present on endogenous hematopoietic stem cells (HSC). Briquilimab has been shown in pre-clinical and early clinical studies to safely deplete human and non-human primate HSC with minimal toxicity.

Primary Objective:

- To determine whether allogeneic hematopoietic cell transplantation with Briquilimab-based conditioning results in sustained donor engraftment by 100 days post-transplant in participants with GATA2 deficiency

Eligibility:

- Recipients aged 6-70 years old with pathogenic germline mutations in GATA2 and clinical manifestations consistent with a diagnosis of GATA2 deficiency
- Have an 8/8 Human leukocyte antigen (HLA)-matched related or unrelated donor or a 7/8 HLA-matched unrelated donor or haploidentical related donor
- Have “early stage” GATA2 deficiency defined as a hypocellular for age bone marrow with less than 5% blasts and normal or favorable cytogenetics (defined as “good” or “very good” cytogenetics risk groups plus trisomy 8)

Design:

- All participants with GATA2 deficiency will receive a pre-transplant conditioning regimen consisting of Briquilimab administered as a single intravenous (IV) infusion on day -11 (range day -13 to -10) with pharmacokinetics, followed by fludarabine or fludarabine/cyclophosphamide IV infusions (3 or 5 days depending on the donor) and 200 cGy total body irradiation (TBI) on day -1. HCT will be infused on day 0.
- Participants with an 8/8 HLA-matched related or unrelated donor assigned to Arm A will receive a fludarabine for three days on days -4, -3, and -2.

- Participants with a 7/8 HLA-matched unrelated donor or a haploidentical related donor assigned to Arm B will receive a fludarabine for five days on days -6, -5, -4, -3, and -2, cyclophosphamide for 2 days on days -6 and -5
- Post-transplant immunosuppression for Graft Versus Host Disease (GVHD) prophylaxis for recipients of Arms A and B will consist of cyclophosphamide for 2 days on days +3 and +4, along with mycophenolate mofetil from day +5 to approximately day +35 and tacrolimus from day +5 to approximately day +180. If there is no evidence of GVHD, tacrolimus will be stopped or tapered at approximately day +180

TABLE OF CONTENTS

PRÉCIS	2
TABLE OF CONTENTS	4
STATEMENT OF COMPLIANCE	11
1 INTRODUCTION	11
1.1 Study Objectives	11
1.1.1 Primary Objective.....	11
1.1.2 Secondary Objectives	11
1.1.3 Exploratory Objectives	11
1.2 BACKGROUND	12
1.2.1 GATA2 Deficiency.....	12
1.2.2 Previous Experience with Allogeneic Hematopoietic Stem Cell Transplant for Patients with GATA2 Mutations	13
1.2.3 Briquilimab Anti-Human CD117 Monoclonal Antibody.....	14
1.2.4 Rationale for Conditioning Regimens	15
1.2.5 GVHD Prophylaxis.....	18
1.2.6 Immune Reconstitution Following Allogeneic Transplant.....	18
2 ELIGIBILITY ASSESSMENT AND ENROLLMENT	19
2.1 Eligibility Criteria	19
2.1.1 Inclusion Criteria	19
2.1.2 Exclusion Criteria	20
2.2 Recruitment Strategies	21
2.3 Screening Evaluation	21
2.3.1 Screening Activities Performed Before a Consent for Screening Has Been Signed	21
2.3.2 Screening Activities Performed After a Consent for Screening Has Been Signed	21
2.3.3 Donor Selection and Prioritization	22
2.4 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES	23
2.4.1 Screen Failures.....	23
2.4.2 Treatment Assignment.....	24
3 STUDY IMPLEMENTATION	24
3.1 Study Design.....	24
3.2 Drug Administration	25

3.2.1	Briquilimab	26
3.2.2	Conditioning Regimen for 8/8 Matched Related and Unrelated Donors with Fludarabine, and TBI (Arm A)	26
3.2.3	Conditioning Regimen for 7/8 URD and Haploidentical Related Donors with Cyclophosphamide, Fludarabine, and TBI (Arm B)	27
3.2.4	Transplantation Day 0	27
3.2.5	Post-Transplant GVHD Prophylaxis	28
3.3	Dose Modifications	28
3.3.1	Briquilimab	28
3.3.2	HSC transplant	29
3.3.3	Fludarabine	29
3.3.4	Cyclophosphamide	29
3.3.5	Tacrolimus	29
3.3.6	Mycophenolate mofetil	29
3.4	Study stopping rules	29
3.5	On Study Assessments/Evaluations	30
3.5.1	Timing of Procedures	30
3.5.2	Description of Procedures	31
3.5.3	Correlative/Exploratory Assessments	34
3.6	Study Calendar	35
3.6.1	Screening, Baseline and Preparative Regimen	35
3.6.2	Day of transplant and Follow Up	39
3.7	Radiation Guidelines	42
3.8	Costs and Compensation	42
3.8.1	Costs	42
3.8.2	Compensation	42
3.8.3	Reimbursement	42
3.9	Criteria for Removal from Protocol Therapy and Off Study Criteria	42
3.9.1	Criteria for removal from protocol therapy	42
3.9.2	Off-Study Criteria	43
3.9.3	Lost to Follow-up	43
4	CONCOMITANT MEDICATIONS/MEASURES	43
4.1	Supportive Care	43

4.1.1	Infection Prophylaxis.....	43
4.1.2	Blood Product Support	43
4.1.3	Nutritional Support	44
4.1.4	Anti-emetic Usage	44
4.1.5	Intravenous Immune Globulin (IVIG).....	44
4.1.6	Prevention of Hemorrhagic Cystitis	44
4.1.7	Growth Factors	44
4.1.8	Additional Cell Infusions for Graft Failure, Impending Graft Failure, or Poor Graft Function	45
4.1.9	Use of Corticosteroids	45
4.2	Treatment of Graft-Versus-Host Disease.....	45
5	CORRELATIVE STUDIES FOR RESEARCH	45
5.1	Biospecimen Collection	46
5.1.1	Immune Reconstitution Studies.....	46
5.1.2	Pharmacokinetic properties of Briquilimab.....	46
5.2	Storage, Use, and Sharing of Specimens and Data (Including for Secondary Research) 47	
5.2.1	Sample Tracking and Processing.....	47
5.2.2	Sample Storage and Disposition.....	47
5.2.3	Protocol Completion/Sample Destruction	47
5.3	Samples for Genetic/Genomic Analysis	48
5.3.1	GATA2 Assay	48
5.3.2	Description of how privacy and confidentiality of medical information/biological specimens will be maximized.....	48
5.3.3	Management of Results	48
6	DATA COLLECTION AND EVALUATION	48
6.1	Data Collection	48
6.2	Data Sharing Plans	49
6.2.1	Human Data Sharing Plan	49
6.2.2	Genomic Data Sharing Plan.....	50
6.3	Response Criteria	50
6.4	Toxicity Criteria.....	51
7	NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN...51	

7.1	Definitions.....	51
7.2	OHSRP Office of Compliance and Training / IRB Reporting.....	51
7.2.1	Expedited Reporting	51
7.2.2	IRB Requirements for PI Reporting at Continuing Review	51
7.3	NCI Clinical Director Reporting.....	52
7.4	NIH Required Data and Safety Monitoring Plan	52
7.4.1	Principal Investigator/Research Team.....	52
7.4.2	Safety Monitoring Committee (SMC).....	52
8	SPONSOR PROTOCOL/SAFETY REPORTING.....	52
8.1	Definitions.....	53
8.1.1	Adverse Event.....	53
8.1.2	Serious Adverse Event (SAE)	53
8.1.3	Life-threatening	53
8.1.4	Severity	53
8.1.5	Relationship to Study Product	54
8.1.6	Adverse Events of Special Interest (AESI)	54
8.2	Assessment of Safety Events	54
8.3	Reporting of Serious Adverse Events	54
8.4	Wavier of expedited reporting to CCR	55
8.5	Safety Reporting Criteria to the Pharmaceutical Collaborators.....	55
8.6	Reporting Pregnancy.....	55
8.6.1	Maternal exposure	55
8.6.2	Paternal exposure.....	55
8.7	Regulatory Reporting for Studies Conducted Under CCR-Sponsored IND.....	56
8.8	Sponsor Protocol Deviation Reporting	56
9	CLINICAL MONITORING.....	56
10	STATISTICAL CONSIDERATIONS	57
10.1	Objectives and Endpoints.....	57
10.2	Sample Size Determination	59
10.3	Populations for Analyses.....	59
10.4	Statistical Analyses.....	59
10.4.1	General Approach.....	59
10.4.2	Analysis of the Primary Endpoints	59

10.4.3	Analysis of the Secondary Endpoints	59
10.4.4	Safety of HCT	61
10.4.5	Baseline Descriptive Statistics	62
10.4.6	Planned Interim Analyses	62
10.4.7	Sub-Group Analyses	62
10.4.8	Exploratory Analyses	62
11	COLLABORATIVE AGREEMENTS	63
11.1	Cooperative Research and Development Agreement (CRADA)	63
12	HUMAN SUBJECTS PROTECTIONS	63
12.1	Rationale For Subject Selection	63
12.2	Participation of Children	63
12.3	Risk/Benefit Assessment	63
12.3.1	Known Potential Risks	63
12.3.2	Known Potential Benefits	68
12.3.3	Assessment of Potential Risks and Benefits for Recipients	68
12.4	Consent and Assent Process and Documentation	68
12.4.1	Consent Process for Minors	69
13	REGULATORY AND OPERATIONAL CONSIDERATIONS	70
13.1	Study Discontinuation and Closure	70
13.2	Quality Assurance and Quality Control	71
13.3	Conflict of Interest Policy	71
13.4	Confidentiality and Privacy	71
14	PHARMACEUTICAL INFORMATION	72
14.1	Briquilimab; JSP191 (IND# 164877)	72
14.1.1	Source, Acquisition and Accountability	72
14.1.2	Formulation, Appearance, Packaging, and Labeling	72
14.1.3	Product Storage and Stability	73
14.1.4	Administration	73
14.1.5	Toxicity	73
14.2	Fludarabine	73
14.2.1	Source/Acquisition and Accountability	73
14.2.2	Formulation, Appearance, Packaging, and Labeling	74
14.2.3	Product Storage and Stability	74

14.2.4	Preparation	74
14.2.5	Toxicity	74
14.3	Cyclophosphamide	74
14.3.1	Source/Acquisition and Accountability	74
14.3.2	Formulation, Appearance, Packaging, and Labeling.....	75
14.3.3	Product Storage and Stability	75
14.3.4	Preparation.....	75
14.3.5	Toxicity.....	75
14.4	Mycophenolate Mofetil	76
14.4.1	Source/Acquisition and Accountability	76
14.4.2	Formulation, Appearance, Packaging, and Labeling.....	76
14.4.3	Product Storage and Stability	76
14.4.4	Preparation.....	76
14.4.5	Toxicity.....	76
14.5	Tacrolimus.....	77
14.5.1	Source/Acquisition and Accountability	77
14.5.2	Formulation, Appearance, Packaging, and Labeling.....	77
14.5.3	Product Storage and Stability	77
14.5.4	Preparation.....	77
14.5.5	Toxicity.....	77
14.6	GATA2 Assay (Sanger sequencing on the peripheral blood)	78
15	REFERENCES	79
16	ABBREVIATIONS	81
17	APPENDICES	86
17.1	Appendix A: Revised International Prognostic Scoring System for Myelodysplastic Syndromes Risk Assessment Calculator	86
17.2	Appendix B – The World Health Organization (WHO) 2016 classification of myelodysplastic syndromes (MDS).....	87
17.3	Appendix C: BONE MARROW CELLULARITY CUTOFFS TO DEFINE HYPOCELLULAR FOR AGE.....	89
17.4	Appendix D: Performance Status Criteria.....	90
17.5	Appendix E: Schwartz Formula	91
17.6	Appendix F: Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI)	92

17.7	Appendix G – GVHD Grading and Scoring	94
17.7.1	Acute GVHD Staging and Grading	94
17.7.2	Chronic GVHD Diagnosis and Staging.....	94

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To determine whether allogeneic hematopoietic cell transplantation with Briquilimab-based conditioning results in sustained donor engraftment by 100 days post-transplant in participants with GATA2 deficiency

1.1.2 Secondary Objectives

- To determine whether allogeneic hematopoietic cell transplantation with Briquilimab-based conditioning results in restoration of normal hematopoiesis by one-year post-transplant in participants with GATA2 deficiency
- To evaluate:
 - the safety of allogeneic HCT in participants with GATA2 deficiency conditioned with Briquilimab
 - 3 years overall survival
 - 3 years event-free survival
 - 3 years incidence of secondary graft failure
 - 3 years incidence and severity of acute and chronic GVHD

1.1.3 Exploratory Objectives

- To characterize immune reconstitution following HCT in participants with GATA2 deficiency conditioned with Briquilimab
- To evaluate the pharmacokinetic properties of Briquilimab in participants with GATA2 deficiency

1.2 BACKGROUND

1.2.1 GATA2 Deficiency

In 2009, Dr. Steve Holland's group in the National Institute of Allergy and Infectious Diseases identified a unique immunodeficiency disease syndrome, subsequently named MonoMAC, in which patients have a severe deficiency of monocytes (Mono) in the peripheral blood, and the propensity to develop *Mycobacterium avium* complex (MAC) and other nontuberculous mycobacteria (NTM) infections. [1] The vast majority of these patients have been shown to harbor mutations in the GATA2 gene. [2] The important differences between patients with GATA2 deficiency and previously described primary immunodeficiency diseases are that patients with GATA2 deficiency have: 1) onset in late adolescence or early adulthood of life-threatening opportunistic infections, primarily NTM, 2) a peripheral blood leukocyte subset profile with the presence of T-lymphocytes, but a severe deficiency of B-lymphocytes, NK cells, and monocytes, 3) a genetic component suggestive of a dominant pattern of inheritance, 4) frequent progression to myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), and acute myelogenous leukemia (AML), and 5) mutations in one allele of GATA2. This contrasts with most genetic primary immunodeficiency diseases (PID)s which manifest in infancy, rarely have both disseminated NTM infections, lack T-lymphocytes, and do not progress to MDS/AML. In approximately one-half of the patients, the disease is familial with one or more first-degree relatives harboring a GATA2 mutation. [3]

Patients with GATA2 deficiency present in their late teens or early twenties, and ultimately succumb to either disseminated infection or MDS/AML in 2-10 years. [3] It appears that the loss of monocytes and NK cells accounts for the propensity to develop opportunistic infections with NTM and fungal organisms, including histoplasmosis and aspergillus. The onset of MDS is variable, but when it occurs, it usually develops within several years of the onset of the disease. Current management of GATA2 deficiency is palliative and revolves around treatment with antibiotics, anti-viral, anti-tuberculous, and anti-fungal agents. However, relapses with additional opportunistic infections occur leading to progressive disability. The lung is the organ system most frequently affected. Total lung pulmonary alveolar lavage has been used to transiently improve pulmonary function. HCT has been used successfully to treat both genetic immunodeficiency diseases and MDS/AML, the two characteristics of the patients with mutations in GATA2, and therefore represents a potential therapy to reverse the inevitably fatal course in these patients. [4, 5]

Both familial and sporadic cases of GATA2 mutation occur in this syndrome. To date, over 150 distinct mutations in *GATA2* have been identified, including recurrent missense mutations affecting the zinc finger-2 domain (R398W and T354M) (Figure 1). [6] Discrete insertion/deletion mutations leading to frame shifts and premature termination implicate haploinsufficiency as the likely mechanism of action. These mutations were identified in a number of families, indicating germ line transmission in those kindreds. Thus, *GATA2* joins *RUNX1* and *CEBPA* as familial leukemia predisposition genes.

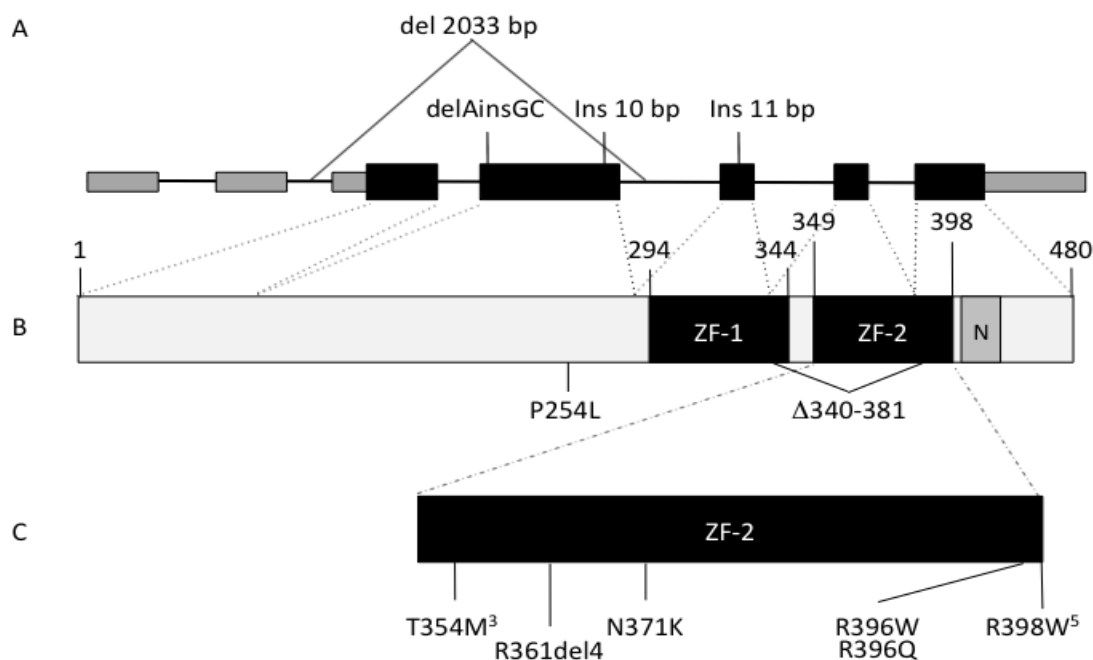


Figure 1: A. Genomic organization of *GATA2* showing two 5' untranslated and five coding exons. Dark boxes indicate coding regions. Insertion/deletion mutations predicted to result in null alleles are shown above. B. Protein domains of *GATA2*, showing N and C-terminal zinc fingers (ZF-1, ZF-2) and nuclear localization signal (N). C. Missense and in-frame deletion mutations identified within ZF-2. Superscript numerals indicate the number of independent mutations.

1.2.2 Previous Experience with Allogeneic Hematopoietic Stem Cell Transplant for Patients with *GATA2* Mutations

A previous study— “Pilot and Feasibility Study of Reduced-Intensity Hematopoietic Stem Cell Transplant for MonoMAC” (NCT00923364) — was initiated in 2009 when *GATA2* mutations were not yet known to lead to the disease manifestations in what was termed “MonoMAC.” [1] The first four patients eligible for allogeneic hematopoietic stem cell transplant on the protocol were all seriously ill with three patients requiring oxygen. Thus, a reduced-intensity protocol was initiated to avoid the almost-certain early mortality in these patients with a high-dose conditioning regimen.

We carried out allogeneic hematopoietic stem cell transplants on a total of fourteen patients with *GATA2* mutations on protocol 09-C-0096 (NCT00923364) using a nonmyeloablative conditioning regimen: matched related donors (MRD) and unrelated donors (URD) recipients received fludarabine 30 mg/m²/day for three days and a single dose of 200 cGy total body irradiation; umbilical cord blood (UCB) recipients received a single dose of 50 mg/kg of cyclophosphamide on day -6, fludarabine 30 mg/m²/day for 5 days, and 200 cGy TBI; haploidentical related donor recipients received cyclophosphamide 14.5 mg/kg/day on days -6 and -5, fludarabine 30 mg/m²/day for 5 days, and 200 cGy TBI. [4] Four patients received MRD

peripheral blood stem cells (PBSCs), 4 patients received PBSC from 10/10 HLA-matched unrelated donors, 4 patients received umbilical cord blood units, and two patients received haploidentical donor transplants. There was one relapse that occurred in a recipient of an MRD transplant, one case of primary graft failure that occurred in a recipient of an umbilical cord blood transplant, and one graft rejection that occurred in a recipient of a URD transplant. Nine of 11 evaluable patients engrafted at a median of 10 days (range 0-76): engraftment was not evaluable in a recipient of a UCB transplant and the recipient of a haploidentical transplant due to deaths early in the post-transplant period. All patients who engrafted had reconstitution of the monocyte, NK, and B-lymphocyte compartments, and all had a reversal of the infection susceptibility phenotype which is characteristic of the disease. Lastly, in our cohort of patients with mutations in GATA2, progression to MDS/AML/CMML necessitated a preceding course of chemotherapy in three patients in order to decrease the blast count to less than 5%. These results have been reported. [4]

In 2018 we reported our initial results of a clinical trial of allogeneic HCT for GATA2 deficiency using a high-dose conditioning regimen with busulfan and fludarabine for MRD and URD, and a busulfan based regimen for haploidentical related donors (HRD) (NCT 01861106). [5] We reported an 86% disease-free survival in 22 patients. However, with continuing accrual, the subsequent analysis indicated that despite a 10/10 HLA match of MRD and URD, there was a 31% incidence of grade III-IV acute GVHD (aGVHD) with Tacrolimus/Methotrexate (Tacro/MTX) prophylaxis. In contrast, there was no grade III-IV aGVHD in the HRD recipients, all of whom received GVHD prophylaxis with post-transplantation cyclophosphamide (PT/Cy) followed by tacrolimus/mycophenolate (Tacro/MMF). The protocol was subsequently amended to replace Tacro/MTX with PT/Cy in the regimen for MRD and URD patients.

We now have data on 59 patients who have a busulfan-based conditioning regimen and have a one-year follow-up, including 17 haploidentical related donor recipients (D. Hickstein, submitted). Of these 59 patients, 52 are alive for overall survival of 88% and event-free survival of 83%. We have been particularly successful in eradicating myelodysplastic clones with very good, good, and intermediate cytogenetics, including trisomy 8, using our current regimen. [7] Even in a haploidentical related donor setting using PT/CY, we have been able to eradicate trisomy 8 clones in all instances. However, cytogenetic changes represent the single most important prognostic variable in MDS and AML. [8] [7] Unfavorable (poor risk or very poor risk) cytogenetics, such as monosomy 7, confers a higher risk of relapse.

Patients with GATA2 deficiency are predisposed to transform from a hypoplastic MDS to AML and CMML, and the high-dose conditioning regimen did decrease the need for a preceding course of chemotherapy prior to transplant and resulted in a reduced incidence of relapse. However, despite the overall success rates, there were seven deaths in the MRD and URD treatment arms, indicating that there remains room for improvement in this group of patients with considerable underlying conditions. A less intensive conditioning regimen for “early stage” patients with GATA2 deficiency – defined as those with a hypocellular bone marrow with < 5% blasts and normal or favorable cytogenetics – may reduce the mortality of the regimen while still resulting in reversal of the disease phenotype.

1.2.3 Briquilimab Anti-Human CD117 Monoclonal Antibody

CD117 or c-Kit is the tyrosine kinase transmembrane receptor for stem cell factor (SCF) expressed on normal HSCs and progenitor (CD34+) cell populations; SCF signaling through CD117 is essential for the survival, maintenance, and proliferation of HSCs. [9] Czechowicz et al. previously

demonstrated that administration of the neutralizing anti-mouse Kit antibody ACK-2 to immunodeficient mice results in transient depletion of >98% of endogenous HSCs in mouse marrow. [10] Furthermore, infusion of purified donor HSC into recipient mice during a window of time when the serum levels of ACK2 fall below 2 µg/mL and before recovery of endogenous hematopoiesis resulted in robust and durable engraftment with donor myeloid chimerism levels of up to 90%.

Briquilimab (previously known as AMG 191, JSP191) is a monoclonal antibody that recognizes and antagonizes human c-Kit with high affinity and has been shown in preclinical studies to safely and efficiently deplete non-human primate HSCs and human HSCs xenografted into immunodeficient mice. [11] Briquilimab is currently being evaluated for clinical safety and efficacy as the sole conditioning agent in children with severe combined immunodeficiency (SCID) in whom initial HCT failed (NCT02963064). Early results demonstrated that Briquilimab safely clears HSC niches and allows for donor HSC engraftment in patients with SCID with evidence of sustained donor engraftment in 6 of 9 patients [12]. There were no significant infusion reactions and no Briquilimab -related serious adverse events

In another ongoing study (NCT04429191), 17 patients ranging from 62 to 79 years of age have received allogeneic HCT for MRD-positive MDS/AML to date using matched related or unrelated donors. Patients were conditioned with 0.6 mg/kg of Briquilimab (the dose being used in this protocol) combined with fludarabine 90 mg/m² and TBI 200-300 cGy (the same backbone we will be using for our matched donor recipients). All 17 patients had neutrophil recovery between day +19 and day +26, and each of the 14 evaluable subjects achieved full myeloid donor chimerism (mean 98.1± 1.2%) [13]. As in the SCID study, there were no significant infusion reactions and no Briquilimab-related serious adverse events.

Per the most recent Briquilimab Development Safety Report (IND 140444), in Study NCT02963064, 5 related nonserious AEs were reported in 3 of 14 (21.4%) subjects, including 1 case each of paresthesia (Grade 1), pure red cell aplasia (Grade 2), infusion-related throat itching (Grade 1), infusion-related cough (Grade 1), and infusion-related nasal congestion (Grade 1). In Study NCT04429191, 10 related nonserious AEs were reported in 7 of 15 (46.7%) subjects, including 1 case each of platelet count decreased (Grade 1), nausea (Grade 1), maculopapular rash (Grade 1), fatigue (Grade 1), reticulocyte count decreased (Grade 1) and headache (Grade 1). There were 3 Grade 3-4 hematological events (2 cases of neutropenia and 1 case of pure red cell aplasia). These hematological adverse events were self-limiting and the result of the known and intended pharmacodynamic effects of Briquilimab (i.e., depletion of bone marrow lineages).

This protocol was designed to include Briquilimab in an established and well-tolerated nonmyeloablative conditioning regimen consisting of fludarabine 30 mg/m²/day for three days and a single dose of 200 cGy total body irradiation as a strategy to improve donor stem cell engraftment without increasing toxicity.[4] If successful, Briquilimab would be the first biologic product to target endogenous stem cells and allow their replacement by corrective cells. Thus, the implications of success in this study extend beyond the use of Briquilimab in GATA2 patients to the many patient groups that undergo HCT for other disease indications.

1.2.4 Rationale for Conditioning Regimens

The regimen proposed for the 7/8 HLA-matched unrelated and haploidentical related donor treatment arm of this protocol is based on a non-myeloablative conditioning regimen used by John Hopkin's Medical Institute (JHMI) (NCT01203722), which consists of cyclophosphamide 14.5

mg/kg on days -6 and -5, fludarabine 30 mg/m²/day on days -6 to -2, and TBI 200 cGy on day -1. [14] [15] [16] The JHMI regimen resulted in high rates of engraftment using both mismatched related (haploidentical) donors [14, 16] and mismatched unrelated donors [15]; however, relapse was common with rates ranging from 35% to 55% in these cohorts of extensively pre-treated patients. For instance, in the 2010 study, 21 of 66 patients had failed at least one autologous transplant prior to a haploidentical related donor transplant. [14] We modified this regimen in our current protocol (13-C-0132, NCT01861106) to prevent graft rejection and prevent relapse by adding two days of busulfan on days -4 and -3. We have had only one graft rejection in 17 haploidentical related donor recipients on 13-C-0132. The patient was successfully re-transplanted using the same paternal donor following conditioning with rabbit Anti-thymocyte globulin (ATG) and TBI 400 cGy and peripheral blood stem cells. The remaining 16 (94%) patients all had high levels of engraftment with >90% myeloid and >50% CD3+ T cell chimerism at day +100. The addition of the Briquilimab antibody to the JHMI conditioning regimen is designed to replace the 2 days of busulfan that we are using in our current protocol.

In the HLA-matched related or unrelated donor arm of the protocol, the Briquilimab antibody is being added to the fludarabine 30 mg/m² per day on days -4 to -2 and TBI 200 cGy on day -1 regimen that was used in our earlier GATA2 transplant protocol 09-C-0096 (NCT 009233364). [4] In that protocol, one of four matched related donor transplants relapsed, and one of four matched unrelated donor recipients was rejected. The addition of the Briquilimab antibody to the HLA-matched donor arm of the protocol is designed to decrease the risk of graft rejection that we observed in 09-C-0096. This is also the same Briquilimab antibody-based conditioning regimen that has been used successfully in patients with measurable residual disease (MRD)-positive AML/MDS (NCT04429191). [17] It should be noted that patients on the HLA-matched related or unrelated donor arm on our current protocol (13-C-0132) have done well with busulfan and fludarabine conditioning. There has been only one case of graft failure, and 21 of 23 (91%) patients had high levels of engraftment with >90% myeloid and >50% CD3+ T cell chimerism at day +100. The hope is that patients on this protocol will achieve similar rates of engraftment without the associated toxicity of busulfan chemotherapy. However, stringent stopping criteria have been proposed for this protocol to take into account the success of the 13-C-0132 protocol. Notably, for this protocol, we are selecting GATA2 patients with a hypocellular marrow, no increase in blasts, and normal or favorable risk cytogenetics (defined as “good” or “very good” cytogenetics risk groups in [Appendix A](#) plus trisomy 8).

The optimal conditioning dose of Briquilimab is unknown. In a dose-escalation study for participants with severe combined immune deficiency (NCT02963064), participants were assessed in successive dose-escalation cohorts as follows: 0.1, 0.3, and 1.0 mg/kg administered as a single IV infusion. Allogeneic HSCs were infused when Briquilimab levels reached ≤500 ng/mL. This occurred at < 7 days with 0.1 mg/kg dosing, near 7 days with 0.3 mg/kg dosing, and at 14-21 days with 1.0 mg/kg dosing (see [Figure 2](#) below). The extended window at the highest dose prompted the use of an intermediate dose of 0.6 mg/kg, and preliminary data suggest that a dose of 0.6 mg/kg may be optimal with respect to conditioning effect and time from antibody administration to reach the target level to allow infusion of donor HSC. This is also the dose being used with the success in the MRD-positive AML/MDS study (NCT04429192). As such, participants enrolled in this study will receive 0.6 mg/kg of Briquilimab, and pharmacokinetics (PK) will be assessed.

All subjects by ID (dose, mg/kg)

Black, blue, red, white = 0.1, 0.3, 0.6, 1.0 mg/kg

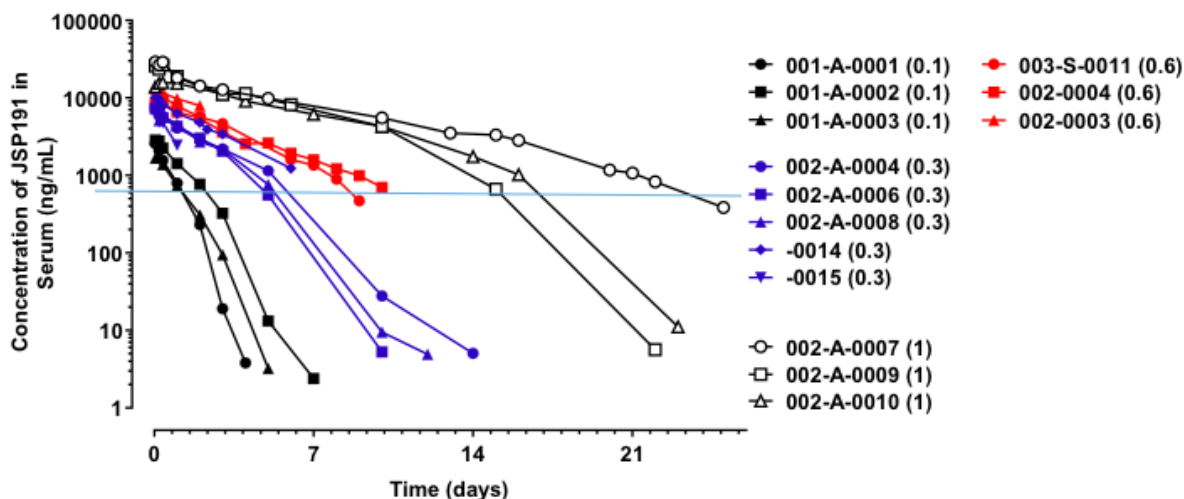


Figure 2. Serum concentration of Briquilimab with time following infusion of Briquilimab at doses of 0.1, 0.3, 0.6 and 1 mg/kg on a dose escalation study for participants with SCID. The pale blue horizontal line indicates the Briquilimab level of 500 ng/mL below which stem cells were infused on the SCID study.

Update for August 2024:

PK data from 49 participants in the SCID (NCT02963064) and MDS/AML (NCT04429191) studies were recently analyzed and used to develop a population PK model of Briquilimab [18]. A 2-compartment model with combined linear and non-linear elimination best described the PK of Briquilimab, and body weight was the sole covariate of the PK parameters (Table 1). For a typical subject with a body weight of 70 kg, the median time to reach target concentrations of 500, 1000, and 2000 ng/mL after a single dose of 0.6 mg/kg was calculated as 12.3, 10.4, and 7.7 days, respectively. However, GATA2 patients were not included in the development of the population PK model, and as such, real-time PKs will continue to be collected for participants on this protocol.

Table 1 Final Briquilimab population PK model [18]

	Final Model		Bootstrap (N = 500)	
PK Model Parameters				
Parameter	Estimate	95% CI	Median	95% CI
CL (mL/h/70kg)	17.6	[14.4, 20.7]	17.6	[13.5, 22.1]
V _{max} (ng/h/70kg)	51434.8	[39284, 63583]	51435.0	[36890.0, 65774.0]
K _m (ng/mL)	71.5	[50.9, 92.2]	71.5	[45.1, 107.0]
V _c (mL/70kg)	3444.0	[3214, 3674]	3444.0	[3211.0, 3681.4]
V _p (mL/70kg)	1613.3	[1230, 1997]	1613.3	[1142.4, 2110.1]
Q (mL/h/70kg)	21.2	[16.4, 26.0]	21.2	[15.1, 29.3]
Correlation between Random Effects				
CL and V _c	23.6 %	[13.6, 30.7]	23.6 %	[14.5, 31.7]
Between-subject Variability (BSV)				
CL	37.4 %	[24.3, 47.6 %]	37.4 %	[25.6, 49.9 %]
V _{max}	44.6 %	[21.9, 60.9 %]	44.6 %	[26.9, 71.6 %]
V _c	22.6 %	[16.9, 27.2 %]	22.6 %	[17.4, 27.2 %]
Residual Error				
Proportional	14.4 %	[12.3, 16.6 %]	14.4 %	[12.2, 16.4 %]

95% CI, 95% Confidence interval; CL, clearance; V_{max}, maximum metabolic rate of Michaelis elimination; K_m, Michaelis-Menten constant; V_c, central volume; V_p, peripheral volume; Q, intercompartmental clearance. For bootstrap, the number of replicates was 500.

1.2.5 GVHD Prophylaxis

The purpose of GVHD prophylaxis following allogeneic HCT is to prevent GVHD and enable engraftment without an excess rate of disease relapse. Historically, the most commonly used drugs are cyclosporine (CSA), methotrexate (MTX), corticosteroids, and tacrolimus. A large phase III trial comparing tacrolimus and CSA concluded that there was a lower acute GVHD in the tacrolimus group (17.5% v 48.0%, P<0.0001), and a comparable chronic GVHD in two groups (47.3% v 47.8%).[\[19\]](#)

Two groups have now published very encouraging data on the use of post-transplant cyclophosphamide (PT/Cy) in HLA-matched related and unrelated donor recipients (NCT00134017, NCT01427881). [\[14, 20, 21\]](#)

The Johns Hopkins group has considerable experience in the use of post-transplant cyclophosphamide in the matched related and unrelated donor setting, as well as the haploidentical related donor setting. In a prospective phase 2 study (NCT01427881), high-dose cyclophosphamide (Cy) was given as a single-agent prophylaxis on days 3 and 4 after HLA-matched related or unrelated bone marrow transplant (BMT) with either Cytoxan/TBI or busulfan/fludarabine conditioning.[\[20\]](#) The cumulative incidence of grades II-IV GVHD, grades III-IV GVHD, and chronic GVHD were 43%, 10%, and 10%, respectively. In a follow-up study (NCT00809276), high-dose Cy was given on days 3 and 4 after HLA-matched related or unrelated HCT with busulfan/fludarabine conditioning. The cumulative incidence frequencies of grades II-IV GVHD, grades III-IV GVHD, and chronic GVHD were 51%, 15%, and 14%, respectively. More recently, the Seattle group used PT/Cy following busulfan/fludarabine conditioning in matched related and unrelated donors and had no grade III-IV GVHD and only 15% chronic GVHD (NCT01427881).

1.2.6 Immune Reconstitution Following Allogeneic Transplant

A characteristic of GATA2 deficiency is a severe deficiency of monocytes and B and NK cells.[\[3\]](#) The reconstitution of these cell populations is one aspect of the normal hematopoiesis that will

be assessed in this study. In addition, T cell immune reconstitution after transplantation reflects the balance of peripheral expansion of memory populations and the generation of new naive T cells through renewed thymopoiesis. Factors such as host and viral antigens can drive CD8 memory/effector expansion, whereas acute and chronic GVHD can reduce thymic function and capacity for thymopoiesis. A severe reduction in donor T cell populations may impact CD8 memory/effector repopulation. Alternatively, a decline in the incidence of GVHD (and its associated high dose steroid therapy) may enhance post-transplant thymopoiesis and recovery of T cell populations. This protocol's structure supports analysis of the recovery of overall T, B, and NK cell numbers and chimerism, as well as specific repopulation of naive, effector and regulatory populations of T, B, and NK cells.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

- 2.1.1.1 Age ≥ 6 and ≤ 70 years old
- 2.1.1.2 Germline mutation in the GATA2 gene, predicted to be deleterious or previously reported in GATA2 deficiency as determined by targeted GATA2 sequencing performed at the NIH
- 2.1.1.3 Clinical manifestation(s) consistent with a diagnosis of GATA2 deficiency, including any of the following (**Note:** only one clinical manifestation is required):
 - History of severe, disfiguring, and/or recurrent infections
 - Low monocyte (< 190 cells/ μ L), B cell (< 61 cells/ μ L) and/or NK cell (< 126 cells/ μ L) counts
 - Myelodysplastic syndrome by World Health Organization (WHO) criteria (see [Appendix B](#))
- 2.1.1.4 "Early stage" GATA2 deficiency defined as a hypocellular for age bone marrow (see [Appendix C](#)) with less than 5% blasts and normal cytogenetics or favorable cytogenetics (defined as "good" or "very good" cytogenetics risk groups in [Appendix A](#) plus trisomy 8)
- 2.1.1.5 Availability of an 8/8 HLA-matched related or unrelated donor, a 7/8 HLA-matched unrelated donor or a haploidentical related donor
- 2.1.1.6 Lansky (for participants < 16 years of age) or Karnofsky (for participants ≥ 16 years of age) performance status of $\geq 40\%$ (see [Appendix D](#))
- 2.1.1.7 Left ventricular ejection fraction $> 40\%$, preferably by 2-D echocardiogram (echo) obtained within 90 days prior to treatment initiation
- 2.1.1.8 Participants must have adequate organ function as defined below:

Total bilirubin	≤ 2.5 x upper limit of normal (ULN)
Alanine transaminase (ALT) and aspartate	≤ 5 x ULN

aminotransferase (AST)	
Creatinine	<p>Adult participants: ≤ 2.0 mg/dl and creatinine clearance ≥ 30 ml/min.</p> <p>Pediatric participants (<18 years old): creatinine <1.5 mg/dL and a creatinine clearance using the Schwartz Formula (see Appendix E) > 30 mL/min/1.73m²</p>

- 2.1.1.9 Pulmonary function tests (PFT)s: FEV1 and adjusted DLCO $>30\%$. Children who are unable to cooperate for PFTs due to age are still eligible if no evidence of dyspnea at rest and no need for supplemental oxygen
- 2.1.1.10 Women of childbearing potential (WOCBP) and men must agree to use highly effective contraception (hormonal, intrauterine device (IUD), abstinence, tubal ligation, partner has had the previous vasectomy) at the study entry, for the duration of study treatment, and for at least one-year post-allogeneic HCT or 12 months after completion of chemotherapy preparative administration if HCT is not performed for women and for 4 months for the same for men.
- 2.1.1.11 Breastfeeding participants must be willing to discontinue breastfeeding
- 2.1.1.12 Willingness to remain in the NIH hospital or, if discharged, stay close to the NIH (60 minutes' drive), for a minimum of 100 days after transplant or longer if there are complications. The participants must commit to having an adult caregiver with them during the first 100 days after transplant in case of discharging from the hospital before 100 days verified by social worker
- 2.1.1.13 Participants with hepatitis B virus (HBV) or hepatitis C virus (HCV) antibody-positive testing are allowed if HBV DNA <100 IU/m or HCV RNA level is undetectable. Additionally, transplantation must be approved by a hepatology consult for these participants
- 2.1.1.14 Participants or parents/guardians must be able to understand and willing to sign a written informed consent document

2.1.2 Exclusion Criteria

- 2.1.2.1 Participants with a Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) score ([Appendix F](#)) > 8
- 2.1.2.2 Participants who have received any investigational agents within 4 weeks before treatment initiation with the exception of virus-specific T cells for the treatment of viral infection/reactivation prior to allogeneic HCT
- 2.1.2.3 Participants with a history of hematologic malignancy (e.g., AML, CMML). Note: participants with MDS are included
- 2.1.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to agents (fludarabine, cyclophosphamide, tacrolimus, mycophenolate mofetil, granulocyte-colony stimulating factor (G-CSF)) used in the study
- 2.1.2.5 Presence of active malignancy. Note: participants with malignancy driven by viruses

(e.g., human papillomavirus (HPV) or HPV or Epstein-Barr virus (EBV)) are allowed as the immune reconstitution after transplant may control the malignancy and participants with MDS are allowed

2.1.2.6 Human immunodeficiency virus (HIV)-infected participants

2.1.2.7 Pregnancy (confirmed with β -HCG serum or urine pregnancy test performed in WOCBP at screening)

2.1.2.8 Uncontrolled intercurrent illness or social situations (as determined by social work consult) that would limit compliance with study requirements

2.2 RECRUITMENT STRATEGIES

This protocol may be abstracted into a plain language announcement posted on NIH websites, including clinicaltrials.gov and the CCR website, and on NIH social media platforms. IRB review and approval of listings of clinical trials on the internet are not required when the information provided is limited to basic trial information such as title, purpose. All other participant-directed materials will be submitted for review by the IRB.

2.3 SCREENING EVALUATION

2.3.1 Screening Activities Performed Before a Consent for Screening Has Been Signed

Minimal risk activities that may be performed before the participant has signed a consent include the following:

- Email, written, in person or telephone or video communications with prospective participants
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

2.3.2 Screening Activities Performed After a Consent for Screening Has Been Signed

The following activities will be performed only after the subject has signed the study consent OR the consent for study 13-I-0157 The Natural History of GATA2 Deficiency and Related Disorders (provided the procedure is permitted on that study) on which screening activities may also be performed. Assessments performed at other clinical facilities or on another protocol at NIH within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

Any time before treatment initiation:

- GATA2 targeted gene sequencing (GATA2 assay) performed at the NIH

Testing to determine the availability of a suitable donor and to aid in donor selection:

- High resolution HLA typing at HLA-A, -B, -C, -DR, and -DQ loci by the Department of Transfusion Medicine (HLA typing must be performed twice at any time in the two years prior to donor cell collection)

- Anti-donor HLA antibody screens must also be performed for all participants against their donor
- Blood typing (ABO/Rh)

Within 90 days before treatment initiation:

- Complete medical history and physical examination (PE), including weight, height, and vital signs
- Assessment of Lansky (for participants < 16 years of age) or Karnofsky (for participants ≥ 16 years of age) ([Appendix D](#))
- Review of current medications
- HCT-CI score ([Appendix F](#))
- Complete blood cell count (CBC) with differential
- Total bilirubin, ALT, AST, creatinine
- 24-hour urine collection for CrCl in adult participants
- HIV, Hepatitis B, and C serology
- Hepatitis B and C viral load in participants positive for Hepatitis B and C serology
- 2D echocardiogram
- EKG
- PFTs, including measurement of FEV1, and DLCO. Children who are unable to cooperate for PFTs due to age, clinical performance (i.e., dyspnea, exercise intolerance) and oxygen saturation will be utilized as an assessment of pulmonary function
- Bone marrow biopsy and aspirate. Bone marrow biopsy studies will include flow cytometry, cytogenetics, molecular testing, immunohistochemistry, and fluorescence *in situ* hybridization as appropriate
- Hepatology consultation for participants positive for HBV or HCV
- Social work consult required prior to excluding based on social situations per item [2.1.2.8](#)

Within 7 days before treatment initiation:

- Serum or urine Beta Human Chorionic Gonadotropin (β-HCG) (WOCBP only)

2.3.3 Donor Selection and Prioritization

Related and unrelated donors may be used for the clinical donation of hematopoietic stem cells for participants on this protocol. The donation activities, including procedure consents, are covered by clinical guidelines and are not considered research activity. Multiple potential donors may undergo clinical evaluation concurrently. Related donors may be evaluated and undergo cell collection on study #04-C-0165. Unrelated donors will be identified through Be The Match® in accordance with the current transplant center participation agreement between the National Marrow Donor Program (NMDP) and NIH.

In the event that two or more eligible and suitable donors are identified, the following order of priority for donor selection will be used for clinical donation:

- HLA In order of priority:
 - HLA-matched related donor (8/8 at HLA-A, -B, -C, and –DR loci)
 - HLA-matched unrelated donor (8/8 at HLA-A, -B, -C, and –DR loci)
 - HLA-haploidentical related donor
 - HLA-matched unrelated donor (7/8 at HLA-A, -B, -C, and –DR loci)
- ABO In order of priority:
 - ABO crossmatch compatible
 - Minor ABO incompatible
 - Major ABO incompatible
- Cytomegalovirus (CMV) serostatus: CMV negative donor preferred if the recipient is CMV negative; CMV positive donor preferred if the recipient is CMV positive
- Epstein-Barr Virus (EBV) serostatus: EBV negative donor preferred if the recipient is EBV negative; EBV positive donor is preferred if the recipient is EBV positive
- Sex: In order of priority:
 - Male
 - Nulliparous female
 - Multiparous female

Other factors such as donor age, health history, and availability will be integrated into the donor selection process and may be prioritized over HLA, ABO, CMV serostatus, EBV serostatus, and sex. Prioritization of donors beyond those listed above are suggested but not mandated by the protocol.

2.4 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at:

[https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-\(ADCR\).aspx?Mode=Edit](https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit).

2.4.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of transient underlying condition not related to the condition under study may be rescreened once the underlying condition has resolved.

2.4.2 Treatment Assignment

Cohorts

Number	Name	Description
1	Cohort 1	Participants with GATA2 who have an 8/8 HLA-matched related or unrelated donor
2	Cohort 2	Participants with GATA2 who have a 7/8 HLA-matched unrelated donor or a haploidentical related donor

Arms

Number	Name	Description
1	Arm A	Briquilimab, fludarabine, 200 cGy TBI
2	Arm B	Briquilimab, fludarabine, cyclophosphamide, 200 Gy TBI

Arm Assignment

Participants in cohort 1 will be directly assigned to arm A, participants in cohort 2 will be directly assigned to arm B.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a single-center, phase II study to evaluate the safety and efficacy of allogeneic HCT for participants with GATA2 deficiency who are conditioned with Briquilimab.

Participants will be admitted at the start of the preparative regimen and continue to be hospitalized until they have engrafted and are no longer requiring intravenous fluids or medications and able to maintain adequate PO intake. This usually requires 4 weeks from the time of the stem cell infusion.

Participants will be closely followed for 3 years post-HCT.

Briquilimab will be administered as a single IV dose on any day between day -13 and -10, preferably on day -11. The pharmacokinetics (PK) of Briquilimab will be determined following its administration by a validated enzyme-linked immunosorbent assay (ELISA) assay. PK samples will be collected starting immediately after infusion of the dose of Briquilimab and continue for 2 days. These PK samples will be used to perform PK modeling to predict Briquilimab levels over time. The date of HSC infusion will be delayed if the Briquilimab antibody PK modeling predicts that the Briquilimab level on day 0 is not expected to be <2000 ng/mL. The date of HSC infusion will be rescheduled to the day the PK model predicts the Briquilimab antibody level will be <2000 ng/mL or up to four days thereafter. Additional PK samples will be drawn on a research basis, but these samples will not be used to determine the date of HSC infusion.

Table 2 Sample Conditioning Regimen and Pharmacokinetic Sampling Schedule for Cohort 1 with Briquilimab Infusion on Day -11

Sun	Mon	Tues	Weds	Thurs	Fri	Sat
	Day -11 Briquilimab PK ^b	Day -10 PK	Day -9 PK	Day -8	Day -7 PK	Day -6
Day -5	Day -4 fludarabine	Day -3 fludarabine PK	Day -2 fludarabine	Day -1 TBI 200 cGy PK	Day 0 ^a HCT infusion PK	

^a Infusion date may be adjusted based on Briquilimab antibody PK data.

^b PK samples will be drawn at time points described in section [5.1.2](#).

Table 3 Sample Conditioning Regimen and Pharmacokinetic Sampling Schedule for Cohort 2 with Briquilimab Infusion on Day -11

Sun	Mon	Tues	Weds	Thurs	Fri	Sat
	Day -11 Briquilimab PK ^b	Day -10 PK	Day -9 PK	Day -8	Day -7 PK	Day -6 fludarabine cyclophosphamide
Day -5 fludarabine cyclophosphamide	Day -4 fludarabine	Day -3 fludarabine PK	Day -2 fludarabine	Day -1 TBI 200 cGy PK	Day 0 ^a HCT infusion PK	

^a Infusion date may be adjusted based on Briquilimab antibody PK data.

^b PK samples will be drawn at time points described in section [5.1.2](#).

Target HSC Dose: The target HSC dose is any dose $>5 \times 10^6$ and $\leq 10 \times 10^6$ CD34+ cells/kg recipient body weight.

Only peripheral blood stem cells will be used as a graft source in this protocol.

32 participants are expected to be enrolled in the protocol.

3.2 DRUG ADMINISTRATION

Central line access will be required prior to the start of the preparative regimen. Clinical determination for the most appropriate line type and placement will be made on a case-by-case basis.

Note: Every effort will be made to target the infusion of study drugs as outlined in the protocol as closely as possible; however, a window of +/- 10 minutes of the timing is allowed to account for variability of infusion pumps.

3.2.1 Briquilimab

3.2.1.1 Premedication for Briquilimab

Participants will receive pre-medications within 2 hours prior to infusion of Briquilimab. The pre-medication regimen will be:

- Acetaminophen 10 mg/kg (max 650 mg) orally
- Diphenhydramine 1 mg/kg (max 50 mg) given IV or orally
- Hydrocortisone 1 mg/kg (max 100 mg) IV

3.2.1.2 Briquilimab Administration

Briquilimab will be administered as a single 0.6 mg/kg IV dose between day -13 and -10, preferably on day -11, to all participants. Briquilimab will be infused over a minimum duration of 1 hour or, for those that receive an infusion volume greater than 250 mL, the infusion rate must not exceed 250 mL/hr.

Infuse the total dose volume of Briquilimab intravenously through the CVC or a peripheral IV. The line should be completely flushed with 5% dextrose at the end of the infusion to ensure administration of the entire dose.

- Pre-infusion, end of infusion (\pm 10 min), and 1-hour post-infusion (\pm 10 min) vital signs will be obtained. All participants should be monitored for at least 4 hours after completion of the Briquilimab infusion for AEs. AEs will be documented and reported.
- Participants who experience any treatment-related adverse events during the observation period should be further monitored as clinically appropriate (e.g., for up to 24 hours post-dose).

3.2.1.3 Briquilimab Infusion-related reactions

For mild, non-life-threatening infusion-related reactions (Grades 1–2 Common Terminology Criteria for Adverse Events (CTCAE v5), Briquilimab infusion will be temporarily halted. Once all symptoms have resolved, the infusion may be restarted at one-half the rate at which the reaction occurred, with the administration of additional pre-medications as directed by the attending physician. For severe infusion-related reactions (\geq Grade 3 CTCAE v5), the infusion will be discontinued. PK studies will be drawn on all participants. If participants are clinically stable (i.e., Glasgow Coma Scale of 13 or higher and not intubated, not on inotropes or vasopressors, and not receiving dialysis or continuous renal replacement therapy), conditioning regimen and infusion of the cells will continue according to the protocol. If participants are not clinically stable (i.e., Glasgow Coma Scale of $<$ 13, on inotropes or vasopressors, or receiving dialysis or continuous renal replacement), these participants will be taken off treatment.

3.2.2 Conditioning Regimen for 8/8 Matched Related and Unrelated Donors with Fludarabine, and TBI (Arm A)

Participants in Arm A will receive a conditioning regimen as explained in [Table 4](#).

Table 4. Arm A

Agent	Dose	Days
Fludarabine ^a	30 mg/m ² IV infusion over 30 min once daily for 3 days	Days -4, -3, and -2
Total body Irradiation ^b	200 cGy	Day -1

^a The dose of fludarabine will be dosed based on actual body weight and the dose adjusted for renal dysfunction. Fludarabine will be reduced to 24 mg/m² for participants with a creatinine clearance of ≤ 70 mL/min/1.73m². The creatinine clearance obtained during baseline will be used. A pre-fludarabine 24-hour creatinine clearance will not be repeated prior to Day -4 unless clinically indicated.

^b Total body irradiation dose of 200cGy will be delivered as per the Radiation Oncology Branch standard of practice.

3.2.3 Conditioning Regimen for 7/8 URD and Haploidentical Related Donors with Cyclophosphamide, Fludarabine, and TBI (Arm B)

Participants in Arm B will receive a conditioning regimen as explained in [Table 5](#).

Table 5. Arm B

Agent	Dose	Days
Fludarabine ^a	30 mg/m ² IV infusion over 30 min once daily for 5 days	Days -6, -5, -4, -3, and -2
Cyclophosphamide ^b	14.5 mg/kg once daily for two days	Days -6 and -5
Total body Irradiation ^c	200 cGy	Day -1

^a The dose of fludarabine will be dosed based on actual body weight and the dose adjusted for renal dysfunction. Fludarabine will be reduced to 24 mg/m² for participants with a creatinine clearance of ≤ 70 mL/min/1.73m². The creatinine clearance obtained during baseline will be used. A pre-fludarabine 24-hour creatinine clearance will not be repeated prior to Day -6 unless clinically indicated

^b Cyclophosphamide will be dosed on actual body weight. Participants will be given 500 mL of 0.9% sodium chloride over 1-2 hours prior to and following each cyclophosphamide dose (1000 mL total). Mesna will not be used for uroprotection in the pre-transplant cyclophosphamide regimen but will be employed in the higher dose post-transplant GVHD prophylaxis regimen

^c Total body irradiation dose of 200 cGy will be delivered as per the Radiation Oncology Branch standard of practice.

3.2.4 Transplantation Day 0

On day 0, the recipient will receive fresh or cryopreserved stem cells from the donor. If cryopreserved, the stem cell product will be thawed and immediately administered intravenously. The graft will not be manipulated to deplete T cells. The target dose is any dose $> 5 \times 10^6$ and $\leq 10 \times 10^6$ CD34+ cells/kg recipient body weight.

3.2.5 Post-Transplant GVHD Prophylaxis

All recipients will receive post-transplant cyclophosphamide followed by tacrolimus and mycophenolate mofetil as explained in [Table 6](#).

Table 6. GVHD prophylaxis

Agent	Dose	Days
Cyclophosphamide ^a	50 mg/kg IV once daily over 2 hours according to ideal body weight ^b	Days +3 and +4
Tacrolimus ^c	0.02 mg/kg/day IV continuous infusion according to actual body weight	Starting on Day +5 until conditions described in section 3.2.5.1 are met
Mycophenolate mofetil	15 mg/kg IV over 2 hours according to actual body weight three times per day	Starting on Day +5 until approximately Day +35 (\pm 2 days)

^a Cyclophosphamide on day +3 should be given between 60-72 hours after the start of the stem cell infusion. On day +4, cyclophosphamide should be given approximately 24 hours after the dose on day +3.

^b Ideal body weight (IBW) (based on the Center for Disease Control (CDC) growth charts for participants ≤ 20 years) should be used to determine cyclophosphamide dose unless the participant weighs less than ideal body weight, in which case actual body weight should be used.

Ideal body weight for males >20 years is $IBW = 50 \text{ kg} + 2.3 \text{ kg} \times (\text{height in inches} - 60)$, and ideal body weight for females >20 years is $IBW = 45.5 \text{ kg} + 2.3 \text{ kg} \times (\text{height in inches} - 60)$. CDC growth curves will be used to determine IBW based on the 50th percentile for age for participants up to 20 years.

^c Tacrolimus and mycophenolate mofetil may also be initiated PO at an equivalent dose in patients tolerating oral intake.

3.2.5.1 GVHD Prophylaxis with Tacrolimus

Tacrolimus will be administered as described in [Table 6](#) for a target level of 5 to 10 ng/ml.

3.2.5.2 GVHD Prophylaxis with mycophenolate mofetil

Mycophenolate mofetil will be administered as described in [Table 6](#).

3.2.5.3 GVHD Prophylaxis with Cyclophosphamide

Cyclophosphamide will be administered as described in [Table 6](#). Cyclophosphamide will be accompanied by Mesna 50 mg/kg IV as a continuous infusion over 24 hours once daily x 2 days on Days +3 and +4 for uroprotection. Additional measures to prevent cyclophosphamide-induced hemorrhagic cystitis such as hydration and diuresis may be used based on the below NIH BMT Consortium supportive care guidelines http://intranet.cc.nih.gov/bmt/clinicalcare/pdf/HemCystitis_Prevent_guideline_2007.pdf

3.3 DOSE MODIFICATIONS

3.3.1 Briquilimab

Dose modifications of Briquilimab are not allowed.

3.3.2 HSC transplant

If donor apheresis does not yield a targeted dose, any dose of CD34+ cells per kg will be allowed to administer as this is necessary for participants' safety.

If PBSC cell transplant results in dimethyl sulfoxide (DMSO)-related toxicities (chills, muscle aches), drugs such as diphenhydramine and meperidine may be administered one time.

3.3.3 Fludarabine

Dose modifications of fludarabine are not allowed except for participants with renal impairment as explained in sections [3.2.2](#) and [3.2.3](#).

3.3.4 Cyclophosphamide

Only one day of post-transplant cyclophosphamide will be given if the recipient has a baseline ejection fraction of < 50% or when deemed appropriate by the PI for a history of cardiac dysfunction.

3.3.5 Tacrolimus

The dose may be modified in the presence of significant drug interactions that cannot be avoided.

Doses of tacrolimus will be adjusted according to levels monitored at least once a week for the first 100 days post-HCT and/or upon symptoms or concerning drug-related toxicities.

Levels may be monitored at a frequency per the PI's discretion after day +100. The target level will be 5 to 10 ng/ml.

For participants initiated on IV tacrolimus, tacrolimus will be converted to an equivalent oral dose using a 1:3 conversion when the participant is reliably taking oral medications. For participants on >0.5 mg tacrolimus per day, the total daily dose will be divided into two equal doses, one dose given approximately every 12 hours. For participants on ≤ 0.5 mg tacrolimus per day, the dose may be administered as a daily dose

The total dose of tacrolimus will continue until approximately day +180 (± 14 days), and then will be progressively reduced, as long as the severity of GVHD is less than grade II and the participant does not require systemic steroids. Tacrolimus may be stopped or tapered before day +180 if there is a concern for toxicity or relapse. Additionally, the Principal Investigator (PI) may choose another immunosuppressive agent in place of tacrolimus in the event of toxicity from the tacrolimus.

Participants may be given cyclosporine in place of tacrolimus if tacrolimus is unavailable or there are difficulties in obtaining tacrolimus levels at the NIH.

3.3.6 Mycophenolate mofetil

The dose may be modified in the presence of significant drug interactions that cannot be avoided.

When the participant is reliably taking oral medications, mycophenolate will be converted to an equivalent oral dose. The total daily dose will be divided into three equal doses, one dose given approximately every 8 hours. The total daily dose should not exceed 3 grams per day.

3.4 STUDY STOPPING RULES

For safety reasons, the enrolment into a given Arm will be temporarily halted until an expedited safety report has been evaluated by the IND Sponsor and SMC, and the decision to continue trial is approved by the Sponsor/SMC for the following event (s):

- 3 participants in 10 in a given Arm have died by day +180 due to treatment-related causes (and no other stopping rules are implemented)
- 3 participants in 10 in a given Arm have failed to achieve sustained donor engraftment ($\leq 10\%$ T-cell and $\leq 90\%$ myeloid donor cells) by 100 days post-transplant (and no other stopping rules are implemented)
- 3 participants in 10 in a given Arm have experienced grade 3-4 aGVHD not responsive to one week of high-dose steroids (and no other stopping rules are implemented)

3.5 ON STUDY ASSESSMENTS/EVALUATIONS

3.5.1 Timing of Procedures

The following describes all tests and procedures to be conducted on the study and during treatment. Assessments will be performed according to the Study Calendar (section 3.6).

For each time period, consider the following order of assessments:

- **Screening:** Refer to section 2.3.2.
- **Baseline:** Baseline evaluations should be performed prior to the start of Briquilimab infusion according to the schedule in the Study Calendar (section 3.6). Tests performed as part of screening may not need to be repeated if they were performed within the window specified in the Study Calendar (section 3.6).
- **Study Drug Administration:** Briquilimab will be administered on any day between day -13 and -10, preferably on day -11. The preparative regimen will start on Day -4 (Cohort 1) or Day -6 (Cohort 2), the transplant will be done on Day 0.
- **Unscheduled Visits:** In the event of an unscheduled/unplanned visit (e.g., additional clinical assessment(s) due to toxicity or GVHD), the investigator should use the best clinical judgment as to the necessary assessments. In the event that the decision is made to continue treatment, all tests/assessments as required by the next visit on the Study Calendar (section 3.6) should still be conducted (or repeated) within the applicable windows. If a decision is made to discontinue treatment, the participant should have a post-therapy follow-up with tests/assessments completed (or repeated) within the applicable windows.

3.5.1.1 Follow-up

After the transplant, the participants will be evaluated daily while inpatient and then at least once weekly while outpatient during the first 100 days after transplantation. After 100 days, participants will be evaluated at days 180 (+/- 30 days), 360 (+/- 30 days), then yearly (± 90 days) for years 2-3. See Study Calendar (section 3.6) for the schedule of clinical evaluations. **Note:** Participants can be evaluated more often if clinically indicated.

After Day 100 visit, in rare cases when the participant is not able to come for the following visits, the follow-up may be conducted by phone, email, or other NIH-approved remote platforms used in compliance with local policy, including HRPP Policy 303. In these cases, we will ask participants to visit local oncologist and send us results of all tests and procedures planned to be performed on this protocol.

Participants will be followed for 3 years after transplant on this protocol.

Participants will be recommended to lessen or avoid some day-to-day household activities and public activities for at least 6 months after the transplant to reduce the chance of infection and other complications post-transplant. These restrictions could potentially extend for a longer time.

3.5.2 Description of Procedures

- Medical history: a review of treatment history, any ongoing medical conditions, and medical history pertaining to eligibility on study and involvement during the study.
- Physical exam: a review of organ systems, height, weight, and vital signs (i.e., temperature, pulse, respiration, blood pressure, pulse oximetry) for assessment of eligibility, safety and GVHD. Height will only be measured at screening and baseline.
- Performance status (Lansky/Karnofsky): an assessment of activities of daily living; see [Appendix D](#) pertaining to eligibility and assessment of GVHD.
- GVHD evaluation ([Appendix G, Study Instrument](#))
- HCT-CI Score, [Appendix F](#) for assessment of eligibility
- Laboratory assessments: the following comprises the required tests/analytes. These assessments may be performed at CLIA (or equivalent) certified laboratories outside the Clinical Center and results forwarded to the study team for review and management. Given that the methodologies utilized are similar across all laboratories, no significant variability is expected and there is no anticipation that study data will be affected.

Given that the methodologies utilized are similar across all laboratories, no significant variability is expected and there is no anticipation that study data will be affected. Note: Panels containing the tests below may be ordered in lieu of individual tests:

- High resolution HLA typing at HLA-A, -B, -C, -DR, and -DQ loci by the Department of Transfusion Medicine for donor matching.
- Anti-donor HLA antibody screen must also be performed for all recipients against their donor for donor matching.
- Type and Screen (ABO/Rh) for donor matching
- GATA2 assay to estimate eligibility
- CBC with differential to assess eligibility, safety, and engraftment
- Reticulocyte count to assess engraftment
- [Acute](#) Care Panel: sodium (Na), potassium (K), chloride (Cl), total CO₂ (bicarbonate), creatinine, glucose, urea nitrogen (BUN) to assess safety
- [Mineral](#) Panel: albumin, calcium total (Ca), magnesium total (Mg), phosphorus (P) to assess safety
- [Hepatic](#) Panel: alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin to assess safety and evaluate GVHD
- Baseline assessments and may be assessed post-baseline as clinically indicated:
 - Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen
 - Total protein, lactate dehydrogenase (LDH), uric acid

- Fasting **Lipid** Panel: total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol
- C reactive protein (CRP), erythrocyte sedimentation rate (ESR)
- Isohemagglutinin titer, except for recipients with AB blood type
- Thyroid stimulating hormone (TSH), free thyroxin (T4)
- Iron and Transferrin
- Cortisol drawn between 6-8 AM (cortisol <18 mcg/dl should be followed with an adrenocorticotrophic hormone (ACTH) stimulation test) (only for participants on steroids within the past 2 months)
- Urinalysis with microscopic evaluation to assess safety
- Spot urine protein (UPr) to creatinine (Cr) ratio to assess safety
- 24-hour urine collection for creatinine clearance to assess eligibility and safety
- QuantiFERON tuberculosis (TB) Gold testing for tuberculosis to assess safety
- Serum or urine β -HCG performed to determine eligibility and treatment initiation (WOCBP only)
- Antibody screens (IgG \pm IgM) for HAV, Human T-Lymphotropic Virus (HTLV-1/2), Trypanosoma cruzi (T cruzi), Herpes Simplex Virus (HSV) 1/2, Varicella Zoster Virus (VZV), West Nile virus, Toxoplasmosis; syphilis screen (RPR)
- HIV, Hepatitis B, and C serology to assess eligibility
- Hepatitis B and C viral load in participants positive for Hepatitis B and C serology to assess eligibility
- EBV and CMV serology and EBV early antigen to characterize immune reconstitution. **NOTE:** Recipients on chronic IgG replacement may need viral polymerase chain reaction (PCR)s in lieu of or in addition to antibody testing, as clinically indicated and available, as well as specifically timed serologic testing to minimize immunoglobulin replacement interference with serology results
- PCR in blood for EBV, CMV, and adenovirus to characterize immune reconstitution
- T Lymphocytes, B Lymphocytes, and Natural Killer Cells (TBNK) to characterize immune reconstitution
- Quantitative immunoglobulins (IgG, IgA, IgM) to characterize immune reconstitution
- Vaccine titers for tetanus, diphtheria, and pneumococcus to characterize immune reconstitution
- Tacrolimus level in blood

Other procedures:

- Electrocardiogram (EKG) – 12-lead mandatory at screening to determine eligibility and during the study if clinically indicated
- 2D Echocardiogram to assess eligibility and to evaluate GVHD

- Pulmonary function tests (PFTs) to assess eligibility and to evaluate GVHD
- Imaging
 - Non-contrast CT scan of the chest, abdomen, and pelvis at baseline mandatory and after HCT if clinically indicated to assess safety
 - Dual Energy X-Ray Absorptiometry (DEXA) (only if clinically indicated at baseline and after HCT)
 - Positron Emission Tomography (PET)-CT scan (only if clinically indicated at baseline and after HCT)

Scans will be performed per routine technique. Note: Scans may be performed outside of the Clinical Center and the result forwarded to the study team for review at screening or any time during the study. Given that the methodologies utilized are similar across all facilities, no significant variability is expected and there is no anticipation that study data will be affected.

- Ophthalmologic evaluation to evaluate GVHD.
- Dermatologic, nutrition, infectious disease (ID), and social worker evaluations to assess safety
- Dental consultation to evaluate GVHD. Note: dental records indicating adequate dental evaluation and management in the 6 months prior to HCT may be substituted
- Radiation Oncology consultation
- Age-appropriate gynecologic consultation for female participants to evaluate GVHD. Gynecology evaluation may be performed at home; post-transplant gynecology follow-up is highly recommended but not mandatory.
- Hepatology consultation for participants positive for HBV or HCV to assess eligibility
- Bone marrow biopsy, aspirate & cytogenetics will be performed on participants at the NIH CC at baseline if the screening marrow and aspirate were performed outside, if interim therapy is administered or if clinically indicated. With flow cytometry, as well as immunohistochemistry (IHC), molecular testing, cytogenetics/ Fluorescence in Situ Hybridization (FISH), and next-generation sequencing MDS panel as appropriate; chimerism if post-allo HCT, unless an aspirate is unattainable due to clinical reasons. Molecular pathology for T cell clonality is required at baseline and one year only.
- Determination of Donor/Host Chimerism After Allogeneic HCT: will be performed by the Clinical Center Department of Laboratory Medicine (DLM) by PCR analysis of the variable number of tandem repeats. STR profiling of the donor and recipient to be used for chimerism determination post-HCT will be performed by Clinical Center Pathology prior to allogeneic HCT. Donor chimerism studies on the peripheral blood and bone marrow will be performed as outlined in the Study Calendar (section 3.6). Additional chimerism assessments should be performed as clinically indicated in participants where there is a concern for decreasing donor chimerism and graft failure.
- Adverse events and concomitant medication review: adverse events and concomitant medication will be continuously monitored throughout the study as explained in section 6.1.

3.5.3 Correlative/Exploratory Assessments

See section [5](#).

3.6 STUDY CALENDAR

3.6.1 Screening, Baseline and Preparative Regimen

Procedure	Screening	Baseline		Preparative regimen, Days										
				-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1
Window(s):	≤ 90 days	≤ 28 days	≤ 7 days	-2/+3 day	N/A									
Medical History	X													
PE	X ^a	X		X	X	X	X	X	X	X	X	X	X	X
Height	X	X												
Weight	X	X		X	X	X	X	X	X	X	X	X	X	X
Vital signs	X ^a	X		X	X	X	X	X	X	X	X	X	X	X
Performance status (Appendix D)	X	X												
HCT-CI score (Appendix F)	X	X												
GATA2 assay (anytime)	X													
CBC with differential	X	X		X			X		X ^b	X ^b	X	X	X	X
Total bilirubin, ALT, AST, creatinine	X													
Acute, Hepatic, and Mineral panels		X		X			X		X ^b	X ^b	X	X	X	X
PT/PTT, fibrinogen		X		X								X		
Serum or urine β-HCG (FOCBP only)	X (≤ 7 days)		X											
Total protein		X		X								X		
LDH		X		X								X		

Procedure	Screening	Baseline		Preparative regimen, Days										
				-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1
Window(s):	≤ 90 days	≤ 28 days	≤ 7 days	-2/+3 day	N/A									
Uric acid		X												
Quantitative immunoglobulins (IgG, IgA, IgM)		X												
Fasting Lipid panel		X												
TBNK		X												
CRP		X												
ESR		X												
Isohemagglutinins (except for participants with AB blood type)		X												
T4 and TSH		X												
Reticulocyte Count		X												
Iron and Transferrin		X												
Urinalysis with microscopic evaluation		X		X										X
Spot UPr/Cr ratio		X												
24-hour urine collection for creatinine clearance	X (adult participants)	X												
Cortisol drawn between 6-8AM (only for participants on steroids within the past 2 months)		X												
QuantiFERON TB Gold		X												
HIV, Hepatitis B, and C serology	X													

Procedure	Screening	Baseline		Preparative regimen, Days										
				-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1
Window(s):	≤ 90 days	≤ 28 days	≤ 7 days	-2/+3 day	N/A									
Hepatitis A serology		X												
Hepatitis B and C viral load in participants positive for Hepatitis B and C serology	X													
Serologies for HTLV-1/2, T cruzi, HSV 1/2, VZV, West Nile virus, Toxoplasmosis; syphilis screen (RPR)		X												
EBV and CMV serology		X												
EBV early antigen		X												
PCR in blood for EBV, CMV and adenovirus		X		X								X		
Vaccine titers for tetanus, diphtheria and pneumococcus		X												
HLA typing	X													
Anti-donor HLA antibody screens	X													
STR profile		X												
ABO/Rh	X	X												
Bone marrow biopsy, aspirate & cytogenetics	X													
PFTs, 2D echo	X													
EKG	X													

Procedure	Screening	Baseline		Preparative regimen, Days										
				-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1
Window(s):	≤ 90 days	≤ 28 days	≤ 7 days	-2/+3 day	N/A									
CT scan of chest, abdomen, and pelvis		X												
Baseline symptoms evaluation		X												
Current Medications	X	X		X										X
Adverse events				X	X	X	X	X	X	X	X	X	X	X
Hepatology consultation for participants positive for HBV or HCV	X													
Infectious Disease consultation		X												
Dermatology consultation		X												
Ophthalmologic consultation		X												
Radiation Oncology consultation		X												
Dental consultation		X												
Gynecologic consultation for female participants		X												
Social work consultation	X (if needed per 2.1.2.8)	X												
Nutrition assessment		X												
Briquilimab				X										
Fludarabine (Cohort 1)											X	X	X	
Fludarabine (Cohort 2)									X	X	X	X	X	

Procedure	Screening	Baseline		Preparative regimen, Days										
				-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1
Window(s):	≤ 90 days	≤ 28 days	≤ 7 days	-2/+3 day	N/A									
Cyclophosphamide (Cohort 2)									X	X				
TBI														X
PID flow panel (section 5)		X												
Briquilimab PK (section 5)				X	X	X		X				X		X

^a PE and vital signs collection as explained in section 3.2.1.2

^b Required for Cohort 2 only.

3.6.2 Day of transplant and Follow Up

Procedures	Days							Year 2	Year 3
	0	1-100	30	60	100	180	360		
Windows	N/A	N/A	± 7 days	± 10 days	± 20 days	± 30 days	± 60 days	± 90 days	± 90 days
Performance status (Appendix D)			X	X	X	X	X	X	X
Medical History			X	X	X	X	X	X	X
PE	X	X ^a	X	X	X	X	X	X	X
GVHD evaluation (Appendix G, Study Instrument)		X ^a	X	X	X	X	X	X	X

Procedures	Days							Year 2	Year 3
	0	1-100	30	60	100	180	360		
Windows	N/A	N/A	± 7 days	± 10 days	± 20 days	± 30 days	± 60 days	± 90 days	± 90 days
Vital signs, weight	X	X ^a	X	X	X	X	X	X	X
CBC with differential	X	X ^a	X	X	X	X	X	X	X
Acute and Mineral panels	X	X ^a	X	X	X				
Hepatic panel	X	X ^a	X	X	X	X	X	X	X
LDH, PT, PTT, fibrinogen, total protein	X	X ^b	X	X	X ^b				
Fasting Lipid panel and iron studies, ESR, CRP, spot UPr/Cr ratio			X	X	X				
Reticulocyte count		X ^b	X	X	X	X	X	X	X
TBNK			X	X					
Quant IGs (IgG, IgA, IgM),			X	X	X	X	X	X	X
Urinalysis with microscopic evaluation	X	X ^b	X	X	X				
ABO and Rh	X ^c	X ^c							
CMV and EBV serology							X	X	X
PCR in blood for EBV, CMV, and adenovirus	X	X ^b	X	X	X	X	X	X	X
Donor chimerism in blood (whole blood, CD3 and myeloid)			X	X	X	X	X	X	X
Vaccine titers for tetanus, diphtheria, and pneumococcus							X	X	X
Bone marrow biopsy, aspirate & cytogenetics					X		X		
PFTs, 2D echo						X	X	X	X
Dental and Ophthalmic evaluation							X		

Procedures	Days							Year 2	Year 3
	0	1-100	30	60	100	180	360		
Windows	N/A	N/A	± 7 days	± 10 days	± 20 days	± 30 days	± 60 days	± 90 days	± 90 days
Gynecologic evaluation (female participants only)							X	X	X
Adverse Events	X	X	X	X	X				
Current/Concomitant Medications	X	X ^a	X	X	X	X	X	X	X
HCT	X								
GVHD prophylaxis (section 3.2.5)		X							
Tacrolimus level		X ^b	X ^b	X ^b	X ^b				
Supportive care (section 4.1)		X	X	X	X	X	X	X	X
Briquilimab PK levels (section 5.1.2)	X								
PID flow panel (section 5.1.1)					X	X	X	X	X

^a Performed daily during initial hospitalization for transplant. Once weekly evaluations are sufficient thereafter regardless of hospitalization status.

^b Performed weekly. LDH, PT, PTT, fibrinogen, total protein and urinalysis will be performed weekly during initial hospitalization for transplant and then only if clinically indicated. Urinalysis may be deferred if participant is or becomes anuric. If participant has completed Day 100 evaluations between Day 80 and Day 100 and is discharged to their home physician prior to Day 100, weekly labs do not need to be completed.

^c Performed every four days during initial hospitalization for transplant and if clinically indicated thereafter.

3.7 RADIATION GUIDELINES

For total body irradiation (TBI), participants will be seen in consultation with a radiation oncologist. Following consultation, participants will be measured to determine the maximal lateral separation at the level of the hip with the participants in the treatment position. The lateral head and neck separation will also be measured to determine the appropriate thickness of compensators as needed for the treatment. Participants will receive TBI on day -1 as per standard of practice. The total dose will be 200 cGy. For opposed lateral treatment fields, dose will be prescribed to the lateral midplane at an extended distance to isocenter. Head and neck compensation will be used as needed to minimize dose heterogeneity. Modifications to the radiation treatment plan, with the exception of the total dose, may be made at the discretion of the treating radiation oncologist based on the subject's thickness or other technical factors.

3.8 COSTS AND COMPENSATION

3.8.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not generally be provided or paid for by the NIH Clinical Center.

3.8.2 Compensation

Participants will not be compensated on this study.

3.8.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from the study, effort must be made to have all participants complete a safety visit approximately 100 days after transplant or 30 days after Briquilimab was administered if transplant is not done.

3.9.1 Criteria for removal from protocol therapy

- Progressive disability, that makes participant not eligible for transplant per criteria in section [2.1](#)
- Severe Briquilimab infusion-related reaction as explained in section [3.2.1.3](#)
- No HCT response (transplant failure) as explained in section [6.3](#)
- Participant requests to be withdrawn from active therapy
- Investigator discretion
- Participant becomes pregnant
- Donor becomes unavailable

3.9.2 Off-Study Criteria

- Participant does not receive transplant for any reason. Note: 30 days safety follow up visit after Briquilimab must be completed if preparative regimen is started
- Participant has completed this 3 years study
- Participant requests to be withdrawn from the study
- Death
- Study is cancelled for any reason
- Investigator's discretion
- Lost to follow-up
- PI decision to end this study
- Screen failure

3.9.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 month and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an **IRB-approved** certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

4 CONCOMITANT MEDICATIONS/MEASURES

Note: Other medications may be substituted, or medications may be held at the discretion of the treating investigator. Below are guidelines and suggested medications and schedule to be used, however, they can be altered by the treating physician as clinically indicated.

4.1 SUPPORTIVE CARE

4.1.1 Infection Prophylaxis

For a full description of infection prophylaxis please refer to the NIH BMT Consortium Supportive Care Guidelines at <https://intranet.cc.nih.gov/bmt/education/infectious-mgmt-guidelines>.

4.1.2 Blood Product Support

- a) Participants' blood counts will be monitored daily during the hospitalization. Participants will receive packed red blood cells and platelets, as needed to maintain hemoglobin (Hb) > 8.0

gm/dl (or higher, if clinically indicated), and platelets $> 10,000/\text{mm}^3$ (or higher, if clinically indicated)

- b) All blood products, with the exception of the stem cell product and Donor Cell Infusion (DCI), will be irradiated
- c) Leukocyte filters will be utilized for all blood and platelet transfusions to decrease sensitization to transfused leukocytes and decrease the risk of CMV infection. The participant, who is seronegative for CMV and whose donor is seronegative, should receive CMV-negative blood products whenever possible
- d) Participants who clinically require transfusions pre-HCT will receive irradiated blood and cellular blood products beginning a minimum of two weeks prior to allogeneic HCT. Transfusion of irradiated blood and cellular blood products will continue to at least one year after transplantation. Participants receiving immunosuppressive medication will continue to have all blood and cellular blood products irradiated until discontinuation of immunosuppressive treatment
- e) Participants sensitized to HLA or platelet specific antigens should receive HLA matched apheresis platelet collections

4.1.3 Nutritional Support

If mucositis or GVHD prevents adequate PO intake, parenteral hyperalimentation will be instituted and discontinued with input from the Pharmacy and Nutrition Departments. Oral intake will resume when clinically appropriate under the supervision of the dietary service of the Clinical Center.

4.1.4 Anti-emetic Usage

Anti-emetic usage will follow recommendations from the Pharmacy.

4.1.5 Intravenous Immune Globulin (IVIG)

IVIG (the standard dose is 500 mg/kg/week) may be used for the prevention of bacterial infections in allogeneic HCT recipients with severe hypogammaglobulinemia (serum IgG level $< 400 \text{ mg/dL}$) per the Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation recipients [23].

4.1.6 Prevention of Hemorrhagic Cystitis

Hemorrhagic cystitis is a well-recognized potential complication of high-dose cyclophosphamide therapy. The approach to the prevention of hemorrhagic cystitis is as outlined in the NIH BMT Consortium Supportive Care Guidelines at:

https://intranet.cc.nih.gov/sites/nihintranet/files/intranet-files/bmt/_pdf/HemCystitis_Prevent_guideline.pdf

4.1.7 Growth Factors

G-CSF (filgrastim) may begin on day +5, as clinically indicated at a dose of 5 mcg/kg/day (actual body weight) and is administered daily subcutaneously or IV until the absolute neutrophil count is $\geq 1000 \text{ cells/mm}^3$ for three days or ≥ 5000 for one day. Rounding to the nearest vial or syringe size is allowed. Additional G-CSF may be administered as clinically warranted or may be stopped early. For participants with absolute neutrophil count $\geq 1000 \text{ cells/mm}^3$ on day +5, G-CSF can be

held until counts begin to nadir at the discretion of the PI. Pegfilgrastim and GM-CSF are not permitted.

4.1.8 Additional Cell Infusions for Graft Failure, Impending Graft Failure, or Poor Graft Function

Participants who experience graft failure (primary or secondary), impending graft failure (falling counts and/or donor chimerism after initial engraftment in the absence of relapse), or poor graft function post-transplant (hypoplastic bone marrow, complete or near-complete donor chimerism, absence of relapse or cytopenia's clinically thought to be caused by medication or infection, severe cytopenia's in at least two lines [Hb < 10 g/dL, platelet count < 30 x 10⁹/L, neutrophil count < 1.0 x 10⁹/L] lasting at least 2 weeks beyond day +14 and with transfusion requirement) will be taken Off Treatment (Off Therapy) but will remain On Study (On Protocol) to enable them to be eligible to receive a donor lymphocyte infusion (DLI), G-CSF mobilized Peripheral Blood Stem Cell (PBSC), G-CSF mobilized PBSC with CD34⁺-selected cell boost, or a second transplant, depending upon the circumstances. These cellular therapies would be salvage maneuvers to attempt to rescue participants from life-threatening poor graft function or complete graft failure. The same donor for the most recent HCT will be used. Stem cell boosts will be used preferentially in participants with full or mixed (i.e., >10%) donor myeloid chimerism and multi-lineage cytopenia, and DLI will be used preferentially in participants with full (i.e., >90%) donor myeloid chimerism but low <50% donor CD3 chimerism. The product ultimately administered to the participant will be up to the clinical discretion of the PI/Lead Associate Investigator. Chemotherapy is used at the discretion of the PI. In all circumstances, a fresh product will be preferred, although a cryopreserved product will be acceptable.

4.1.9 Use of Corticosteroids

During the peri-transplant period starting on day -2, all participants on corticosteroids will be switched to maintenance hydrocortisone (15 mg/m²/day div BID or TID for pediatric participants and 20 mg PO qam + 10 mg PO qpm for adult participants) if clinically feasible. On day +5, they may be switched back to their pre-transplant dose of steroids and managed per clinical necessity. If acute adrenal insufficiency develops, the participant will be given stress doses of hydrocortisone.

4.2 TREATMENT OF GRAFT-VERSUS-HOST DISEASE

In participants in whom GVHD is suspected, standard clinical criteria and biopsy findings (when clinically indicated) will be used to establish the diagnosis. Acute GVHD will be assessed according to the 1994 Consensus Conference on Acute GVHD Grading criteria. [24] Chronic GVHD will be assessed according to the 2014 Chronic GVHD Consensus Project. [25] See [Appendix G and Study Instrument](#) for details concerning the assessment of acute and chronic GVHD. Participants with clinical Grade I (Stage 1 or Stage 2) GVHD of the skin without any other organ involvement will be treated with a topical corticosteroid cream. In general, participants with ≥ Grade II acute GVHD will be treated with high-dose, systemic corticosteroids. Participants who fail to respond to corticosteroids will be considered for second-line immunosuppressive therapy. These agents may include tacrolimus (if the participant is not already on tacrolimus), mycophenolate mofetil, alpha-1-antitrypsin, infliximab (Remicade), pentostatin, etanercept, alemtuzumab, basiliximab, tocilizumab, or ruxolitinib. Ibrutinib is a steroid-sparing agent commonly used for the treatment of chronic GVHD. Other commercially available agents that have been evaluated for steroid-refractory GVHD may be considered.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

All research specimens will be initially stored in Biospecimen Processing Core (BPC) see section [5.2.1.1](#).

Test/assay	Volume blood (approx.)	Type of tube*	Collection point	Location of specimen^
Immune Reconstitution	6 ml of blood	Dark Lavender tubes	Section 5.1.1	Department of Laboratory Medicine
Pharmacokinetic properties of Briquilimab	3 mL of blood	SST (red)	Section 5.1.2	Eurofins
GATA2 targeted sequencing	1 ml	Streck tube	Screening	Immunology service, NIH

* Tubes/media may be adjusted at the time of collection based upon materials available and/or to ensure the best viable samples are collected for planned routine and/or research analysis at the time of the procedure

^The location of specimen processing or analysis may be adjusted with the permission of the PI or laboratory investigator.

Note: Platforms and procedures may be adjusted based upon current technology and/or collaborations in place at the time of actual analyses.

5.1.1 Immune Reconstitution Studies

A Primary Immunodeficiency Disease PID Flow Panel will be performed in an NIH Department of Laboratory Medicine at baseline, +100 (± 20 days), +180 days (± 30 days), one year (± 60 days), 2 years (± 90 days) and 3 years (± 90 days) post-transplant.

5.1.2 Pharmacokinetic properties of Briquilimab

Briquilimab levels will be measured using a validated ELISA assay and modeling of Briquilimab clearance will be performed to determine the timing of onset of chemotherapy conditioning and HSC infusion. day of HSC infusion. Available PK results reported for each participant in real-time will be used to iteratively model the Briquilimab terminal half-life ($t_{1/2}$) and individualize the timing of chemotherapy conditioning and HSC infusion. A minimum of three data points will be used to estimate the terminal $t_{1/2}$ and will be based on visual inspection and the adjusted R² value generated using WinNonLin software. The use of maximum concentration (C_{max}) as a data point will be avoided. Serum samples sent to Eurofins will be analyzed and data reported to the Sponsor and/or its designee within 48 hours of shipment.

Blood samples will be drawn for Briquilimab PK assessment according to the schedule below.

Study Day						Transplant Day 0
-11 ¹	-10	-9	-7 +/- 1 day	-3 +/- 1 day	-1	Day 0
Immediately after infusion (+10 min), 4 (+/-1) hours, 8 (+/-1) hours	X	X	X	X	X	X

¹ Study Day -11 may be any day between day -13 and -10 and is the day of Briquilimab infusion

5.2 STORAGE, USE, AND SHARING OF SPECIMENS AND DATA (INCLUDING FOR SECONDARY RESEARCH)

5.2.1 Sample Tracking and Processing

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside the National Institutes for Health (NIH) without appropriate approvals and/or agreements if required.

5.2.1.1 Samples Managed by Biospecimen Processing Core (BPC)

Please e-mail at NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main BPC number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.2.2 Sample Storage and Disposition

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in a database. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned. It is the responsibility of the Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of a sample tracking database (e.g., Labmatrix). It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, to correlate results with sample characteristics.

5.2.3 Protocol Completion/Sample Destruction

Any specimens remaining at the completion of the protocol will be stored indefinitely in the conditions described above. The study will remain open so long as sample or data analysis continues. All samples and data from consenting participants will be stored in identifiable format

until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed or returned to the participant, if so requested. The participant's samples and data will be excluded from future distributions, but those which already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section 7.2.

With the permission of the participant, specimens and data collected on this study, identifiable through a code available to the study team, will be stored indefinitely and used for secondary research, including genetic research. Furthermore, the data and/or specimens, may be shared with other investigators in identifiable or coded (code key not available to recipient) format for secondary research. Any investigator conducting secondary research in human subjects will seek either additional regulatory approval or exemption for research as appropriate.

Data will also be shared in public database per the study's data sharing plan in compliance with NIH policies.

In addition, specimens/data may be anonymized and further research, including genetic research, conducted at the site or other institutions without participant consent. Participants will be informed that the possibility for this type of research exists.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.3.1 GATA2 Assay

GATA2 targeted sequencing will be performed at the time of screening to confirm eligibility.

5.3.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

As stated in section 5.2, unique identifiers are attached to samples and are linked through the secure database to medical record information, with the key provided only to researchers on the study. Therefore, potential identification would only occur in the event of a data breach – an unlikely event given the security standards of the databases utilized. A certificate of confidentiality has been obtained (section 13.4. Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy (6.2.2). The pedigree analysis will not be performed.

5.3.3 Management of Results

Only one gene, GATA2 will be sequenced, so no secondary findings will be discovered.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into password protected 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency, and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed

data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Document AEs from the first study intervention, Briquilimab infusion through 100 days after transplant or 30 days after Briquilimab infusion if the transplant is not done. After 100 days, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

The PI (or PI designee) evaluation of each AE not captured in the clinical database determining that it meets the criteria above will be documented in the source documents. Note: the investigator performing the assessment must be a licensed clinician listed on the FDA form 1572.

Participants' demographics, disease characteristics, treatment and complication history, and outcomes data will be collected for research purposes. Data on disease re-evaluation following HCT will be collected. All clinical data pertaining to a participant's death while on the protocol will be collected.

Supportive care therapies, such as infectious disease prophylaxis, immunoglobulin replacement, GVHD treatments, etc., are not considered part of the protocol-specified therapy and AEs caused by these therapies will not be documented.

End of Study Procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations: National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every

attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the Principal Investigator.

6.2.2 Genomic Data Sharing Plan

This study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

Therefore, unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

Participants will be assessed at days +30, +60, and +100, and 6, 12, 24, and 36 months post-transplant for the clinical and hematological response. The one-year time point will be the date used for the Response Assessment.

Complete HCT Response consists of sustained donor engraftment defined as neutrophil recovery with $\text{ANC} \geq 500/\text{mm}^3$ for 3 consecutive days associated with $> 90\%$ myeloid and $>10\%$ CD3+ T cell donor chimerism by 100 days post-transplant and restoration of normal hematopoiesis with normalization of peripheral blood counts (Hb >8 g/dL, platelet count $> 100,000/\mu\text{L}$ and $\text{ANC} >1,500/\mu\text{L}$) and no cytogenetic abnormalities detected on bone marrow biopsy and aspirate by one-year post-transplant. Note that non-hematologic manifestations of GATA2 deficiency such as lymphedema may still be present.

Partial HCT Response consists of sustained neutrophil recovery with $< 90\%$ myeloid and/or $< 10\%$ CD3+ T cell donor chimerism by 100 days post-transplant but more than 10% donor chimerism and correction of one or two of three blood count parameters.

No HCT Response consists of failure to achieve donor engraftment and failure to restore any of the three parameters of reversal of abnormal hematopoiesis.

Event-free survival is defined as survival without death, graft failure, or receipt of a second transplant.

Clinical Response is defined as the normalization of peripheral blood cell counts (defined above in Complete HCT Response) and resolution of pre-existing infection(s).

Sustained donor engraftment is defined as neutrophil recovery with $\text{ANC} \geq 500/\text{mm}^3$ for 3 consecutive days associated with $>90\%$ myeloid and $>10\%$ CD3+ T cell donor chimerism by 100 days post-transplant and restoration of normal hematopoiesis by one-year post-transplant.

Failure to achieve sustained donor engraftment may be due to primary graft failure defined as the lack of donor-derived neutrophil engraftment by day +60 after transplant. Participants will be considered to have primary graft failure/rejection provided they meet any criteria listed below:

- Absence of neutrophil recovery $\geq 500/\mu\text{L}$ combined with donor whole blood or myeloid peripheral blood chimerism $< 10\%$ measured on day 60 (+/-10 days)

- Primary autologous count recovery with < 10% donor whole blood or myeloid peripheral blood chimerism at count recovery
- Administration of a rescue stem cell product prior to (or around) day +60 for failure to engraft, as determined by the institutional clinical investigator

Incidence of secondary graft failure/graft rejection is defined as initial donor-derived neutrophil engraftment followed by the subsequent loss of donor chimerism to < 10% donor whole blood or myeloid peripheral blood chimerism. A participant who receives a second HCT without documented loss of donor chimerism will also be considered to have secondary graft failure unless the second transplant was performed for residual or relapsed MDS.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Note: Acute GVHD will be assessed according to the 1994 Consensus Conference on Acute GVHD Grading criteria. [24] Chronic GVHD will be assessed according to the 2014 Chronic GVHD Consensus Project. [25]

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here: <https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-800Series-ComplianceandResearchEventReportingRequirements>.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here: <https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-800Series-ComplianceandResearchEventReportingRequirements>.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem or present new information that might affect the willingness of participants to enroll or remain on the study will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here: <https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-800Series-ComplianceandResearchEventReportingRequirements>.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis every week when participants are being actively treated on the trial to discuss each participant.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator.

Events meeting requirements for expedited reporting as described in section 7.2.1 will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.4.2 Safety Monitoring Committee (SMC)

This protocol will be periodically reviewed by an intramural Safety Monitoring Committee, comprising physicians, biostatisticians and a lay member selected based on experience, area of expertise, reputation for objectivity, absence of conflicts of interest and knowledge of or experience with clinical trial research. Initial review will occur as soon as possible after the annual NIH Intramural IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC based on the risks presented in the study. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period.

The SMC will operate under the rules of an approved charter that will be written and reviewed at the organization meeting of the SMC. Each review will focus on unexpected protocol-specific safety issues that are identified during the conduct of the clinical trial.

Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section [8.1.3](#))
- Inpatient hospitalization or prolongation of existing hospitalization
 - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
 - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
 - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria
- 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 a serious adverse drug experience 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.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

Mild infusion-associated hypersensitivity reactions related to Briquilimab including cough and nasal congestion will be reported to the Sponsor quarterly.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

SAEs will be reported to the Sponsor for the period from the first study intervention, Briquilimab infusion through 100 days after transplant or 30 days after Briquilimab infusion if the transplant is not done. After 100 days, only SAEs related to the study intervention will be reported to OSRO Safety.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets protocol-defined serious criteria must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section [8.4](#).

All SAE reporting must include the elements described in section [8.2](#).

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov. CCR SAE report form and instructions can be found at:

<https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=bNMDO6&CID=789d6979-ee94-4817-bb40-d2c45a9d7aeb>

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAVIER OF EXPEDITED REPORTING TO CCR

As death due to disease progression is part of the study objectives (OS, EFS), and captured as endpoints in this study, it will not be reported in expedited manner to the Sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

Any events described in section **3.4 Study stopping rules**, will be submitted immediately (within 24 hours of awareness) to OSRO Safety.

8.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

Reporting will be per the collaborative agreement.

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov. Forms and instructions can be found here: <https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=bNMDO6&CID=789d6979-ee94-4817-bb40-d2c45a9d7aeb>

8.6.1 Maternal exposure

If a participant becomes pregnant after initiation of study therapy through the 1 year after transplant or 12 months after completion of chemotherapy preparative administration if transplant is not performed, the study treatment (if still being administered) should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the pregnancy becomes known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study treatment and for 1 year after transplant or 4 months after completion of chemotherapy preparative administration if transplant is not performed.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies occurring from the date of the start of preparative regimen 1 year after transplant or 4 months after completion of chemotherapy preparative administration if transplant not performed, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change

to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether allogeneic hematopoietic cell transplantation with Briquilimab-based conditioning results in sustained donor engraftment by 100 days post-transplant in participants with GATA2 deficiency	CBC with differential performed daily during initial hospitalization and once weekly thereafter through 100 days post-transplant. Peripheral whole blood, myeloid and T cell chimerism at days 30, 60 and 100.	Standard endpoint for phase II trial
Secondary		
To determine whether allogeneic hematopoietic cell transplantation with Briquilimab-based conditioning results in restoration of normal hematopoiesis by one-year post-transplant in participants with GATA2 deficiency	CBC with differential performed daily during initial hospitalization, once weekly thereafter through day +100, at 6 months and at one year. Bone marrow biopsy and aspiration on day +100 and one year.	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
The safety of allogeneic HCT in participants with GATA2 deficiency conditioned with Briquilimab	Any toxicities identified between Briquilimab infusion through 100 days after transplant or 30 days after Briquilimab infusion if the transplant is not done will be collected on the days study drug is administered, as well as at the follow-up visits. AEs are reported by type and grade. Beyond 100 days after transplant, only adverse events which are serious and related to the study intervention will be recorded and reported.	Standard endpoints for cancer clinical trials
3-year overall survival	Participants assessed daily during initial hospitalization, once weekly thereafter through day +100, at 6 months, then annually after completion of study therapy for 3 years.	
3-year event-free survival	Participants assessed daily during initial hospitalization, once weekly thereafter through day +100, at 6 months, then annually after completion of study therapy for 3 years.	
3-year incidence of secondary graft failure	Participants assessed daily during initial hospitalization, once weekly thereafter through day +100, at 6 months, then annually after completion of study therapy for 3 years	
3-year incidence and severity of acute and chronic GVHD	Incidence of grade III-IV acute GVHD at day 100 and moderate to severe chronic GVHD are assessed at one year, two years, and 3 years post-transplant in Cohort 1 and Cohort 2.	
Exploratory		
To characterize immune reconstitution following HCT in participants with GATA2 deficiency conditioned with Briquilimab	Specimens for assessments collected per section 5 with the last collection at 2 years	Exploratory analysis
To evaluate the pharmacokinetic properties of Briquilimab in participants with GATA2 deficiency	See section 10.4.8.1	

10.2 SAMPLE SIZE DETERMINATION

Participants who are assigned to each treatment arm will be considered as two separate groups for purposes of sample size determination. For purposes of sample size determination, the study will aim to determine whether allogeneic HCT in participants with early stage GATA2 deficiency results in sustained donor engraftment defined in section 6.3.

Meeting this objective at one year, including reversal of clinical phenotype, will be considered a successful outcome for an individual participant (a 'success').

The trial will use a single stage design for each cohort to accrue participants according to the following: it is not known what fraction of participants may experience a success, but it will be considered desirable if the fraction were clearly greater than 60%.

In each cohort, when the sample size is 15, an exact binomial test with a 10% one-sided significance level will have 82.3% power to detect the difference between a 60% success rate and an 85% success rate. As an example, if 12 of the 15 participants have a successful outcome by one year, the lower 90% one-sided confidence bound on 12/15 (80%) is 60.7%, thus this would be a result which exceeds the 60% which was to be ruled out. In addition, 12/15 has a one-sided 90% upper confidence bound of 92.4%, demonstrating consistency with 85% or better. It is expected that up to 6 recipients per year may enroll in this trial. Thus, to enroll 15 evaluable recipients per cohort, a total of 30, accrual is expected to be completed within 5 years. Also, to allow for inevaluable participants (2) and screen failures (8), the accrual ceiling for this trial will be set at 40 total participants.

10.3 POPULATIONS FOR ANALYSES

For evaluation of the primary endpoint, a modified intention to treat the population will be used. Any participants who have received pre-transplant conditioning and who have undergone HCT will be included in the primary analysis. Any participant who has undergone pre-transplant conditioning will be considered evaluable for toxicity and safety evaluations, as well as evaluation of the pharmacokinetic properties of Briquilimab.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

The fraction of evaluated participants who have undergone the protocol-specified pre-treatment conditioning and HCT will be evaluated for the fraction which is able to have a success obtained.

10.4.2 Analysis of the Primary Endpoints

The fraction of evaluated participants who have donor engraftment defined as neutrophil recovery with $\text{ANC} \geq 500/\text{mm}^3$ for 3 consecutive days associated with $> 90\%$ myeloid and $>10\%$ CD3+ T cell donor chimerism by 100 days post-transplant reported along with one-sided 90% confidence intervals and a two-sided 95% confidence interval.

10.4.3 Analysis of the Secondary Endpoints

Restoration of normal hematopoiesis will be evaluated as the fraction of evaluated participants who have restoration of normal hematopoiesis defined by the normalization of peripheral blood counts and absence of cytogenetic abnormalities on bone marrow biopsy and aspirate at one-year post-transplant reported along with a 95% two-sided confidence interval.

Overall survival and event-free survival will be evaluated using the Kaplan-Meier method for all evaluable participants beginning at their date of transplant, along with the median value and the 95% confidence interval at the median, separately by cohort. An event is defined as death, receipt of a second transplant, or graft failure.

Incidence of secondary graft failure is defined as initial donor-derived neutrophil engraftment followed by the subsequent loss of donor chimerism to < 10% donor whole blood or myeloid peripheral blood chimerism within 3 years after transplant. A participant who receives a second HCT without documented loss of donor chimerism will also be considered to have secondary graft failure. The fraction of participants who have secondary graft failure will be reported along with a 95% two-sided confidence interval, separately by cohort.

To determine the incidence of grade III-IV acute GVHD at day 100 and moderate to severe GVHD at one year and two years post-transplant, the fractions will be reported separately by cohort using simple estimates along with 95% two-sided confidence intervals. In addition, cumulative incidence curves accounting for the competing risk of transplant-related mortality will be constructed by cohort, with the values reported at day 100, one, and two years, along with a 95% two-sided confidence interval.

10.4.3.1 Failure to achieve sustained donor engraftment

Separately by arm, participants will continue to be accrued to a given arm provided that no greater than 2 participants in 10 on a given arm has failed to achieve sustained donor engraftment where sustained donor engraftment is defined as neutrophil recovery with ANC \geq 500/mm³ for 3 consecutive days associated with >90% myeloid and >10% CD3+ T cell donor chimerism by 100 days post-transplant.

The following table, based on binomial probability calculations, shows the probability of having 3 or more participants fail to achieve sustained donor engraftment by 10 participants, for a set of possible underlying true probabilities.

Probability of day +100 failure to achieve sustained donor engraftment	Probability of early termination due to day +100 failure to achieve sustained donor engraftment
0.05	0.011
0.10	0.07
0.15	0.18
0.20	0.32
0.25	0.47

Thus, if the true probability of failure to achieve sustained donor engraftment is about 20%, there is a 32% probability that 3 or more participants will have this occur within the 10 participants on a specific arm and thus need to end accrual to this arm as soon as this can be determined.

For safety analysis, see section [10.4.4](#).

10.4.4 Safety of HCT

To determine the safety of allogeneic HCT in participants with GATA2 deficiency conditioned with Briquilimab, including transplant-related toxicity, the adverse events for all participants will be reported by type and grade of event. The participants who are enrolled will have their grades and types of toxicities noted and tabled as appropriate, by arm. Other evaluations will be performed as indicated in section [10.4.3](#).

10.4.4.1 Transplant-related Mortality (TRM)

Separately by arm, participants will continue to be accrued to a given arm provided that no greater than 2 participants in 10 on a given arm have died by day +180 due to treatment-related causes (and no other stopping rules are implemented). The following table, based on binomial probability calculations, shows the probability of having 3 or more participants die from treatment-related causes by 10 participants, for a set of possible underlying true probabilities.

Probability of day +180 TRM	Probability of early termination due to day +180 TRM
0.10	0.07
0.20	0.32
0.30	0.62
0.35	0.74
0.40	0.83

Thus, if the true probability of day +180 TRM is about 35%, there is a 74% probability that 3 or more participants will have this occur within the 10 participants on a given arm and thus need to end accrual to that particular arm as soon as this can be determined.

10.4.4.2 Grade 3-4 aGVHD not responsive to one week of high-dose steroids

Separately by arm, participants will continue to be accrued to a given arm provided that no greater than 2 participants in 10 on a given arm has experienced grade 3-4 aGVHD not responsive to one week of high-dose steroids (and no other stopping rules are implemented). The following table, based on binomial probability calculations, shows the probability of having 3 or more participants experience grade 3-4 aGVHD not responsive to one week of high-dose steroids by 10 participants, for a set of possible underlying true probabilities.

Probability of grade 3-4 aGVHD not responsive to one week of high-dose steroids	Probability of early termination due to grade 3-4 aGVHD not responsive to one week of high-dose steroids
0.10	0.07
0.20	0.32
0.30	0.62
0.35	0.74
0.40	0.83

Thus, if the true probability of grade 3-4 aGVHD not responsive to one week of high dose steroids is about 35%, there is a 74% probability that 3 or more participants will have this occur within the 10 participants on a given arm, and thus need to end accrual to that arm as soon as this can be determined.

10.4.5 Baseline Descriptive Statistics

Baseline demographic data on all participants in the arms will be reported overall as well as separately by the treatment arm.

10.4.6 Planned Interim Analyses

NA.

10.4.7 Sub-Group Analyses

Results will be reported according to the treatment arm.

10.4.8 Exploratory Analyses

Immune reconstitution following HCT will be analyzed using descriptive or comparative statistics as appropriate. Results will be reported in an exploratory manner. If any statistical tests are performed, they will be done without adjustment for multiple comparisons and in the context of the exploratory nature of the evaluations.

10.4.8.1 Non-Linear Mixed Effect Modeling

Formal modeling of the PK data for all participants will commence upon completion of study enrollment and when PK samples are available for analysis. Concentration-time data will be summarized by N, mean, standard deviation (SD), median, min, max, and % coefficient of variation (CV). Individual and mean concentration versus time curves will be graphically presented. PK parameters will be estimated using standard population PK methodologies and non-linear mixed effect modeling (NONMEM 7.3 software). Population PK model development will be guided by exploratory analysis, diagnostic plots, and changes in objective function value. Based on standard principles of allometric scaling, the weight will be built into the base a priori model and scaled to a reference participant having the median population weight. For values falling below the Limit of Quantification (LOQ) of the assay, a value of one half the LOQ (1 ng/mL) will be

used. [26] Parameter estimates to be determined include: clearance (CL), volume of distribution (Vd), $t_{1/2}$, maximum concentration (C_{\max}), minimum concentration (C_{\min}), and area-under-the-curve concentration time curve from zero to infinity ($AUC_{0-\infty}$), derived from the empirical Bayes estimates of individual clearance. The influence of clinical covariates on drug clearance will be investigated, including participant demographics (weight, height, body surface area, age, sex), and laboratory markers (cell counts, renal function, hepatic function).

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

A CRADA is under negotiation with Jasper Therapeutics for the supply of Briquilimab.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

This study was designed to include women and minorities but was not designed to measure differences in intervention effects. Males and females will be recruited with no preference for sex. No exclusion to this study will be based on race. Minorities will actively be recruited to participate.

Pregnant women are excluded from this study because study treatment has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with study drugs, breastfeeding should be discontinued if the mother is treated with study drugs.

HIV-positive participants are excluded due to the high rate of post-transplant complications in this group.

12.2 PARTICIPATION OF CHILDREN

Children are included in this study since GATA2 deficiency may manifest at a young age and allotransplant is a potentially curative therapy that can provide a survival advantage to these participants. Participants below the age of 6 are excluded given the inability to provide medical intensive care should the participant require it.

12.3 RISK/BENEFIT ASSESSMENT

12.3.1 Known Potential Risks

12.3.1.1 Briquilimab

See section 1.2.3 for safety profile of Briquilimab.

GATA2 deficient participants have higher graft rejection and graft failure rates than participants with Severe Combined Immune Deficiency (SCID). It is not yet known whether replacing chemotherapeutic agents with Briquilimab will be able to provide enough myelosuppression to enable donor engraftment in participants with GATA2 deficiency.

There is not enough data to predict toxicity of study drugs combination. Only the common events will be considered expected for regulatory purposes (see sections 14.1.5, 14.2.5, 14.3.5, 14.4.5, 14.5.5)

12.3.1.2 Allogeneic HCT

The risk of death or other complications from the transplant can vary greatly, depending on many factors, including the age of the participant, the health of the participant at the time of transplant,

and how the transplant is performed. In similar transplant studies, the risk of death in the first-year post-transplant is around 10-20%.

Although highly unlikely, it is possible for a participant to acquire allergies, such as drug, food, or environmental, from the donor. Donors are asked about serious or significant allergies. If there is a known drug allergy, after transplant that family of drugs will be avoided for the recipient. While it is possible that the recipient could acquire an immune system problem from the donor, we extensively screen donors for significant autoimmune problems and do not use donors with known autoimmune problems that interfere with the donor's health.

There is a small chance (about 5-10%) the recipient will rejection of the donor's stem cells. In such cases, a second transplant from either the same or different donor would be needed to decrease the risk of infection, bleeding, and death. Support could be given as transfusions, growth factors, and antibiotics.

Due to the transplant, chemotherapy, and/or radiation utilized pre- and post- transplant, there is a high likelihood that participants will lose the ability to have children in the future.

There is around a 5% chance of a participant developing stem cell infusion reaction (a fever, chills, body aches, trouble breathing, anemia, or dark urine during or after the stem cell infusion).

Participants can develop a nutritional deficiency, that is usually temporary.

12.3.1.3 Infection

The immunosuppression utilized in this study is associated with an increased risk of opportunistic infection. Post-transplant there is an increased risk of infection while the participant's immune system recovers. Participants will need to avoid or modify activities where large groups of people may be encountered and take extra precautions to avoid infection. Participants will be closely monitored for infection and treated with effective therapies, if available.

12.3.1.4 Organ Toxicity

Complications of the organs can occur after transplant.

There is around a 5% chance of a participant developing a severe liver complication (sinusoidal obstructive syndrome; SOS) as a result of the chemotherapy. Severe SOS can lead to liver failure and death.

Lung complications are infrequent (occurring in 3-8% of recipients) but can rarely be severe or life-threatening and can sometimes result in irreversible lung damage.

12.3.1.5 Graft versus Host Disease (GVHD) and late transplant complications

GVHD is a potential complication of transplant that remains a significant cause of morbidity and mortality. Occurring soon after transplant, acute GVHD most commonly attacks the skin, gut, and liver. Symptoms can include (but are not limited to) itchy rash, heartburn, diarrhea, nausea, changes in liver function, or jaundice with liver failure. With the use of a PTCy-based GVHD prophylaxis regimen, the risk of chronic GVHD is estimated at around 10-15%. Chronic GVHD commonly attacks the skin, eyes, mouth, liver, or intestines. Symptoms can include (but are not limited to) dryness of mouth or eyes, loss of appetite, weakness, hair loss, changes in the skin, liver damage, shortness of breath. Severe chronic GVHD can increase the risk of infection or death.

People who get transplants are at increased risk for developing certain types of cancers such as cancers of the mouth, throat, and skin. Some of that increased cancer risk is related to chronic graft-versus-host disease, but some are related to prior chemotherapy exposure.

12.3.1.6 DMSO

Risks include nausea, vomiting, and diarrhea. Most commonly it causes an unpleasant taste and smell (like garlic). Other side effects that have been reported include facial flushing, loss of appetite, and flu-like symptoms.

12.3.1.7 Preparative regimen and supportive therapies

The chemotherapy agents and supportive medications used in this study are FDA-approved agents with well-known toxicity profiles. Refer to section [14](#) for a summary of toxicities.

12.3.1.8 TBI

The side effects of total body irradiation have been well described. The most common include nausea and mucositis. There also exists a risk of hypothyroidism, cataracts, interstitial pneumonitis, nephropathy, and an unspecified long-term risk of developing secondary malignancies. Importantly, the majority of the non-neoplastic effects were subclinical and/or reversible. The risks are as follows:

During or shortly after treatment

Common:

- Fever
- Alopecia
- Nausea
- Vomiting
- Diarrhea
- Mucositis
- Anemia
- Lymphocyte count decreased
- Neutrophil count decreased
- Platelet count decreased
- White blood cell decreased
- Dermatitis radiation
- Dry mouth
- Salivary duct inflammation

Uncommon:

- Temporary acute kidney injury
- Temporary hepatic failure

- Temporary respiratory failure

After Treatment (months to years)

Common:

- Reproductive system disorders
- Cataract
- Cognitive disturbance in children (age 7 or younger)

Uncommon:

- Hypothyroidism
- Dyspnea
- Permanent acute kidney injury
- Permanent hepatic failure
- Permanent respiratory failure
- Portal vein thrombosis

Rare:

- Treatment related secondary malignancy
- Death.

12.3.1.9 Exposure to Ionizing Radiation

During a year in this research study participants may be exposed to 200 cGy of radiation from TBI and from CT scan for disease valuation (approximately 1.1 rem per year). The amount of radiation from CT scan adds minimal additional risk to the higher radiation doses received in the course of treatment.

12.3.1.10 CT scans

In addition to the radiation risks discussed above, CT scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heart rate, and swelling.

12.3.1.11 Blood Collection

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting and infection. When large amounts of blood are collected, a low red blood cell count (anemia) can develop.

Up to 221.8 ml of blood may be collected at any day, up to 660.5 ml may be collected within 8 weeks as this is necessary for participant's safety.

12.3.1.12 Central Venous Catheter (CVC)

All participants receive study therapy through a central line or an existing mediport. The risks of this procedure include pain, bleeding, bruising, and pneumothorax. The long-term risks of the

catheter include infection and blood clotting. All care will be taken to minimize complications of central insertion during the procedure.

12.3.1.13 Bone Marrow Aspiration/Biopsy

The risk of bone marrow aspiration/biopsy is generally mild pain but rarely bleeding, bruising, injury to internal organs or infection can occur at the biopsy site. Serious risks are very rare but include fat embolism. To minimize pain, local anesthesia will be administered prior to the procedure to numb the area.

12.3.1.14 Sedation

Bone marrow biopsies and CVC insertion may be done under conscious sedation with Fentanyl and Midazolam (Versed). Potential side effects of sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These are generally mild and last no more than a few hours.

12.3.1.15 General Anesthesia

The risks of sedation include decreased rate of breathing while under sedation and aspiration (saliva or stomach contents breathed into the lungs). Additional risks include a drop in heart rate or blood pressure. In the rare event that this should occur, the anesthesiologist may have to put a longer breathing tube into the participant's mouth and windpipe, use a respirator, and give medications to raise the participant's blood pressure. If a severe reaction occurs during the sedation procedure the participant will be resuscitated.

The FDA has issued a safety warning about anesthesia in children, especially anesthesia lasting longer than three hours or repeated anesthesia even if it is brief. Research has shown learning and behavioral problems in animals undergoing long anesthesia or repeated brief anesthesia. Similar problems may be more likely in children who have had long anesthesia or repeated brief anesthesia. However, research in children has not found learning or behavior problems after one short exposure to anesthesia. An anesthesiologist will talk to the participant and their parents about the risks and benefits of general anesthesia being used in this study.

12.3.1.16 EKG

Risks include some minor skin irritation from the electrodes.

12.3.1.17 ECHO and urine collection

There are no physical risks from these procedures.

12.3.1.18 PFTs

Participants may feel dizzy or faint from the rapid breathing required for the test.

12.3.1.19 Consultations

There are no physical risks associated with consultations with dental, nutrition, ophthalmology, dermatology, and rheumatology evaluations.

12.3.1.20 Data loss/losing data

This includes the risk that data obtained during this study, including data related to genotype, can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the participants, family members, or health care providers, this risk will be included in the informed consent document

12.3.2 Known Potential Benefits

The participants may obtain a direct benefit from allogeneic HCT, as it is a potentially curative therapy for GATA2 deficiency. The participants may obtain further benefit from the use of Briquilimab in place of standard busulfan chemotherapy, as it is expected to have less associated toxicity.

12.3.3 Assessment of Potential Risks and Benefits for Recipients

Participants in this study may be directly benefited by this treatment protocol.

The approximate survival of participants with GATA2 deficiency with conventional treatment is approximately five years from the time of the presentation of the disease, and there are no other treatment options for participants with this disease that provide any significant survival advantage. Allogeneic HCT is the only available potentially curative therapy for GATA2 deficiency, and interim results from Protocol #13-C-0132N demonstrated an impressive 2-year event-free survival rate of 83% for 59 participants with GATA2 deficiency who underwent allogeneic HCT using busulfan-based conditioning regimens.

However, traditional HCT approaches using alkylating agents such as busulfan may be associated with significant transplant-related toxicity as well as late effects. This protocol aims to decrease the risk of transplant-related toxicity by using Briquilimab in place of standard busulfan chemotherapy. It is hypothesized that the transplant approach used in this study will result in the successful transfer of allogeneic stem cells with reduced morbidity and mortality from the transplant preparative regimen. Furthermore, the use of post-transplant cyclophosphamide, tacrolimus, and mycophenolate mofetil reduces the risk of GVHD. Potential adverse reactions attributable to the administration of the study drugs utilized in this trial are discussed above.

12.4 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including [HRPP Policy 303](#)) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found here:

[https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-\(ADCR\).aspx?Mode=Edit](https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit).

12.4.1 Consent Process for Minors

Consent will be obtained from parent(s)/guardians of minor children as described in section [12.4](#).

Note that in situations where there is joint custody of a child, both parents must sign consent. If only one parent can be present at NIH, the other parent's consent can be obtained remotely via the procedure described in section [12.4](#).

12.4.1.1 Assent of children

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. The assent process will take place in conjunction with consent; therefore, in person and remote assent are permitted under the same circumstances as in person and remote consent. Children under the age of 18, but who are age 12 or older will be asked to sign an age appropriate assent form if the assent is available in the participants preferred language. If not available, participants may sign the appropriate line in the consent document (in the participant's language) to attest to assent. Children under the age of 12 will not be required to provide assent as they typically do not have the cognitive ability to fully understand the nature of research. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

12.4.1.2 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require that consent be obtained from the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. We request waiver of informed consent for those individuals who become lost to follow up or who have been taken off study prior to reaching the age of majority.

For subjects that were enrolled as minors and off study when turning 18, we will follow the procedures outlined in section 3.9.3 to re-consent them and have enrolled as an adult participant.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (f):

- (1) The research involves no more than minimal risk to the subjects.
 - a. Analysis of samples and data from this study involves no additional risks to subjects.
- (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
 - a. Retention of these samples or data does not affect the welfare of subjects.
- (3) The research could not practicably be carried out without the waiver or alteration.
 - a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.
- (4) The research could not practicably be carried out without using such information or biospecimens in an identifiable format
 - a. Studies performed may involve the correlation of clinical outcomes and clinical interventions with laboratory studies. Such information would be unavailable we did not have access to medical record numbers, a form of identifiable information
- (5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

We only request a waiver of consent for those subjects who have been lost to follow-up or who have been taken off study prior to reaching the age of majority.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

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

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and, as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 BRIQUILIMAB; JSP191 (IND# 164877)

14.1.1 Source, Acquisition and Accountability

Investigational supplies of JSP191 also called Briquilimab will be supplied by Jasper Therapeutics and delivered directly to the CC Pharmacy.

Upon extraction of Briquilimab from the vial, Briquilimab must be administered within 4 hours.

Preparation of the clinical supplies will be performed by a using aseptic techniques and under sterile conditions in a laminar-flow hood with controlled room temperature (15 to 25°C). Prolonged exposure to light should be avoided. The pharmacist will prepare the individual participant dose on the morning of infusion and will ensure that the investigational product dispensed is prepared and labeled.

IV bags will be delivered from the Pharmacy to participant unit where drug will be infused to the participant.

14.1.2 Formulation, Appearance, Packaging, and Labeling

Briquilimab will be provided as a liquid for IV infusion. Storage must be at $\leq -20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for frozen supply or $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for refrigerated supply until used. Preparation of the drug for injection should follow the instructions outlined in the Pharmacy Manual. Following preparation for administration, the drug can be stored at 2-25°C for no more than 4 hours. After this period, the IP syringes must be discarded.

14.1.3 Product Storage and Stability

Briquilimab should be stored protected from light and according to the storage and expiration (where required) information provided on the label or Certificate of Analysis. Storage must be at $\leq -20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for frozen supply or $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for refrigerated supply until used. Preparation of the drug for injection should follow the instructions outlined in the Pharmacy Manual. Following preparation for administration, the drug can be stored at $2-25^{\circ}\text{C}$ for no more than 4 hours. After this period, the IP syringes must be discarded.

14.1.4 Administration

See section [3.2.1.2](#).

14.1.5 Toxicity

Only the common events will be considered expected for regulatory purposes.

Likely

- Headache
- Cough
- Sore throat
- Nasal congestion
- Fever
- Maculo-papular rash
- Nausea
- Vomiting
- Anemia
- White blood cell decreased
- Lymphocyte count decreased
- Neutrophil count decreased
- Platelet count decreased
- Bone marrow hypocellular
- Epistaxis

Less likely

- Paresthesia
- Severe hypersensitivity

See section [12.3.1.1](#).

14.2 FLUDARABINE

14.2.1 Source/Acquisition and Accountability

Fludarabine will be provided by the Clinical Center Pharmacy according to standard pharmacy

procedures. Fludarabine will be delivered directly to the Clinical Center Pharmacy. Individual IV bags will be prepared for each study participant according to an assigned dose by the Pharmacy personnel. IV bags will be delivered from the Pharmacy to participant unit where drug will be infused to the participant.

14.2.2 Formulation, Appearance, Packaging, and Labeling

Please refer to the package insert for additional information.

14.2.3 Product Storage and Stability

Please refer to the package insert for additional information.

14.2.4 Preparation

Please refer to the package insert for additional information.

14.2.5 Toxicity

Likely

- Anemia
- Lymphocyte count decreased
- Neutrophil count decreased
- Platelet count decreased
- White blood cell decreased

Less likely

- Nausea
- Vomiting
- Long term Lymphocyte count decreased which could increase the risk of infection
- Infection

Rare, but serious

- Seizure, Depressed level of consciousness, Blindness, other Nervous system disorders
- Pneumonitis
- Acute kidney injury
- Allergic reaction

14.3 CYCLOPHOSPHAMIDE

14.3.1 Source/Acquisition and Accountability

Cyclophosphamide will be provided by the Clinical Center Pharmacy according to standard pharmacy procedures. Cyclophosphamide will be delivered directly to the Clinical Center Pharmacy. Individual IV bags will be prepared for each study participant according to an assigned dose by the Pharmacy personnel. IV bags will be delivered from the Pharmacy to participant unit where drug will be infused to the participant.

14.3.2 Formulation, Appearance, Packaging, and Labeling

Please refer to the package insert for additional information.

14.3.3 Product Storage and Stability

Please refer to the package insert for additional information.

14.3.4 Preparation

Please refer to the package insert for additional information.

14.3.5 Toxicity

Likely

- Fever
- Infection, especially when white blood cell count is low
- Anemia which may cause tiredness, or may require transfusion
- Bruising, bleeding
- Blood in urine
- Nausea, vomiting, diarrhea, loss of appetite, pain in belly
- Sores in mouth which may cause difficulty swallowing
- Absence of menstrual period which may decrease the ability to have children
- Hair loss, skin changes, rash, change in nails
- Blurred vision, vision changes

Less likely

- Fluid around the heart
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- Loss or absence of sperm which may lead to an inability to father children

Rare, but serious

- Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness
- Swelling of the body including the brain which may cause dizziness, confusion
- Damage to the lungs or scarring of the lungs which may cause shortness of breath
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Hepatic veno-occlusive disease is a condition that is characterized by damage to blood vessels in the liver and liver cells. Although it may be mild and not require further treatment, sometimes it may cause a severe decrease in liver function and may be life threatening or fatal.
- Kidney damage which may cause swelling, may require dialysis
- A new cancer (e.g., leukemia, lymphoma, sarcoma etc.) resulting from treatment of a prior cancer
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body.
- Impaired wound healing
- Urinary and/ or kidney including blood in urine, painful urination, fever, urgency,

inability to urinate, loss of bladder control and pain.

- Abnormal heartbeats: including atrial fibrillation and flutter and ventricular arrhythmias causing your heart to be fast or irregular resulting in a pounding or racing heart, dizziness, weakness, feeling light-headed or shortness of breath.
- Decreased levels of sodium in the blood, which can cause confusion, seizures, fatigue and low levels of consciousness.

In addition, because cyclophosphamide may contain alcohol, it may impair a person's ability to drive or operate machinery immediately after the infusion.

14.4 MYCOPHENOLATE MOFETIL

14.4.1 Source/Acquisition and Accountability

Mycophenolate mofetil will be provided by the Clinical Center Pharmacy according to standard pharmacy procedures. Mycophenolate mofetil will be delivered directly to the Clinical Center Pharmacy. Individual IV bags will be prepared for each study participant according to an assigned dose by the Pharmacy personnel. IV bags will be delivered from the Pharmacy to participant unit where drug will be infused to the participant.

14.4.2 Formulation, Appearance, Packaging, and Labeling

Please refer to the package insert for additional information.

14.4.3 Product Storage and Stability

Please refer to the package insert for additional information.

14.4.4 Preparation

Please refer to the package insert for additional information.

14.4.5 Toxicity

Likely

- Neutrophil count decreased
- Anemia
- Gastroesophageal reflux disease
- Nausea
- Diarrhea
- Infection

Less likely

- Rash
- Pruritis

Rare, but serious

- Treatment related secondary malignancy
- Allergic reaction

14.5 TACROLIMUS

14.5.1 Source/Acquisition and Accountability

Tacrolimus will be provided by the Clinical Center Pharmacy according to standard pharmacy procedures. Tacrolimus will be delivered directly to the Clinical Center Pharmacy. Individual IV bags will be prepared for each study participant according to an assigned dose by the Pharmacy personnel. IV bags will be delivered from the Pharmacy to participant unit where drug will be infused to the participant.

14.5.2 Formulation, Appearance, Packaging, and Labeling

Please refer to the package insert for additional information.

14.5.3 Product Storage and Stability

Please refer to the package insert for additional information.

14.5.4 Preparation

Please refer to the package insert for additional information.

14.5.5 Toxicity

Please refer to the package insert for additional information.

Likely

- Headache
- Tremor
- Psychiatric disorders
- Hypertension
- Acute kidney injury
- Constipation
- Diarrhea
- Abdominal pain
- Insomnia

Less likely

- Hepatic failure
- Hyperglycemia
- Anemia
- Allergic reaction
- Photosensitivity
- Hyperlipidemia

Rare, but serious

- Seizure

- Depressed level of consciousness

14.6 GATA2 ASSAY (SANGER SEQUENCING ON THE PERIPHERAL BLOOD)

GATA2 targeted Sanger sequencing assay is not FDA approved; it is being used as a treatment determining in-vitro diagnostic device in this study. According to 21 CFR 812.3(m), a significant risk device presents a potential for serious risk to the health, safety, and welfare of a participant and meets the significant risk criteria listed in the table below along with the sponsor's conclusions with regard to the applicability of these criteria to the current study. The device has been assessed by the sponsor as a non-significant risk per the below.

Significant Risk Criteria	Applicable to the current study	Justification
Is an implant	No	GATA2 targeted sequencing assay is not introduced into the participant
Is used in supporting or sustaining human life	No	The device is diagnostic
Is of substantial importance in diagnosing mitigating or treating disease or preventing impairment of human health	No	While the device is diagnostic, we do not believe it presents a potential for serious risk to the health and welfare of the participant. The assessment of GATA2 mutation status is only used to help to increase the possibility that all persons enrolling in the study might derive benefit from therapy. Persons that are deemed ineligible to enroll on the basis of this test are eligible for studies within ID-CTP that are not reliant on this test.
Otherwise poses a risk	No	Testing will be performed on a fresh sample that is collected at screening for confirmation of diagnosis. No additional collection of the sample will occur for purposes of GATA2 testing.

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16 ABBREVIATIONS

<u>Abbreviation</u>	<u>Term</u>
ABO	Blood Types A, B, and O
ACAT	Ability to Consent Assessment Team
ACTH	Adrenocorticotrophic Hormone
AE	Adverse Event/Adverse Experience
aGVHD	Acute Graft Versus Host Disease
AI	Associate Investigator
ALT	Alanine Transaminase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate Aminotransferase
ATG	Anti-thymocyte globulin
AUC	Area under the curve
b-HCG	Beta Human Chorionic Gonadotropin
BID	Bis in die (twice a day)
BM	Bone marrow
BMT	Bone Marrow Transplant
BPC	Biospecimen Processing Core
BSA	Body Surface area
BTRIS	Biomedical Translational Research Information System
BUN	Blood Urea Nitrogen
Ca	Calcium
CAP	College of American Pathologists
CBC	Complete Blood Cell Count
CC	Clinical Center
CCI	Charlson Comorbidity Index
CCR	Center for Cancer Research
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CI	Confidence Interval
Cl	Chloride
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
C _{max}	Maximum concentration
C _{min}	Minimum concentration
CMML	Chronic Myelomonocytic Leukemia
CMV	Cytomegalovirus
CO ₂	Carbon Dioxide
CONSORT	Consolidated Standards of Reporting Trials

<u>Abbreviation</u>	<u>Term</u>
Cr	Creatinine
CRF	Case Report Form
CRIS	Clinical Records Information System
CRP	C Reactive Protein
CSA	Cyclosporine
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Connective tissue disease
CTEP	Cancer Therapy Evaluation Program
CV	Coefficient of variation
CVC	Central venous catheter
CY	Cyclophosphamide
dbGAP	Database of Genotypes and Phenotypes
DCI	Donor Cell Infusion
DEXA	Dual Energy X-Ray Absorptiometry
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
DLI	Donor Lymphocyte Infusion
DLM	Department of Laboratory Medicine
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
DTM	Department of Transfusion Medicine
EBV	Epstein-Barr Virus
echo	Echocardiogram
EDTA	Ethylenediaminetetraacetic Acid
EF	Ejection fraction
EFS	Event-free survival
EKG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume
FISH	Fluorescence in Situ Hybridization
GATA2	GATA-binding Factor 2
G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GMP	Good Manufacturing Practices
GMP	Granulocyte-monocyte progenitors
GVHD	Graft Versus Host Disease
GWAS	Genome-wide association studies
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HSC	Hematopoietic stem cells

<u>Abbreviation</u>	<u>Term</u>
HCT	Hematopoietic Cell Transplantation
HCT-CI	Hematopoietic Cell Transplantation -Comorbidity Index
HHS	Health and Human Services
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
H&P	History and Physical Examination
HPV	Human papillomavirus
HRD	Haploidentical related donors
HRPP	Human Research Protection Program
HSV	Herpes Simplex Virus
HTLV	Human T-Lymphotropic Virus
IBW	Ideal body weight
ICH	International Council for Harmonisation
ID	Infectious Disease
ID	Identification
ID-CTP	Immune Deficiency- Cellular Therapy Program
IDE	Investigational Device Exemption
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
IVIG	Intravenous Immune Globulin
JHMI	John Hopkin's Medical Institute
K	Potassium
LAR	Legally Authorized Representative
LDH	Lactate Dehydrogenase
LOQ	Limit of Quantification
MDS	Myelodysplastic Syndrome
MDS-EB	MDS with excess blasts
MDS-MLD	MDS with multilineage dysplasia
MDS-SLD	MDS with single lineage dysplasia
MDS-U	MDS, unclassifiable
Mg	Magnesium
MMF	Mycophenolate mofetil
Mono	Monocytopenia
MAC	Mycobacterium Avium Complex
MRD	Matched related donors
MRD	Measurable residual disease
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
N	Number (typically refers to subjects)
Na	Sodium

<u>Abbreviation</u>	<u>Term</u>
NCI	National Cancer Institute
NCT	National Clinical Trial (number)
NIH	National Institutes of Health
NK	Natural Killer
NMDP	National Marrow Donor Program
NSR	Non-significant risk
NTM	Non-tuberculosis mycobacterial
OHSRP	Office for Human Subjects Research Protections
P	Phosphorus
PB	Peripheral blood
PBSC	Peripheral Blood Stem Cell
PCR	Polymerase chain reaction
PE	Physical Examination
PET	Positron Emission Tomography
PFTs	Pulmonary function tests
PI	Principal Investigator
PID	Primary immunodeficiency diseases
PK	Pharmacokinetic
PO	Per os (by mouth)
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PTCy	Post-Transplant Cyclophosphamide
QC	Quality Control
RA	Rheumatoid arthritis
rCR	Revised Common Rule
RCC	Refractory cytopenia of childhood
Rh	Rhesus
RNA	Ribonucleic Acid
RPR	Syphilis screen
RS	Ring sideroblasts
SAE	Serious Adverse Event/Serious Adverse Experience
SCF	Stem cell factor
SCID	Severe combined immunodeficiency
SD	Standard deviation
SLE	Systemic lupus erythmatosis
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SOS	Sinusoidal Syndrome
SNP	Single nucleotide polymorphisms
STR	Short Tandem Repeat
Tacro/MTX	Tacrolimus/Methotrexate
Tacro/MMF	Tacrolimus/mycophenolate
TB	Tuberculosis
TBI	Total Body Irradiation
TBNK	T Lymphocytes, B Lymphocytes, and Natural Killer Cells
T cruzi	Trypanosoma cruzi

<u>Abbreviation</u>	<u>Term</u>
TID	Three times per day
T4	Thyroxin 4
TSH	Thyroid Stimulating Hormone
TRM	Transplant-Related Mortality
UCB	Umbilical cord blood
ULN	Upper Limit of Normal
UPr	Urine protein
Ursodiol	Ursodeoxycholic acid
URD	Unrelated donors
US	United States
Vd	Volume of distribution
VZV	Varicella Zoster Virus
WOCP	Women of childbearing potential
WHO	World Health Organization

17 APPENDICES

17.1 APPENDIX A: REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MYELOYDYSPLASTIC SYNDROMES RISK ASSESSMENT CALCULATOR

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

17.2 APPENDIX B – THE WORLD HEALTH ORGANIZATION (WHO) 2016 CLASSIFICATION OF MYELOYDYSPLASTIC SYNDROMES (MDS)

Type	Dysplastic lineages	Cytopenias ¹	Ring sideroblasts in erythroid elements of BM	Blasts	Cytogenetics
MDS-SLD	1	1 or 2	RS<15% (or <5% ²)	PB <1% BM <5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS-MLD	2 or 3	1-3	RS<15% (or <5% ²)	PB <1% BM <5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS-RS MDS-RS-SLD	1	1 or 2	RS≥15% (or ≥5% ²)	PB <1% BM <5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS-RS-MLD	2 or 3	1-3	RS≥15% (or ≥5% ²)	PB <1% BM <5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	PB <1% BM <5% No Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS-EB MDS-EB-1	0-3	1-3	None or any	PB 2~4% or BM 5~9%, No Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	PB 5~19% or BM 10%~19% or Auer	Any
MDS-U With 1% PB blast	1-3	1-3	None or any	PB=1% ³ , BM<5%, Auer rods	Any

Type	Dysplastic lineages	Cytopenias ¹	Ring sideroblasts in erythroid elements of BM	Blasts	Cytogenetics
with SLD and pancytopenia	1	3	None or any	PB <1% BM <5% No Auer rods	Any
Defining cytogenetic abnormality	0	1-3	<15% ⁴	PB <1% BM <5% No Auer rods	MDS defining abnormality
RCC	1-3	1-3	None	PB <2% BM <5% No Auer rods	Any

WHO: World Health Organization; MDS: myelodysplastic syndromes; PB: peripheral blood; BM: bone marrow; RS: ring sideroblasts;

MDS-SLD: MDS with single lineage dysplasia; MDS-MLD: MDS with multilineage dysplasia; MDS-EB: MDS with excess blasts; MDS-U: MDS, unclassifiable; RCC: refractory cytopenia of childhood.

¹ Cytopenias MDS-defining: Hb<100g/L, platelets<100×10⁹/L, ANC<1.8×10⁹/L; absolute monocytes count<1.0×10⁹/L

² with SF3B1 mutation

³ 1% PB blasts must be recorded on at least two separate observations

⁴ If with ≥15% ring sideroblasts and significant erythroid dysplasia, and are classified as MDS-RS-SLD

17.3 APPENDIX C: BONE MARROW CELLULARITY CUTOFFS TO DEFINE HYPOCELLULAR FOR AGE

Age group	Cellularity cutoff
6-19 years	< 60%
20-39 years	< 50%
40-59 years	< 40%
≥60 years	< 30%

17.4 APPENDIX D: PERFORMANCE STATUS CRITERIA

Karnofsky Performance Scale		Lansky Play-Performance Scale	
Percent	Description	Percent	Description
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
70	Cares for self, unable to carry on normal activity or to do active work.	70	Both greater restriction of, and less time spent in, active play.
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around most of day; no active play; able to participate in all quiet play and activities
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed
0	Dead.	0	Unresponsive; dead

17.5 APPENDIX E: SCHWARTZ FORMULA

Creatinine clearance calculation (mL/min/1.73m²) = [length (cm) x k]/serum creatinine

k = 0.55 for children age 6 to 13 years old and adolescent females 13-18 years old

k = 0.7 for adolescent males 13-18 years old

17.6 APPENDIX F: HEMATOPOIETIC CELL TRANSPLANTATION-SPECIFIC COMORBIDITY INDEX (HCT-CI)

Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI weighted scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease* congestive heart failure, myocardial infarction or EF < 50%	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild [‡]	Chronic hepatitis, bilirubin > ULN to 1.5 ULN, or AST/ALT > ULN to 2.5 ULN	1
Obesity	Participants with a body mass index > 35 kg/m ²	1
Infection	Requiring continuation of antimicrobial treatment	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine > 2 mg/dL [‡] , on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLCO and/or FEV1 66%-80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the participant's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLCO and/or FEV1 < 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 ULN, or AST/ALT > 2.5 ULN	3

EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; CTD, connective tissue disease; DLCO, diffusion capacity of carbon monoxide.

Abbreviated Title: HCT/Briquilimab/GATA2 Deficiency
Version Date: 06/10/2025

*One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft

‡To convert creatinine from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 88.4.

17.7 APPENDIX G – GVHD GRADING AND SCORING

17.7.1 Acute GVHD Staging and Grading

Extent of organ involvement			
Stage	Skin	Liver (bilirubin)	Gut (stool output per day)
0	No GVHD rash	<2 mg/dL	<50 mL/day or persistent nausea (child: <10 mL/kg/day)
1	Maculopapular rash <25% BSA	2-3 mg/dL	500-999 mL/day (child: 10-19.9 mL/kg/day) or persistent nausea, vomiting or anorexia, with a positive upper GI biopsy
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL	1000-1500 mL/day (child: 20-30 mL/kg/day)
3	Maculopapular rash >50% BSA	6.1-15 mg/dL	Adult: >1500 mL/day (child: >30 mL/kg/day)
4	Generalised erythema plus bullous formation	>15 mg/dL	Severe abdominal pain with or without ileus
Grade	Skin	Liver (bilirubin)	Gut (stool output per day)
I	Stages 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	-	Stage 2-3 or	Stages 2-4
IV	Stage 4 or	Stage 4	-

Abbreviations: BSA = body surface area; GI = gastrointestinal; GVHD = graft-versus-host disease.

17.7.2 Chronic GVHD Diagnosis and Staging

Diagnostic signs and symptoms of chronic GVHD are those that establish the diagnosis of chronic GVHD without need for further testing or evidence of other organ involvement.

Distinctive signs and symptoms of chronic GVHD are those that are not sufficient in isolation to establish a diagnosis of chronic GVHD, where additional testing such as biopsy is needed to establish the diagnosis. *Other features or unclassified manifestations* of chronic GVHD define rare, controversial, or nonspecific features of chronic GVHD that cannot be used to establish the diagnosis. *Common* features are those that are seen in both acute and chronic GVHD. Further details regarding the diagnosis and staging of chronic GVHD are in the National Institutes of Health Consensus Development Project 2014 Working Group Report.