Blinatumomab Bridging Therapy in High-Risk B-Acute Lymphoblastic Leukemia: A Phase 2 Study

Blinatumomab Bridging Therapy (BBT)

Version No. 1.4

Version Date: 06/24/2021

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PROTOCOL REVISION HISTORY

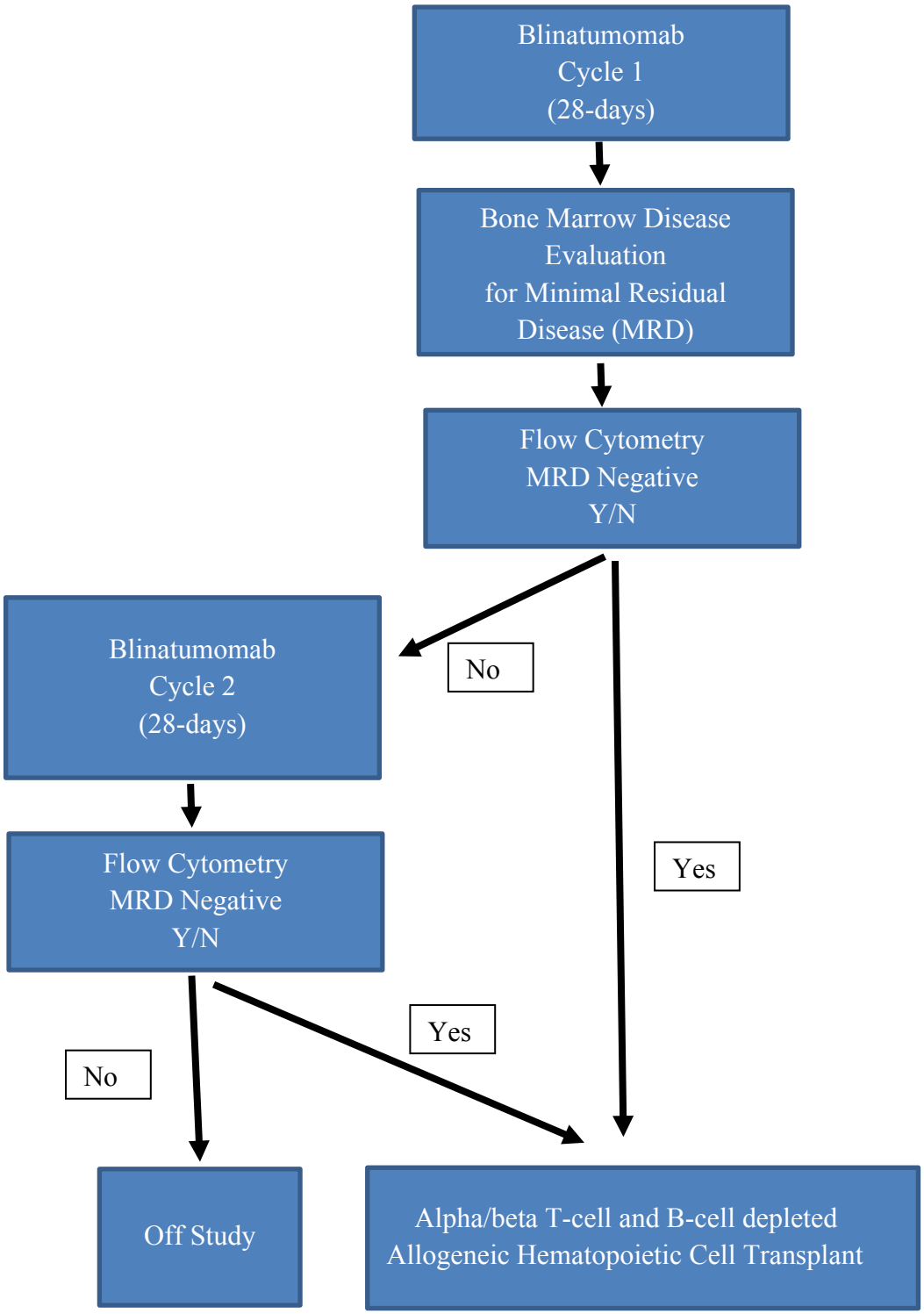
Version No.	Revision Date	Summary of Changes	Consent Revised Yes/No
1.4	06/14/2021	**PI Requested changes as follows:** • Removal of Dr. Mario Otto from the protocol • Addition of TKI use for Ph+ and Ph-like B-ALL to eligibility criteria • Addition of CMV/EBV serologies to screening procedures	Yes • Added viral serologies to screening procedures
1.3	03/01/2021	**PI Requested changes as follows:** • Physician visits changed to weekly in study calendar and Section 5.2.1 • Added additional cycle of blinatumomab for MRD negative subjects that have issues with timing of donor collection on pages • Added note that MRD by HTS does not need to be completed within the 14 day window in section 5.1.3 • Follow up visits to revised as "weekly in Section 5.4.1 • Off study criteria added in Section 5.6.6 • Added option of using local lab for MRD by flow since this can be done at CW lab • Various administrative changes	Yes • Physician visits revised to weekly • Administrative edits
1.2	01/27/2021	**Added NGS testing that identifies BOTH B and T cell proteins. Updated under study calendar, section 5.1.3, section 5.3.1 and section 6.2.**	No
1.1	10/26/2020	**FDA Requested changes as follows:** • Section 6 revised to add minimal organ functions • Section 6.3.5 revised to add a statement referring to Appendix 2 which refers to the current USPI for volume calculations • Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative was added to Section 6.3.7 • Blinatumomab AE List in Section 8.3 was revised as per the risks provided by Amgen • Appendix 2 revised to add "do not shake" to #3 discussing adding IV solution stabilizer • Appendix 2 revised to add a statement for Patients Weighing Under 22 kg • Appendix 2 revised to remove all volume calculation tables and refer to the current USPI for preparation Local Changes as follows: Removal of Lauren Pommert from list of Sub-Investigators	Yes • Added "Do not drive, operate heavy machinery, etc. under risks section • Added CRS, Neurological problems, and Infections as separate bullets to "Health Risks or Problems" • Blina AE list was revised • Added drug monograph for dexamethasone

ABSTRACT

Children, adolescents and young adults with relapse or refractory B-acute lymphoblastic leukemia (B-ALL) often have dismal outcomes with chemotherapy alone. Despite allogeneic hematopoietic cell transplantation (HCT) providing a cure for some of these patients, relapse after HCT continues to be the most common reason of treatment failure. Identifying novel ways to improve post-HCT outcomes in these high-risk patients has been challenging and currently no standard approach has been found. We are testing the ability of a biologically active therapy in blinatumomab, an anti-CD19/CD3 bispecific T-cell engager, to further reduce residual leukemia immediately prior to HCT to improve post-HCT outcomes. This Phase 2 study will deliver 1 to 2 cycles of blinatumomab (28-day continuous infusion) in up to 35 subjects with B-ALL that have experienced a relapse or have persistent disease. Subjects will receive blinatumomab immediately prior to proceeding to HCT with best available donor using an alpha/beta T-cell and B-cell depletion preparative transplant regimen.

EXPERIMENTAL DESIGN SCHEMA

Study population: Patients, ages ≤ 25 years, with B-ALL meeting study eligibility



STUDY CALENDAR

Drug or Clinical Tests to Be Completed①	Baseline	Days 1 to 28	Days 26 - 30
Screening Assessments^	X		
Blinatumomab Cycle 1 and Cycle 2 (if needed)		Continuous infusion	
Clinic Visit - History & Physical Exam		weekly	
Performance Status		weekly	
CBC with differential, CMP*		weekly	
Uric acid, Phosphorus, LDH, PT, PTT, Urinalysis		Day 1	
Disease Evaluation Bone Marrow[#] (aspirate and/or Biopsy) Lumbar Puncture	X		X X

① Laboratory evaluations will be followed more frequently as clinically indicated
^ See Section 5.1.3 for screening assessments
*CMP, comprehensive metabolic panel
[#]Bone marrow evaluations will be performed at the end of each cycle of blinatumomab around Day 28 (+/- 2 days) with minimal residual disease (MRD) testing performed using flow cytometry and high-throughput deep sequencing (HTS). Baseline blast samples will be sent for B-cell and T-cell clonality HTS assessment. If T-cell clonal sequences are detected on the baseline sample, T-cell clonality will continue to be sent along with B-cell clonality on subsequent samples.

PROTOCOL SUMMARY

Title	Blinatumomab Bridge to Allogeneic Hematopoietic Cell Transplantation for B-Acute Lymphoblastic Leukemia: A Phase 2 Study
Protocol Short Name	Blinatumomab Bridging Therapy (BBT)
IND Sponsor	N/A
Principal Investigator/ Study Chair/ Coordinating Center/Sponsor-Investigator	Michael J. Burke, MD Pediatric Clinical Trials Office (CTO) 8701 Watertown Plank Road MFRC Suite 3018 Milwaukee, WI 53226
Study Sites	1) Children's Wisconsin 2) American Family Children's Hospital, Madison WI
Clinical Trial Phase	Phase 2 Study
Study Disease	B-Acute Lymphoblastic Leukemia
Main Eligibility Criteria	Diagnosis of B-ALL in hematologic complete remission (M1 marrow; < 5% blasts in the bone marrow) by morphology or multi-parameter flow cytometry with evidence of minimal residual disease (MRD) ≥ 0.01% **AND** that meets one of the following: a. Patients in first relapse or greater, **OR** b. Patients with very-high risk biology ALL that is proceeding to HCT in first remission (e.g. Induction failure, Severe-hypodiploidy, Ph-like ALL), **OR** c. Patients in 1st CR with persistent disease identified as end of consolidation (EOC) MRD ≥ 0.01%. **AND** with the intent of going on to an allogeneic hematopoietic cell transplantation (HCT) independent of the study • Patients must have an available donor and have intention of proceeding directly to HCT after completion of 1 to 2 cycles of bridging therapy with blinatumomab. • Age ≤ 25 years at time of study enrollment • Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study. At least 7 days must have elapsed from prior chemotherapy. • Patients who have experienced their relapse after HCT are eligible, provided they have no evidence of acute or chronic graft-versus-host disease (GVHD) and are off all transplant immune suppression therapy for at least 7-days (e.g. steroids, cyclosporine, tacrolimus). Steroid therapy for non-GVHD and/or non-leukemia therapy is acceptable.

Study Rationale	Relapse of childhood B-Acute Lymphoblastic Leukemia (B-ALL) is a vexing clinical problem with high rates of subsequent relapse and death with current treatment approaches. This trial will determine if blinatumomab used as a bridge to allogeneic hematopoietic cell transplantation (HCT) can reduce rates of subsequent relapse and improve survival. If successful, this strategy could become standard of care for patients going to HCT for B-ALL with residual disease.
Primary Objectives	To determine the efficacy of blinatumomab given immediately prior to HCT as "bridging therapy" to eliminate minimal residual disease as measured by Flow Cytometry in children, adolescents, and young adults with relapse or refractory B-ALL.
Secondary Objectives	To compare the results of Flow Cytometry-based versus molecular High-Throughput Deep Sequencing (HTS)-based minimal residual disease (MRD) testing following blinatumomab prior to HCT in children, adolescents, and young adults with relapse or refractory B-ALL and how they correlate with post-HCT outcomes.
Study Design	This Phase 2 study will determine the effectiveness of delivering 1 to 2 cycles of blinatumomab (Days 1-28) as bridging therapy in children, adolescent and young adults with relapse or persistent MRD B-ALL. Eligible subjects will receive 1 or 2, 28-day cycles of blinatumomab prior to proceeding to HCT. Centralized MRD assessment will be performed after completion of the 28-days of blinatumomab using both flow cytometry (University of Washington, Brent Wood, MD or local lab if applicable) and High-Throughput Deep Sequencing (HTS) MRD technologies (Adaptive Technologies, Seattle, WA). Subjects who achieve flow cytometry negative MRD (<0.01%) after a single cycle of blinatumomab can proceed directly to HCT whereas subjects who remain MRD positive by flow cytometry may receive a 2nd cycle of blinatumomab. Additionally, subjects who achieved MRD negativity after Cycle 1 but are unable to proceed to HCT based on the timing/scheduling of the donor collection, a 2nd cycle of blinatumomab may be given. Subjects who remain MRD positive by flow cytometry after a 2nd cycle of blinatumomab will come off study. This is part one of two-part study. The current study is measuring the timing of blinatumomab in relation to HCT. In the second part of the study, the subjects move on to receive a transplant if eligible.
Study Agent/Intervention Description	Blinatumomab
Number of Subjects	Up to 35 subjects (25 evaluable subjects are needed who are able to proceed to HCT)
Subject Participation Duration	Patients may continue treatment for 1 to 2 cycles of blinatumomab prior to either coming off protocol or proceeding to HCT.
Duration of Follow up	All subjects, including those who discontinue protocol therapy early, will be followed for 30 days from the end of blinatumomab or until the start of the transplant preparative regimen (or other therapy), whichever occurs earlier.

Estimated Time to Complete Enrollment	30 - 36 months
Statistical Methodology	We will summarize by and compare the subgroups, within the context of a Phase 2 study, of those who are MRD negative by Flow Cytometry (< 0.01%) AND High-Throughput Deep Sequencing (HTS) (MRD undetectable) will be compared to those subjects who are MRD negative by only Flow Cytometry (HTS MRD positive) by demographics and by # of cycles (incomplete, 1 or 2). For comparison of continuous data, we will use a t-test or non-parametric Mann Whitney test, if needed due to distribution. For categorical data we will use a Fisher exact test. **Sample Size and Power Estimate** It is expected that the study will complete in 30 to 36 months. If there is an 80% rate of MRD negative subjects, a total of 25 evaluable subjects will be recruited. The 95% confidence interval will be (0.59,0.93) with 25 patients. If we must recruit 35 total subjects, we would expect that the proportion will be no less than 0.67 with a 95% CI of (0.47,0.83). We expect ~40% (10 patients) will be MRD negative by HTS (undetectable MRD). With 25 evaluable subjects recruited the 95% CI would be (0.21,0.61).

LIST OF ABBREVIATIONS

AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	Alanine Aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BMT	bone marrow transplant
BP	blood pressure
BUN	blood urea nitrogen
CW	Children's Wisconsin
CI	confidence interval
CNS	central nervous system
CR	complete remission
CRF	case report forms
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trials Management System
CTO	Clinical Trials Office
DCTD	Division of Cancer Treatment and Diagnosis
DLT	dose limiting toxicity
DSMC	data safety monitoring committee
DSMP	data safety monitoring plan
ECHO	echocardiogram
FISH	fluorescence in situ hybridization
GVHD	graft versus host disease
HCT	hematopoietic cell transplantation
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
HTS	high-throughput deep sequencing
IRB	Institutional Review Board
ISO	International Organization for Standardization
LDH	lactate dehydrogenase
MACC Fund Center	Midwest Athletes Against Childhood Cancer Fund Center
MCW	Medical College of Wisconsin
MCWCC DSMC	Medical College of Wisconsin Cancer Center Data Safety Monitoring Committee
MRD	minimal residual disease
MUGA	multi gated acquisition scan
NCI	National Cancer Institute
NGS	Next generation sequencing
NOS	not otherwise specified
OnCore™	Online Enterprise Research Management Environment
ORR	overall response rate
OS	overall survival
PCP	pneumocystis carinii pneumonia
PCR	polymerase chain reaction
Pediatric CTO	Pediatric Cancer/Blood Disorder Clinical Trials Office
PI	principal investigator

PR	partial response
RFS	relapse free survival
SAE	serious adverse event
SRC	Scientific Review Committee
SUSAR	suspected unexpected serious adverse reaction
TRM	transplant related morbidity
ULN	upper limit of normal
UPIRSO	unanticipated problems involving risks to subjects or others
USP	United States Pharmacopeia
WBC	white blood count

1.0 BACKGROUND

1.1 Overview

Acute lymphoblastic leukemia (ALL) remains one of the most common hematologic diseases for which allogeneic hematopoietic cell transplantation (HCT) is currently used.[1] Despite improved outcomes of HCT over time for ALL, relapse remains a considerable problem and the leading cause of treatment failure.[2] There is mounting evidence to support that for patients in hematological complete remission (< 5% leukemia in the bone marrow), the presence of minute amounts of leukemia (known as minimal residual disease (MRD)), identified immediately prior to HCT is associated with higher rates of ALL relapse following HCT.[3-12] This trial will determine if blinatumomab used as a bridge to HCT can reduce rates of subsequent relapse and improve post-HCT survival. If successful, this strategy could become standard of care for patients going to HCT for B-ALL with residual disease.

1.2 Rationale for Studying Blinatumomab in Relapse B-ALL

Survival for relapse of B-ALL is suboptimal with outcomes ranging 30-50%.[13] Additionally, there is mounting evidence to support that for patients in hematological remission, the presence of minimal residual disease (MRD), identified immediately prior to allogeneic hematopoietic cell transplantation (HCT), is associated with higher rates of relapse following HCT. Patients who have MRD identified prior to HCT, have relapse rates of 50-60% compared to 10-20% for patients who are MRD negative.[6] In the Children's Oncology Group (COG) study ASCT0431 reporting HCT outcomes in 144 pediatric patients with relapse ALL, those who achieved MRD negativity pre-HCT identified by flow cytometry (FC) reported significantly less relapse at 1-year (20% versus 60%, p=0.4).[12] Even more impressive was the predictability of relapse using high throughput sequencing (HTS) for MRD detection which was superior to FC. Patients on the ASCT0431 study who achieved HTS-MRD negativity pre-HCT had no relapses compared to those who were HTS-MRD positive (0% versus 16%, p=0.02) and significantly greater overall survival (96% versus 77%, p=0.003).[14] Additionally, post-HCT HTS-MRD detection was better at predicting relapse than FC-MRD (p<0.0001), especially early after HCT (day 30 FC-MRD positive relapse rate, 35%; HTS-MRD positive relapse rate, 67%; p=0.004). Thus, introducing therapies for patients who are MRD positive prior to HCT to eliminate MRD and potentially improve post-HCT survival, is a promising approach and the primary focus of this study.

Blinatumomab is a promising novel agent for the treatment of B-lineage lymphoid malignancies.[15-19] Blinatumomab is a bispecific single-chain antibody that targets the CD19 antigen and redirects CD3+ T-cells for selective lysis of tumor cells. In a Phase 2 trial of adult B-ALL, patients with MRD persistence or relapse after Induction and Consolidation therapy received Blinatumomab as a 4-week continuous intravenous infusion at a dose of 15 $\mu g/m^2$/24 hours.[19] Of 21 treated patients, 16 became MRD negative as assessed by quantitative polymerase chain reaction (QT-PCR) for either rearrangements of immunoglobulin or T-cell receptor genes, or specific genetic aberrations. Among the 16 responders, 12 had been molecularly refractory to previous chemotherapy. Probability for relapse-free survival was 78% at a median follow-up of 405 days. Blinatumomab was similarly effective and well tolerated in an anecdotal report of a small series of pediatric cases.[16]

Blinatumomab has been evaluated in children with relapsed/refractory ALL in Phase 1/2 study conducted by the Children's Oncology Group (COG) (MT103-205/AALL1121) and the I-BFM

European childhood leukemia cooperative group with extremely promising results. Forty-nine patients were treated in the Phase 1 portion and 44 patients in the Phase 2.[20] Four patients had dose-limiting toxicities in Cycle 1 (Phase 1). Three experienced Grade 4 cytokine-release syndrome (one attributed to Grade 5 cardiac failure); one had fatal respiratory failure. The maximum-tolerated dosage was 15 µg/m^2/d. Blinatumomab pharmacokinetics was linear across dosage levels and consistent among age groups. On the basis of the Phase 1 data, the recommended Blinatumomab dosage for children with relapsed/refractory ALL was 5 µg/m^2/d for the first 7 days, followed by 15 µg/m^2/d thereafter. Among the 70 patients who received the recommended dosage, 27 (39%; 95% CI, 27% to 51%) achieved complete remission within the first two cycles, 14 (52%) of whom achieved complete MRD response. The most frequent Grade ≥ 3 adverse events were anemia (36%), thrombocytopenia (21%), and hypokalemia (17%). Three patients (4%) and 1 patient (1%) had cytokine-release syndrome of Grade 3 and 4, respectively. Two patients (3%) interrupted treatment after Grade 2 seizures. This trial was the first such trial in pediatrics and demonstrated anti-leukemic activity of single-agent Blinatumomab with complete MRD response in children with relapsed/refractory B-ALL.

In December 2014, the COG opened a Phase 3 study group-wide (>100 institutions) investigating blinatumomab in combination with chemotherapy for children, adolescents and young adults with 1st relapse B-ALL (AALL1331; NCT02101853). The dose used in this study for patients who are in remission is 15 µg/m^2/d (maximum dose of 28 mcg/d). This study continues to accrue.

The level of single agent activity seen with blinatumomab has not been seen in recent Phase 1 ALL studies outside the use of tyrosine kinase inhibitors (TKI) in patients with Philadelphia chromosome positive (Ph+) ALL.

Neurological adverse events have been described with blinatumomab and will be closely monitored on this study. One potential concern regards the safety of combining blinatumomab with IT chemotherapy which is given prior to starting blinatumomab on this study. However, in the previous Phase 1/2 pediatric study cited above, IT methotrexate or IT triples were included prior to Cycle 1, at Day 15 of Cycle 1 and at Day 29 of each cycle with no unusual or increased CNS side effects reported.[20]

Cytokine release syndrome (CRS) has also been described with blinatumomab. This has been more prevalent in patients with a higher leukemia burden, however, can occur in any patient treated with blinatumomab. Pre-medication with dexamethasone will be mandated in the protocol, and at the suggestion of the development of CRS, even after the premedication doses, additional dexamethasone administration is suggested. There is a published case report suggesting that for cases of life-threatening cytokine release syndrome for which dexamethasone and supportive care measures are not adequate, consideration may be given to the administration of tocilizumab, the anti-IL-6 monoclonal antibody.[21]

On July 11, 2017, the US FDA approved blinatumomab for treatment of relapsed or refractory B-cell ALL in adults and children and in March 2018, the US FDA granted accelerated approval to blinatumomab to treat adults and children with B-cell ALL who are in remission but still have MRD. The FDA approved dose of blinatumomab in children and adults who have < 5% leukemia blasts in the bone marrow is 15 µg/m^2/d (patients < 45kg; not to exceed 28 µg/d) and 28 µg/d (patients ≥ 45 kg) as a continuous infusion for 28 days.

2.0 HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

Blinatumomab will successfully reduce the leukemia disease burden (as measured by HTS) for children, adolescents and young adults with relapse or persistent MRD B-ALL when given prior to HCT, resulting in improved post-HCT outcomes.

2.2 Primary Objectives

To determine the efficacy of blinatumomab given immediately prior to HCT as "bridging therapy" to eliminate MRD using flow cytometry in children, adolescents and young adults with relapse or persistent MRD B-ALL.

2.3 Secondary Objectives

To compare the results of Flow Cytometry-based versus molecular High-Throughput Deep Sequencing-based minimal residual disease (MRD) testing following blinatumomab prior to HCT in children, adolescents and young adults with relapse or persistent MRD B-ALL and how these MRD correlate with post-HCT outcomes.

3.0 STUDY DESIGN

3.1 General Description

This Phase 2 study will determine the effectiveness of delivering 1 to 2 cycles of blinatumomab (Days 1-28) as bridging therapy in children, adolescent and young adults with B-ALL and MRD. Eligible subjects, ages ≤ 25 years with the diagnosis of B-ALL in hematologic complete remission (< 5% leukemia in the bone marrow) and evidence of MRD (≥ 0.01%), will receive 1 or 2, 28-day cycles of blinatumomab prior to proceeding to HCT. Centralized MRD assessment will be performed after completion of the 28-days of blinatumomab using both Flow Cytometry (University of Washington, Brent Wood, MD or local lab if applicable) and High-Throughput Deep Sequencing (HTS) MRD technologies (Adaptive Technologies, Seattle, WA). Subjects who achieve Flow Cytometry negative MRD (< 0.01%) after a single cycle of blinatumomab can proceed directly to HCT whereas subjects who remain MRD positive by Flow Cytometry may remain on study to receive a 2nd cycle of blinatumomab. Additionally, subjects who achieved MRD negativity after Cycle 1 but are unable to proceed to HCT based on the timing/scheduling of the donor collection, a 2nd cycle of blinatumomab may be given. This additional cycle of blinatumomab for subjects awaiting donor collection, may be 28 days but can be less if the HCT is ready to proceed (e.g. 14-day blinatumomab infusion). Subjects who remain MRD positive by Flow Cytometry after a 2nd cycle of blinatumomab will be considered a treatment failure and come off study. For patients who achieve MRD negativity via Flow Cytometry and proceed to HCT, centralized HTS MRD assessment (Adaptive Technologies, Seattle, WA) will be used to determine which conditioning regimen will be given as patients who are MRD negative by Flow Cytometry but have MRD identified by HTS will receive standard myeloablative conditioning whereas patients achieving MRD negativity with both Flow Cytometry and HTS (MRD undetectable), will receive non-myeloablative conditioning. This is part one of a two-part study. The current study is measuring the timing of blinatumomab in relation to HCT. In the second part of the study, the subjects move on to receive a transplant if they achieve an MRD negative status.

3.2 Number of Subjects

This Phase 2 study will enroll up to 35 subjects with the goal of achieving 25 evaluable subjects who become MRD negative based on Flow Cytometry after completing 1 to 2 cycles of blinatumomab and successfully proceed to HCT.

3.3 Primary Completion

The study will reach primary completion for enrollment 30 to 36 months from the time the study opens to accrual.

3.4 Study Completion

The study will reach final study completion 42-48 months from the time the study opens to accrual.

4.0 PATIENT SELECTION

Study entry is open to patients regardless of gender or ethnic background. While there will be every effort to seek out and include females and minority patients, the patient population is expected to be no different than that of other acute leukemia studies at the Medical College of Wisconsin.

4.1 Eligibility Criteria

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

4.2 Inclusion Criteria

4.2.1 Diagnosis of B-ALL in hematologic complete remission (defined as an M1 marrow, < 5% blasts) with MRD in the bone marrow (≥ 0.01%) by multi-parameter flow cytometry **and** that meets one of the following:

- Patients in first relapse or greater;

  OR

- Patients with very-high risk biology ALL that is proceeding to HCT in first remission (e.g. Induction failure, Severe-hypodiploidy, Ph-like ALL);

  OR

- Patients who have persistent MRD after Consolidation therapy (End of Consolidation (EOC) MRD positive ≥ 0.01%);

AND with the intent of going on to an allogeneic hematopoietic cell transplantation (HCT) independent of this study

4.2.2 Patients must have an available donor and have intention of proceeding directly to HCT after completion of 1 to 2 cycles of Bridging therapy with blinatumomab.

4.2.3 Age ≤ 25 years at time of study enrollment

4.2.4 Karnofsky Performance Status ≥ 50% for patients 16 years and older and Lansky Play Score ≥ 50 for patients under 16 years of age (see Appendix 1)

4.2.5 Have acceptable organ function as defined within 7 days of study registration:

Renal: creatinine clearance ≥ 60 mL/min/1.73m^2 **or** serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dl)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 year to < 2 years	0.6	0.6
2 years to < 6 years	0.8	0.8
6 years to < 10 years	1.0	1.0
10 years to < 13 years	1.2	1.2
13 years to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

Hepatic: ALT < 5 x upper limit of normal (ULN) and total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age

Cardiac: left ventricular ejection fraction ≥ 40% by ECHO/MUGA

4.2.6 At least 7 days must have elapsed from prior chemotherapy.

4.2.7 Patients who have experienced their relapse after HCT are eligible, provided they have no evidence of acute or chronic Graft-versus-Host Disease (GVHD) and are off all transplant immune suppression therapy for at least 7-days (e.g. steroids, cyclosporine, tacrolimus). Steroid therapy for non-GVHD and/or non-leukemia therapy is acceptable.

4.2.8 Biologic (anti-neoplastic agent): At least 7 days after the last dose of a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair. Patients with Philadelphia-chromosome positive or Philadelphia-chromosome like (PH-Like) BALL are an exception to this eligibility criteria as concomitant TKI therapy is allowed on study (e.g. imatinib, dasatinib, nilotinib).

4.2.9 Monoclonal antibodies: At least 3 half-lives of the antibody must have elapsed after the last dose of monoclonal antibody (i.e. Inotuzumab = 12 days).

4.2.10 Immunotherapy: At least 42 days after the completion of any type of immunotherapy (e.g. tumor vaccines or CAR T-cell therapy) **except monoclonal antibodies.**

4.2.11 XRT: Cranio or craniospinal XRT is prohibited during protocol therapy. ≥ 90 days must have elapsed if prior TBI, cranio or craniospinal XRT

4.2.12 Sexually active females of child-bearing potential must agree to use adequate contraception (diaphragm, birth control pills, injections, intrauterine device [IUD], surgical sterilization, subcutaneous implants, or abstinence, etc.) for the duration of treatment and for 2 months after the last dose of chemotherapy. Sexually active men must agree to use barrier contraceptive for the duration of treatment and for 2 months after the last dose of chemotherapy.

4.2.13 Voluntary written consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

4.3 Exclusion Criteria

4.3.1 History of CNS3 disease and/or active central nervous system (CNS) disease (≥ CNS2)

4.3.2 Receiving concomitant chemotherapy (with the exception of a tyrosine kinase inhibitor (e.g. imatinib, dasatinib, nilotinib) for Philadelphia-chromosome positive or Philadelphia-chromosome Like (Ph-Like) BALL), radiation therapy; immunotherapy or other anti-cancer therapy other than is specified in the protocol.

4.3.3 Systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment)

4.3.4 Pregnant or lactating. The agents used in this study are known to be teratogenic to a fetus and there is no information on the excretion of agents into breast milk. All females of childbearing potential must have a blood test or urine study within 7-days prior to the start of blinatumomab to rule out pregnancy.

4.3.5 Known allergy to blinatumomab

4.3.6 Participating in a concomitant Phase 1 or 2 study

5.0 REGISTRATION PROCEDURES (STUDY ENTRY, STUDY PROCEDURES, END OF TREATMENT AND WITHDRAWL PROCEDURES)

Registration will occur after eligibility is confirmed and the patient/parent has signed the subject consent, but before any treatment has been administered. Questions regarding eligibility should be directed to the Principal Investigator: Michael Burke, MD (phone 414-955-4198; email

mmburke@mcw.edu)

The eligibility checklist will be completed at the time of study enrollment.

5.1 Study Entry Procedures

5.1.1 Required Preregistration Screening Tests and Procedures

Screening assessments must be performed within 14-days prior to enrollment. Any results falling outside of the reference ranges may be repeated at the investigator's discretion. All on-study visit procedures are allowed a window of ± 2 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.
A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF and HIPAA form will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in the Online Enterprise Research Management Environment (OnCore™), the MCW Cancer Center and Pediatric Clinical Trials Office (CTO) Clinical Trial Management System. The system is password protected and meets HIPAA requirements.

5.1.2 Registration Process

Upon completion of the screening evaluation, eligibility confirmation and obtaining written consent, the patient will be registered in the study file by the Department of Pediatrics Division of Hematology/Oncology/BMT MACC Fund Center CTO).

5.1.3 Pretreatment Period

Screening Assessments: The screening procedures and assessments must be completed within 14-days of the Day 1 visit (or the first day of blinatumomab infusion).

- Physical examination
- Vital signs
- Complete medical history
- Baseline conditions assessment
- Documentation of disease assessment (disease-specific staging criteria)
- Performance status (ECOG, KPS, etc.)
- Measurable disease
    - Bone marrow aspirate and/or biopsy (morphology, cytogenetics, FISH and minimal residual disease (MRD) via HTS and flow cytometry). Baseline blast samples will be sent for B-cell and T-cell clonality HTS assessment, since B-lymphoblasts may have detectable T cell receptor (TCR) clones. If T-cell clonal sequences are detected on the baseline sample, T-cell clonality will continue to be sent along with B-cell clonality on subsequent samples (Note that prior MRD by HTS is required, but does not need to be completed within the 14 day window).

- Lumbar Puncture (CSF cytology and cell count)
- History of prior treatments and any residual toxicity relating to prior treatment
- Baseline medications taken within 14-days of Day 1
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
  Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH).
- Coagulation assessment, including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- Urinalysis
- Serum or urine pregnancy test (if applicable) within 7-days prior to the start of blinatumomab
- Electrocardiogram (EKG)
- Cardiac assessment (ECHO, MUGA, etc.)
- CMV serology and EBV serology prior to the start of the first cycle of blinatumomab

5.2 Study Procedures During Treatment

Patients must meet eligibility criteria on Day 1 to be treated as per this protocol.

5.2.1 Study Procedures, Cycle 1 (and cycle 2, if applicable), Weekly

- Physical examination
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
  - Alkaline phosphatase, ALT/AST, total bilirubin, calcium, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate,
- Coagulation assessment, including PT/PTT/INR (Day 1)
- Urinalysis, uric acid, LDH, phosphorus (Day 1)

5.3 End of Treatment

5.3.1 End of Treatment Procedures

To be completed on treatment Day 28 ± 2 days.

- Bone marrow aspirate and/or biopsy (morphology, cytogenetics, FISH and minimal residual disease via HTS and flow cytometry). Baseline blast samples will be sent for B-cell and T-cell clonality assessment. If T-cell clonal sequences are detected on the baseline sample, T-cell clonality will continue to be sent along with B-cell clonality on subsequent samples. If no trackable T-cell sequences are detected, only B-cell HTS will be followed.

- Lumbar puncture (CSF cytology and cell count)

5.4 Post-Treatment

5.4.1 Follow-Up Visits

All subjects, including those who discontinue protocol therapy early, will be followed for 30 days from the completion of blinatumomab or until the start of the transplant preparative regimen (or other therapy), whichever occurs earlier.

The following procedures will be performed at the follow-up visit(s): Weekly

- Physical examination
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
  - Alkaline phosphatase, ALT/AST, total bilirubin, calcium, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate,

5.5 Study Withdrawal Procedures

5.5.1 Duration of Therapy

Treatment will be limited to 1 to 2 cycles of blinatumomab. An additional cycle of Blinatumomab bridging therapy can be given if needed based on timing of donor collection. This additional cycle for subjects awaiting donor collection, may be 28 days but can be less if the HCT is ready to proceed (e.g. 14-day blinatumomab infusion). Subjects will receive protocol therapy unless:

- Subject withdraws consent or is non-compliant
- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable toxicity

5.5.2 Subject-Initiated Withdrawal

A subject may decide to withdraw from the study at any time.

5.5.3 Investigator-Initiated Withdrawal

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a subject's compliance with the prescribed treatment regimen.

5.5.4 Sponsor-Initiated Withdrawal

Sponsor's decision to discontinue the study.

5.5.5 Withdrawal Documentation Procedure

The reason for study withdrawal and the date the subject was removed from the study must be documented in the case report form (CRF). As this study will enroll up to 35 patients in order to capture 25 evaluable subjects, it will account for subjects that may withdraw from study. Any subject who receives any amount of blinatumomab will be evaluable for toxicity and followed until they either come off study or begin a new treatment for their leukemia, which would include HCT.

5.5.6 Off Study Criteria

- Death
- Lost to follow-up
- Patient enrollment onto another anti-cancer therapeutic study with exception to Part 2 of this study
- Withdrawal of consent for any further data submission
- Protocol defined follow up criteria met

6.0 TREATMENT PLAN

6.1 Drug Administration

Up to 2 cycles of continuous infusion blinatumomab will be given based on the end of Cycle 1 disease response. Cycle 2 of blinatumomab can be given to subjects who have achieved remission (< 5% marrow blasts) after Cycle 1 but have persistent disease identified by multi-parameter flow cytometry (minimal residual disease (MRD) positive ≥ 0.01%) after Cycle 1. Additionally, subjects who achieved MRD negativity after Cycle 1 but are unable to proceed to HCT based on the timing/scheduling of the donor collection, a 2nd cycle of blinatumomab may be given. This additional cycle of blinatumomab for subjects awaiting donor collection, may be 28 days but can be less if the HCT is ready to proceed (e.g. 14-day blinatumomab infusion).

Minimal Organ Functions to be Met Before the Start of the Blinatumomab Infusion

Patients must meet the following criteria (prior to blinatumomab infusion)

- No oxygen requirement with oxygen saturations > 90%.
- AST, ALT < 5x upper limit of normal for age; bilirubin < 2 mg/dL.
- Hemoglobin > 8 mg/dL prior to infusion. (May be transfusion dependent).
- Renal function: serum creatinine < 2 x normal for age.
- Exhibit overt hematologic manifestations of relapse or persistent disease. Evidence of recurrent/persistent disease based primarily on flow cytometry, cytogenetics, chimerism analysis, or other molecular studies does not by itself represent grounds for exclusion.

Blinatumomab will be given as a 28-day continuous infusion with 14-days in between Cycle 1 and Cycle 2 as per the package insert and FDA approved labeling.

Cycle	Patient Weight Greater Than or Equal to 45kg (*Fixed-dose*)	Patient Weight Less Than 45kg (*BSA-based dose*)
1: Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
2: Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
Days 29-42	14-day treatment-free interval	14-day treatment-free interval

Hospitalization is recommended for the first 3 days of Cycle 1 and the first 2 days of Cycle 2 (if needed).

Pre-medicate with prednisone or equivalent for MRD-positive B-cell Precursor ALL.

For patients ≥ 18 years of age, pre-medicate with prednisone 100 mg intravenously or equivalent (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of blinatumomab in each cycle.

For pediatric patients (<18 years of age), pre-medicate with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of blinatumomab in Cycle 1 and when restarting an infusion after an interruption of 4 or more hours in the first cycle.

6.2 Sample Collection and Processing for Minimal Residual Disease

Type of Sample	Instructions and Timing of Sample Collection
Bone Marrow Samples for **Flow Cytometry** MRD	• At the end of each blinatumomab cycle (Day 28 ± 2 days).
Bone Marrow Samples for **Flow Cytometry** MRD Bone Marrow Collection and Shipping Procedure	• Bone marrow required for Flow Cytometry clinical evaluation MRD testing should be collected and shipped according to the standard procedures for the local institution. These samples will be evaluated by an approved Flow Cytometry Laboratory. • Results of the clinical evaluation Flow Cytometry MRD testing at each timepoint will be communicated to each local institution by the approved Flow Cytometry Laboratory, and results should be entered into the EDC system by local Clinical Research Coordinators.
Bone Marrow Samples for **High Throughput Sequencing** MRD Samples	• At time of enrollment prior to start of blinatumomab • At the end of each blinatumomab cycle (Day 28 ± 2 days). • Baseline blast samples will be sent for B-cell and T-cell clonality assessment. If T-cell clonal sequences are detected on the baseline sample, T-cell clonality will continue to be sent along with B-cell clonality on subsequent samples. If no trackable T-cell sequences are detected, only B-cell HTS will be followed.

Type of Sample	Instructions and Timing of Sample Collection
Bone Marrow Sample for **High Throughput Sequencing** MRD Collection Procedure	• Collect minimum of 2 mL of marrow into a syringe and place marrow into a large purple EDTA tube that are commonly used in all hospitals. Mix well • Reposition marrow aspirates needle at least once during procedure to ensure the maximum quality of marrow
Specimen Labeling for **High Throughput Sequencing** MRD Sample	Each tube must be labeled with the study ID number, along with the date the sample was obtained. No personal identifying patient information should be included in the specimen or transmittal form.
Specimen Packaging and Shipping for **High Throughput Sequencing** MRD Sample	Adaptive has fresh collection kits with EDTA tubes, ambient packs and pre-paid FedEx labels for domestic sites to use in this trial. Domestic samples should be shipped same day as collection at ambient temperature for overnight delivery to Adaptive. Adaptive is open to accept ambient samples Monday-Saturday. Include the completed and signed Test Requisition Form (obtained from Adaptive's diagnostic Portal) with shipment and send a sample shipment notification email to clinicalservices@adaptivebiotech.com. Ship specimens to: Adaptive Biotechnologies Attn: CLIA Clinical Laboratory 1551 Eastlake Ave E, Ste 200 Seattle, WA 98102

6.3 Drug Information (Blinatumomab)

(Blincynto®, AMG103, MT103, recombinant bispecific antibody derivative)

6.3.1 Source and Pharmacology

Blinatumomab is a fusion protein composed of two single-chain antibodies (scFv), murine anti-CD19 scFv and murine anti-CD3 scFv. Through CD3 binding, blinatumomab recruits and engages T cells for redirected lysis of CD19-positive B cells, including those expressed with B-cell malignancies. T cells are bound by its anti-CD3 moiety, whereas B cells are bound by the anti-CD19 moiety. The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T cell reaction. Treatment with blinatumomab is associated with a rapid depletion of peripheral B cells, accompanied by T cell activation and a transient increase in cytokines.

Blinatumomab consists of a single chain of 504 amino acids with a molecular weight of approximately 54 kDa. The pharmacokinetics of Blinatumomab was assessed over a dose range from 5 to 90 mcg/m2/day (approximately equivalent to 9-162 mcg/day). Following continuous intravenous infusion, the steady state serum concentration (Css) was achieved within a day and remained stable over time. The estimated mean (SD) volume of distribution based on terminal phase (Vz) was 4.52 (2.89) L. The estimated mean (SD) systemic clearance was 2.92 (2.83) L/hour and the estimated mean (SD) half-life was 2.11(1.42) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses. Like other protein therapeutics, blinatumomab is expected to be degraded into small peptides and amino acids via catabolic

pathways. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of adult relapsed/refractory ALL, the mean (SD) Css was 211 (258) pg/mL and 621 (502) pg/mL, respectively.

Currently there are no known drug incompatibilities or interactions with blinatumomab.

6.3.2 Pregnancy and Lactation

Pregnancy Category Unknown: The effect of blinatumomab on fertility has not been evaluated. Blinatumomab is not recommended in pregnant women and in women of childbearing potential not using contraception. It is not known whether blinatumomab or its metabolites are excreted in human milk. Women are not allowed to breastfeed while receiving blinatumomab.

6.3.3 Formulation and Stability

Blinatumomab is available as a 38.5 mcg preservative-free, white to off-white lyophilized powder for injection in 4 mL single-use vial. The agent is formulated with 3.68 mg citric acid monohydrate, 105 mg trehalose dihydrate, and 25.55 mg lysine hydrochloride, and 0.7 mg polysorbate 80, pH 7. The stopper of the vial is latex free.

6.3.4 IV Solution Stabilizer for Blinatumomab is **not for reconstitution of blinatumomab;** it is a component of the final intravenous product. The stabilizer is available as a 10 mL single-use vial of a preservative-free, clear, colorless-to-slightly yellow liquid solution. Each solution consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride, and 0.1% (w/v) polysorbate 80, pH 7. The stopper of the vial is latex free.

Store intact vials of blinatumomab and the IV solution stabilizer of blinatumomab refrigerated at 2° to 8°C (36° to 46°F). Protect from light. Shelf life stability studies of the intact vials of blinatumomab and stabilizer solution are on-going. The stability of the final prepared IV solution is 8 days when stored refrigerated at 2° to 8°C. For storage prior to administration, the prepared infusion solution must be kept at 2° C to 8° C (36°F to 46°F). The total storage and administration time must not exceed 8 days. Once at room temperature, discard the IV bag after 96 hours.

6.3.5 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol. Premedication with dexamethasone is required prior to the first dose of blinatumomab in the first cycle, prior to a step dose and when restarting an infusion after an interruption of 4 or more hours in the first cycle. Refer to the current USPI for volume calculations.

6.3.6 IV Infusion and Infusion Set Details

Blinatumomab must be administered through a central line at rate of 5 mL/hr IV over 24 hours through an acceptable IV line. Only **PVC non-DEHP lines with a 0.2 µm inline filter are acceptable**. Do not flush the IV line as it will create an IV bolus to be administered into the patient. For outpatient administration, use FDA approved pumps. Only the exact volume should be administered; any remaining overfill should be discarded appropriately.

6.3.7 Infusion Pump Requirements

Use a programmable pump that is approved by the appropriate regulatory authority for the country in which the subject is undergoing treatment. The pump alarm must be visual and auditory. The pump must be lockable. **Elastomeric pumps are NOT allowed.** CADD pumps are allowed; however, the cassettes used in CADD pumps are not compatible with blinatumomab and thus, **not** allowed.

Record all infusion interruptions. Technical or logistical interruption must be as minimal as possible and re-start the infusion as soon as possible. If an interruption is longer than four hours, the re-start of the infusion must take place in the hospital under supervision of the investigator. Monitor patients for potential adverse events as described in the protocol and the Investigator Brochure.

Monitor patients for cytokine release syndrome, tumor lysis syndrome, and infusion reaction. Refer to protocol for specific recommendation. Monitor patients for psychiatric events such as confusion, disorientation, and cognitive attention disturbances. Patients should not drive or operate dangerous machinery while receiving blinatumomab.

Risk of Serious Adverse Reactions in Pediatric Patients Due to Benzyl Alcohol Preservative: Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including BLINCYTO (with preservative). The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.

When prescribing BLINCYTO (with preservative) for pediatric patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO (with preservative) (contains 7.4 mg of benzyl alcohol per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known.

Due to the addition of bacteriostatic saline, 7-day infusion bags of Blinatumomab solution contain benzyl alcohol and are not recommended for use in any patients weighing less than 22 kg. Prepare Blinatumomab solution for infusion with preservative-free saline in 24-hour or 48-hour infusion bags for patients weighing less than 22 kg. Please refer to Appendix 2 for infusion instructions for patients weighing less than 22 kg.

6.3.8 Supplier

Blinatumomab and the solution stabilizer for blinatumomab is supplied by Amgen, Inc. and will be distributed by Amgen to Children's Hospital of Wisconsin and American Family Children's Hospital/University of Wisconsin. Do not use commercial supply.

6.3.9 Obtaining the Agent

6.3.9.1 Agent Ordering

Amgen supplied agent may be requested by the eligible participating investigator (or their authorized designee) at each participating institution (Children's Hospital of Wisconsin and American Family Children's Hospital/University of Wisconsin).

To request shipment for this order: gccs@amgen.com or Fax orders to (805) 376-9807
ATTN: Amgen GCSCM CDCs

Order:	**____ Initial ____ Resupply** **____ Rush (shipment within 72 hours of receipt)** **Provide Justification:**	
Study Title:		
Study Sponsor:		
Sponsor Study #:	**Amgen Reference #:**	
Product Description		
Blinatumomab (AMG 103)		
Quantity Requested		
Blinatumomab (AMG 103)	38.5 µg/vial; 15 vials per box	vials/ boxes
IV Solution Stabilizer for Blinatumomab (AMG 103)	10 mL vial; 6 vials per box	vials/ boxes
Site Comments		
Investigator:	**Date of Request:**	
Amgen Site#:	**Preferred Arrival Date:**	

Shipments are processed on Monday through Thursday 12:00 p.m. PST. ***Drug Shipment***

Requests received on Thursday after 12:00 p.m. PST will be shipped on the following Monday.

6.4 Supportive Care Guidelines

All supportive measures consistent with optimal patient care will be given throughout the study.

6.4.1 Venous Access

A central venous access device, preferably a double lumen, is strongly recommended for this study.

Anti-emetics will be used according to standard medical practice. Growth factor use is allowed on this study.

6.4.2 Antimicrobial Prophylaxis

Patients should be placed on standard of care prophylaxis during this time period at the discretion of the treating physician according to institutional guidelines for PCP, HSV, bacterial and fungus.

6.5 Follow-Up Period

All subjects, including those who discontinue protocol therapy early, will be followed for 30 days after the last dose of blinatumomab or until the start of the transplant preparative regimen (or other therapy), whichever occurs earlier.

Subjects removed from the study treatment for unacceptable SAEs will be followed until resolution or stabilization of the adverse event. SAEs will be followed until completion.

7.0 DOSING DELAYS/DOSE MODIFICATIONS

The most frequent serious adverse events noted in patients treated with blinatumomab to date are disorders of the nervous system, both peripheral and central, and systemic cytokine release syndrome (CRS). Both categories of events are more likely to occur within the first week of treatment with blinatumomab, and both categories of events are usually reversible and able to be managed with attentive supportive care.

AEs related to blinatumomab that require treatment interruption (according to table below) and do not resolve to CTCAE (Version 5.0) ≤ Grade 1 within 14 days will require permanent discontinuation of blinatumomab treatment. If the patient is eligible to continue protocol therapy (e.g. HCT), then the patient may, at the discretion of the investigator and family, continue to receive protocol therapy. Otherwise, the patient will be off protocol therapy.

In the case that the AE(s) **DO resolve within 14 days**, blinatumomab treatment may resume at a **reduced dose of 5 mcg/m^2/day** to complete the 28-day course (not counting the duration of treatment interruption).

NOTE: For Grade 4 Nervous System/Psychiatric, Grade 3 or 4 Central Nervous System: Seizure and Grade 4 thromboembolic AEs, blinatumomab must be permanently discontinued.

For patients who had experienced a ≥ Grade 2 Neurologic Systems and Psychiatric AE related to blinatumomab, **no dose escalation beyond 5 mcg/m^2/day will be permitted** for subsequent cycles. For patients who experienced other AEs related to blinatumomab, subsequent cycles will begin at the reduced dose of 5 mcg/m^2/day but **may escalate to 15 mcg/m^2/day** after 7 days if there are no significant blinatumomab-related AEs.

A **second AE** that requires interruption **will require permanent discontinuation** of treatment and the patient will be off protocol therapy.

The resumption of the infusion at the reduced dose should be accompanied by **dexamethasone premedication** as indicated in the relevant subsection of Section 4.0, should be performed in the hospital under supervision of the investigator and patients should be observed for at least 72 hours after the start of the next infusion before considering discharge to the outpatient setting.

Table 1: Dose Modifications for Adverse Events (AE) Occurring During Blinatumomab Administration

Category: AE (CTCAE v5.0)	AE Grade	Patients Greater Than or Equal to 45 kg	Patients Less Than 45 kg
Cytokine Release Syndrome (CRS)	3	Withhold blinatumomab until resolved, then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	Withhold blinatumomab until resolved, then restart blinatumomab at 5 ncg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur.
	4	Discontinue blinatumomab permanently	
Neurologic Toxicity	Seizure	Discontinue blinatumomab permanently if more than one seizure occurs.	
	3	Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.	Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur. If the toxicity occurred at 5 mcg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.
	4	Discontinue blinatumomab permanently	
Other Clinically Relevant Adverse Reactions	3	Withhold blinatumomab until no more than Grade 1 (mild), then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently.	Withhold blinatumomab until no more than Grade 1 (mild), then restart blinatumomab at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently.
	4	Considering discontinuing blinatumomab permanently	

Table Footnotes

1. Grading of cytokine release syndrome (CRS) severity should be performed according to that of

Lee et al (see below table). As many of the symptoms of CRS overlap with those of other medical complications such as infection, attribution should be carefully considered. Accurate application of this grading system requires clinical judgment to confirm that the symptoms are most likely due to CRS rather than to another medical condition. In all grades of CRS, aggressive supportive care is required. In Grade 2 or 3 CRS, careful monitoring of cardiac function is strongly suggested.

Grade 1	Symptoms are not life threatening and require symptomatic treatment only, e.g. fever, nausea, fatigue, headache
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement < 40%, or Hypotension responsive to fluids or low dose of one vasopressor, or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement >=40%, or Hypotension requiring high dose of one vasopressor or multiple vasopressors, or Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support, or Grade 4 organ toxicity (excluding transaminitis)

2. In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients. Among patients that experienced a neurologic event, the median time to the first event was within the first 2 weeks of BLINCYTO treatment and the majority of events resolved. The most common (≥ 10%) manifestations of neurological toxicity were headache, and tremor; the neurological toxicity profile varied by age group. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 13% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders. The majority of neurologic events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation. There is limited experience with BLINCYTO in patients with active ALL in the central nervous system (CNS) or a history of neurologic events. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical studies.

   Monitor patients receiving BLINCYTO for signs and symptoms of neurological toxicities. Advise outpatients on BLINCYTO to contact their healthcare professional if they develop signs or symptoms of neurological toxicities. Interrupt or discontinue BLINCYTO as recommended in Table 1 above.

   Of note, most AEs in the psychiatric disorder category are unlikely to be caused by blinatumomab and generally require supportive care rather than dose modification or discontinuation of blinatumomab (e.g., Insomnia, Depression, Anxiety). Psychiatric AEs that may reflect underlying central nervous system toxicity (e.g., Confusion, Delirium, Hallucinations, Psychosis) are of

greater interest, particularly if accompanied by other AEs in the nervous system disorders category" follow the recommendations from the USPI.

3. In the first days of treatment, transient DIC-like pictures may develop. Because patients are at risk for capillary leak syndrome and cytokine release syndrome, appropriate supportive care with dexamethasone (described above), blood products and factors (packed red cells, platelets, cryoprecipitate, fresh frozen plasma), vitamin K, and/or albumin should be considered according to institutional standards of care. Particularly in the first week of infusion, when the risk of capillary leak and cytokine release is more prominent, appropriate use of blood products and factors is preferred if laboratory indications suggest the need for replacement, as large volumes of crystalloid fluids tend to exacerbate the capillary leak.

4. In the first days of treatment, a rapid transient drop in platelets, neutrophils and/or hemoglobin may be observed. These effects are not necessarily cytokine-mediated. Counts typically recover to baseline during treatment, and usually within two weeks of starting blinatumomab. Transfusion of blood and platelets should be performed according to appropriate institutional standards.

5. In the first days of treatment, transient increases in transaminases up to over 1000 U/L may develop. These have generally returned to baseline in the 1st week of treatment.

6. Decrease in serum immunoglobulins have been observed in patients treated with blinatumomab. Intravenous immunoglobulin should be administered according to institutional standards but is recommended for any patient with a total IgG level below 400. Immunoglobulin must not be administered through the line through which blinatumomab is actively being infused.

   * Definitions of supportive care abbreviations:

   DEX: Dexamethasone should be administered at a total daily dose of at least 0.2 - 0.4 mg/kg/day (maximum 24 mg per day) administered preferably intravenous divided 3 - 4 times daily for at least 1 day but no more than 4 days. The dose should then be stopped or tapered as clinically indicated.

   SZ: Appropriate imaging should be performed to evaluate for possible hemorrhage or thrombosis, and other diagnostic procedures should be performed as clinically appropriate. Prophylactic anticonvulsant treatment with a therapeutic dose of institutional standard agents (e.g., lorazepam, phenytoin, levetiracetam) should be administered if seizures develop, and continued throughout the blinatumomab infusion. Anti-convulsant therapy should be considered starting at least 24 - 48 hours prior to any subsequent blinatumomab infusions and continuing for the remainder of those treatment cycles. Diagnostic measures to exclude potential infectious causes should be conducted once the patient has stabilized (i.e., a lumbar puncture to evaluate for bacterial, viral or fungal sources should be performed). Any identified pathology should be treated as clinically appropriate.

   CNS: A daily finger-nose-finger or writing sample test is recommended according to age-appropriate activities for patients. In adults treated with blinatumomab, it has been found that a daily handwriting sample can often predict future nervous system toxicity before the clinical toxicity develops. In case of a change in finger-nose-finger or handwriting test it is recommended to start dexamethasone on the schedule above to prevent possible deterioration of nervous system toxicity. Patients who experience nervous system toxicity in the first cycle typically do not experience it again in subsequent cycles, although it is possible.

7.1 Management of Cytokine Release Syndrome (CRS), Neurologic Toxicity and Acute Graft Versus Host Disease During or Following Blinatumomab

7.1.1 Cytokine Release Syndrome (CRS)

Treatment of CRS will be based on CTCAE (version 5.0) grading.

Close monitoring of fluid status by intake and output should be undertaken for the first week of blinatumomab infusion. Efforts to keep patients balanced between intake and output should be maintained, even if diuretic therapy (furosemide or similar) is needed to do this. Careful attention to fluid status may prevent deterioration from capillary leak, however even with meticulous attention some patients will experience pulmonary edema and require more aggressive respiratory support. Treating physicians should use their clinical judgment and institutional standards for whatever supportive care measures are needed during this period of time.

See Table 1 for indications to stop infusion of blinatumomab based on toxicity and CTCAE Grade.

Grade 1: Infectious work-up, initiation/escalation of antibiotics per institutional standards. IV fluids, anti-pyretic therapy as indicated with cooling blankets and acetaminophen (avoid NSAIDs). Supportive care measures.

Grade 2: Admission to hospital (if not admitted). IV fluids, infectious work-up, supportive care measures.

Grade ≥ 3: Admission to Intensive Care Unit. Tocilizumab (8 mg/kg IV x 1; max dose 800 mg). Give a 2nd dose of tocilizumab if no response within 12-24 hours. Can give up to 2 doses of tocilizumab in 24 hours. For persistent symptoms, give solumedrol (1-2 mg/kg/day).

7.1.2 Neurologic Toxicity

Treatment of neurologic toxicity will be based on CTCAE (version 5.0) grading.

See Table 1 for indications to stop infusion of blinatumomab based on toxicity and CTCAE Grade.

Grade 1: Clinical vigilance, monitoring, supportive care

Grade 2: Admission to hospital (if not admitted), neuro-checks Q4 hours, supportive care. Dexamethasone (10 mg IV/PO every 6-12 hours; max dose 10 mg Q6 hours) can be started at discretion of provider.

Grade ≥ 3: Admission to Intensive Care Unit. Dexamethasone 10 mg IV/PO every 6-12 hours (max dose 10 mg Q6 hours). If not improving, consider tocilizumab (8 mg/kg IV x 1; max dose 800 mg). Can give up to 2 doses of tocilizumab in 24 hours.

7.1.3 Acute Graft Versus Host Disease (aGVHD)

Treatment of aGVHD that may flare/recur in patients includes both general supportive care of the patient and specific therapy directed at suppressing the immune process resulting in aGVHD. Specific therapy of aGVHD is based on the overall clinical grade of involvement. The grading of aGVHD is part of routine clinical care for patients receiving allogeneic blood or marrow transplants.

1) Patients with Grade 1 aGVHD in the setting of matched unrelated, mismatched unrelated or mismatched related donors may receive treatment of Grade 1 aGVHD at the discretion of the attending physician.
2) First line therapy for Grade ≥ 2 aGVHD:
   (a) Oral prednisone 1-2.5 mg/kg/day (or equivalent methylprednisolone at the discretion of the physician).
   (b) Topical steroids to affected areas of skin. Continue creams until one week after resolution of skin rash.
   (c) Use other immunosuppressive medications as clinically warranted. The introduction of other second line therapies will depend on clinical severity of steroid refractory aGVHD and donor type.

8.0 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Definitions

8.1.1 Adverse Event (AE): Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or condition temporally associated with the use of any study procedure or treatment, regardless of whether it is considered related to the study procedure or treatment. Any worsening of a pre-existing condition or illness will be considered an adverse event. The investigator will evaluate all adverse experiences as to their severity and relationship to the vaccine as well as the regimen as a whole.

8.1.2 Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE (Version 5.0) does not define an AE as necessarily "*caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related to investigational agent/intervention	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

8.1.2.1 Relationship Assessment: In-Depth Definitions

For all collected AEs, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

- **Possibly Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

- **Unrelated:** The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.1.3 Expectedness: An AE is considered unexpected if the specificity or severity of the AE is not consistent with the protocol drug toxicity tables found in Section 8.0, or with available product information, or with the general investigational plan, or is unexpected in the professional opinion of the treating investigator.

8.1.4 Expedited Reporting: SAE reporting to the coordinating site within **five (5) calendar days** of learning of the event

8.1.5 Onset and Resolution of Adverse Events: If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

- If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.
- The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.
- The resolution date of the AE is defined as the date at which the AE returns to baseline

or less than Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

- An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

8.1.6 Protocol Therapy: Any of the study interventions (drugs) administered as part of this study.

8.1.7 Serious Adverse Event (SAE): An adverse event that results in any of the following outcomes:

Death of Patient: An event that results in the death of a patient.

Life-Threatening: An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

Hospitalization: An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility. Additionally, any hospitalization for the purpose of treatment as per the protocol or any standard of care treatment will not be considered an SAE.

Prolongation of Hospitalization: An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.

Congenital Anomaly: An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity: An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome: An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.1.8 Routine Reporting: AE reporting to the coordinating site at the time of the regularly scheduled time points listed in the Case Report Forms (CRFs).

8.2 AE and SAE Reporting on Protocol

8.2.1 Adverse Event Grading

Grade	Description
0	No AE (or within normal limits).
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention (e.g., packing cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE

8.3 Known AEs List

Known Risks and Side Effects Related to Blinatumomab Include Those Which Are:		
Very Common (In 100 people receiving blinatumomab, more than 10 and up to 100 people may have)	**Common** (In 100 people receiving blinatumomab, between 1 and 10 people may have)	**Uncommon** (In 1000 people receiving blinatumomab, between 1 and 10 people may have)
• Anemia (decreased red blood cells) which may require blood transfusion • Thrombocytopenia (decreased platelets, for clotting blood) • Leukopenia (decreased white blood cells) • Pyrexia (fever) • Infusion related reactions • Weight increased • Hypertension (high blood pressure) • Neutropenia (decreased neutrophils with fever • Increased hepatic enzymes (in the blood, which may be due to inflammation or damage to liver cells) • Tachycardia (rapid heart rate) • Edema (swelling of hands, legs, ankles, feet, face, or trunk) • Back pain	• Leukopenia, Lymphopenia (decreased types of white blood cells) • Leukocytosis (increased white blood cells) • Lymphadenopathy (swelling in lymph nodes) • Hyperbilirubinemia (high levels of bilirubin in the blood) • Decreased immunoglobulins (in the blood, proteins made by the body's immune system to fight against infections and foreign substances) • Increased alkaline phosphatase (in the blood can be due problems in your liver or in your bones) • Chills • Chest pain • Pain in the arms, legs and hands • Overdose, Accidental overdose • Weight increased • Hypertension (high blood pressure) • Flushing	• Speech disorder • Cytokine storm, is a severe form of cytokine release syndrome which is described under the "Very Common" column. • Pancreatitis, inflammation of the pancreas that can be life-threatening or may even lead to death. Symptoms can include severe and persistent stomach pain, with or without nausea and vomiting. • Leukoencephalopathy, a rare, serious disorder of the white matter in the brain that can lead to severe disability and death and for which there is no known prevention,

Known Risks and Side Effects Related to Blinatumomab Include Those Which Are:		
Very Common (In 100 people receiving blinatumomab, more than 10 and up to 100 people may have)	**Common** (In 100 people receiving blinatumomab, between 1 and 10 people may have)	**Uncommon** (In 1000 people receiving blinatumomab, between 1 and 10 people may have)
• Bone pain • Headache • Insomnia (difficulty falling and/or staying asleep) • Cough • Rash • Hypotension (low blood pressure) • Infections in the blood including bacteria, fungi, viruses or infections in other organs. Serious infections can happen during and after treatment and can lead to death. Serious infections such as sepsis (infection in the bloodstream), and pneumonia (severe lung infection) have been reported in patients treated with blinatumomab. Your doctor may give you antibiotics to treat the infection or stop your treatment with blinatumomab • Infusion related reactions occur during or after the drug is given through the vein. Symptoms of infusion reaction may include headache, rash, itching, flushing, swelling, shortness of breath, nausea and sometimes vomiting. Severe infusion reactions can cause dizziness, severe skin reactions,	• Dyspnea (difficulty breathing, wheezing or respiratory failure) • Hypersensitivity, allergic reactions to blinatumomab, including hypersensitivity, have been reported. Signs and symptoms of allergic reactions can be very similar to infusion reaction. If you have symptoms of an allergic reaction, you should contact the study doctor or his/her study staff immediately. • Hematophagocytic histiocytosis can occur with cytokine release syndrome, described under the "Very Common" column. It is a life- threatening overactivity of your immune system caused by releasing large amounts of inflammatory cytokines. Your doctor may give you medications such as steroids and/or other medications to prevent or treat cytokine release syndrome. • Tumor lysis syndrome (a group of complications from release of large amounts of potassium, phosphate, and nucleic acid caused by the breakdown of tumor cells after cancer treatment). Tumor lysis syndrome may cause kidney failure, abnormal heart rhythm, and can even lead to death. Patients with moderate kidney failure showed an increased rate of tumor lysis syndrome compared with patients with mild kidney failure or normal kidney function. However, this did not lead to permanent discontinuation of treatment with blinatumomab. Your doctor may give you medicines before your	treatment, or cure. Symptoms can include difficulty thinking, loss of balance, changes in speech or walking, weakness on one side of your body, or blurred or lost vision. • Capillary leak syndrome (leakage of fluid from small blood vessels into other body spaces that could cause swelling of the trunk, arms and legs)

Known Risks and Side Effects Related to Blinatumomab Include Those Which Are:		
Very Common (In 100 people receiving blinatumomab, more than 10 and up to 100 people may have)	**Common** (In 100 people receiving blinatumomab, between 1 and 10 people may have)	**Uncommon** (In 1000 people receiving blinatumomab, between 1 and 10 people may have)
difficulty breathing or swallowing, a decrease in blood pressure, and could be life threatening. Signs and symptoms of infusion reaction can be very similar to cytokine release syndrome. • Cytokine release syndrome is when your body releases substances called cytokines during the blinatumomab infusion. This can cause fever, chills, headache, decreased blood pressure, increased liver enzymes, nausea, and vomiting. Cytokine release syndrome symptoms generally are mild to moderate but occasionally can be serious or life-threatening or may even lead to death. Your doctor may give you medications such as steroids and/or other medications to prevent or treat cytokine release syndrome.	treatment to help prevent tumor lysis syndrome. • Nervous system problems such as tremor (shaking), dizziness, seizures, somnolence (changes in alertness), paresthesia (abnormal skin sensation such as burning, prickling, tingling), hypoaesthesia (numbness), aphasia (difficulty speaking or slurred speech), cognitive disorder (difficulty understanding words), encephalopathy (loss of consciousness, brain malfunction), memory impairment (memory loss), confusion and/or disorientation, or loss of balance. These nervous system problems can be serious, or life-threatening or may even lead to death. Patients with a medical history of neurologic signs and symptoms had a higher rate of neurologic events (such as tremor, dizziness, confusion, encephalopathy and poor coordination). Your doctor will be closely monitoring you and may give you medications such as steroids and/or other medications to treat nervous system problems or stop your treatment with blinatumomab.	

8.4 What & When to Report: Adverse events and Serious Adverse Events that meet the below criteria are to be collected. Use the CTCAE (Version 5.0) to code and grade AEs. These AEs are to be documented from the time the patient initiates protocol therapy until the patient meets off study criteria. The time frame for reporting of AEs depends on the grade, expectedness, attribution, and date of event in relation to the date of the patient's first and last protocol treatment dose. **Grade 1 and 2 AEs do not need to be reported.**

Reporting Requirements for AEs that occur between **Blinatumomab Day 1 until ≤ 30 Days post last dose of Blinatumomab OR until patient starts a new, non-protocol therapy** (whichever occurs first):

	Grade 3		Grade 4	Grade 5
	Unexpected	**Expected**	**Unexpected or Expected**	**Unexpected or Expected**
Unrelated, Unlikely	Routine	No report (Exception: Routine Report Grade 3 infection)	Expedited (Exception Grade 4 hematological AEs to be routine reported)	Expedited
Possible, Probable, Definite	Routine	No report (Exception: Routine Report Grade 3 infection)	Expedited (Exception Grade 4 hematological AEs to be routine reported)	Expedited

Reporting Requirements for AEs that occur between **> 30 Days post last dose of Blinatumomab OR occur after the start of a new, non-protocol therapy (whichever occurs first) until patient meets Off Study criteria:**

	Grade 3		Grade 4	Grade 5
	Unexpected	**Expected**	**Unexpected or Expected**	**Unexpected or Expected**
Unrelated, Unlikely	Routine	No report (Exception: Routine Report Grade 3 infection)	Routine*	Routine*
Possible, Probable, Definite	Routine	No report (Exception: Routine Report Grade 3 infection)	Expedited (Exception Grade 4 hematological AEs to be routine reported)	Expedited

* Grade 4 and Grade 5 events that occur > 30 days post last dose of protocol therapy (or after the start of a new non-protocol therapy) and are considered unrelated or unlikely related to protocol therapy only require ROUTINE reporting (i.e. patient has recovered from protocol therapy).

How to Report:

- **Routine Reporting** – Complete the AE CRF and submit according to the schedule in the CRF instructions to crconc@mcw.edu.
- **Expedited Reporting** – Complete the SAE CRF and email **within 5 calendar days** to crconc@mcw.edu.

Coordinating Site's Responsibilities:

- **Routine Reporting** – To collect all data from participating sites and to submit data into

OnCore for DSMC review at regular intervals.

- **Expedited Reporting** – To collect all data from participating sites, follow-up with participating sites for additional information as needed, and to submit data into OnCore for DSMC review within 5 calendar days. The coordinating site will submit reports to the CHW IRB according to policy. All participating sites should submit any events to the local IRB per local policy.

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

The investigator and his or her team will follow the CHW IRB policies related to unanticipated problems involving risks to subjects or others.

8.6 Time Period and Grade of AE Capture

The period of AE capture will include from the beginning of any study procedures through 30 days following the end of the study treatment OR occur after the start of a new, non-protocol therapy (whichever occurs first) until patient meets Off Study criteria.

The criteria for grading toxicities and criteria for dose modifications will be according to CTCAE (Version 5.0).

8.7 Monitoring and Recording an Adverse Event

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

8.7.2 Prior to the Trial: Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).

8.7.3 Pretreatment Events Following Signed Informed Consent: For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

8.7.4 Treatment Events: For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

8.7.5 Not Serious AEs: For non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

8.8 Follow-Up of Adverse Events

All adverse events will be followed with appropriate medical management 30 days following the last dose of the study drug or treatment or until they are resolved, if they are related to the study treatment.

8.9 Subject Complaints

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

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can contact the Children's Hospital of Wisconsin Institutional Review Board (CHW IRB), whose purpose is to see that the rights and welfare of research participants are adequately protected, and that risks are balanced by potential benefits. A member of this committee is available to speak to you if you have any questions or complaints at 414-337-7133 This information is provided to the subject in their consent.

A product complaint is a verbal, written or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the sponsor and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a sponsor representative. Product complaints in and of themselves are not Reportable Events. If a product complaint results in an SAE, an SAE form should be completed.

8.10 Routine Reporting Procedures for AEs

Reporting to CHW Institutional Review Board

The principal investigator must report events to the CHW IRB within five business days of his/her awareness of the event.

Reporting to Amgen

All Suspected Unexpected Serious Adverse Reactions (SUSARs) are to be reported to Amgen within 24 hours of reporting to a regulatory authority. A line-listing of SAEs needs to be provided to Amgen safety every 6 months.

Please see the table below which outlines reporting information.

Event Type	Report Recipients				
	PI/Study Chair/ Coordinating Center	Institutional Review Board	DSMC	CTO Regulatory Office	Other
Serious Adverse Event	ASAP	5 days (or annual CPR)	5 days	ASAP	
Unanticipated Problems Involving Risks to Subjects of Others	ASAP	5 days (or annual CPR)	5 days	ASAP	
Evidence of Causal Relationship between Drug and AE	ASAP	5 days (or annual CPR)	5 days	ASAP	

Event Type	Report Recipients				
	PI/Study Chair/ Coordinating Center	Institutional Review Board	DSMC	CTO Regulatory Office	Other
Dose-Limiting Toxicity	ASAP	5 days (or annual CPR)	5 days	ASAP	

CPR, continuing progress report

9.0 REPORTING AND DOCUMENTING RESULTS (MEASUREMENT OF EFFECT)

Adverse Event information and reporting is in Section 8.

9.1 Evaluation of Efficacy (or Activity)

9.1.1 Definitions

Evaluable for Toxicity: All patients will be evaluable for toxicity from the time of their first exposure to Blinatumomab.

Evaluable for Objective Response: Only those subjects who have measurable disease present at baseline, have received at least one therapy cycle and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

9.2 Bone Marrow Response Criteria

Complete Remission, MRD Negative (CR MRD)

- A bone marrow with < 5% blasts by morphology (hematologic complete remission); **AND**
- MRD < 0.01% by flow; **AND**
- No evidence of circulating blasts or extramedullary disease; **AND**
- Recovery of peripheral counts (ANC > 500/µL and PLT count > 50,000 µL).
- Qualifying marrow and peripheral counts should be performed within 1 week of each other

Complete Remission (CR)

- A bone marrow with < 5% blasts by morphology (hematologic complete remission); **AND**
- No evidence of circulating blasts or extramedullary disease; **AND**
- Recovery of peripheral counts (ANC > 500/µL and PLT count > 50,000 µL).
- Qualifying marrow and peripheral counts should be performed within 1 week of each other.

Complete Response with Incomplete Count Recovery (CRi)

- A bone marrow with < 5% blasts by morphology (hematologic complete remission); **AND**
- No evidence of circulating blasts or extramedullary disease; **AND**
- Insufficient recovery of absolute neutrophil counts (ANC < 500/µL), and or insufficient recovery of platelets (PLT counts < 50,000/ul),

Partial Remission (PR)

- Complete disappearance of circulating blasts and one of the following:
- A decrease of at least 50% of blasts in the bone marrow with > 5% and ≤ 20% blasts by morphology with recovery of peripheral counts (ANC > 500/µL and PLT count > 50,000 µL)

Note: only patients who entered the study with ≥ 20% blasts in the marrow may be assessed as PR

Stable Disease (SD)

Patient does not satisfy the criterion for either CR, CRi, PR or disease progression.

Progressive Disease (PD)

An increase of at least 25% in the absolute number of bone marrow or circulating leukemic cells, development of new sites of extramedullary disease, or other laboratory or clinical evidence of progression of disease.

Not Evaluable (NE)

Aplastic or severely hypoplastic marrow without any blast percentage. Bone marrow aplasia/hypoplasia is defined as overall marrow cellularity less than 10-20%. In this instance, marrow evaluation should be repeated every 1-2 weeks until response determination can be made.

Relapse

After documentation of remission, one bone marrow aspirate and/or biopsy showing ≥ 5% leukemic blasts or pathological evidence of extramedullary disease.

9.3 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE (Version 5.0) for reporting of nonhematologic adverse events and modified criteria for hematologic adverse events. See Section 8.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Endpoints/Efficacy Variables

10.1.1 Primary Efficacy Variables

The primary efficacy variable is the percent of subjects that remain in Complete Remission (CR) and become Flow Cytometry-MRD negative (FC-MRD negative) < 0.01% (Flow Cytometry performed at the University of Washington, Brent Wood, MD or local lab if applicable) after completion of 1 or 2 cycles of blinatumomab.

10.1.2 Secondary Efficacy Variables

- The percent of subjects that remain in CR, achieve MRD negative by Flow Cytometry (< 0.01%) and by molecular High-Throughput Deep Sequencing (HTS-MRD negative) (MRD undetectable) (Adaptive Technologies, Seattle, WA) after completion of 1 to 2 cycles of Blinatumomab.

10.2 Study Design

This is an open label non-blinded Phase 2 study of up to 35 children, adolescent and young adults with B-ALL and MRD ≥ 0.01%. The study will continue until there are at least 25 evaluable subjects who are FC-MRD negative (< 0.01%) or 35 subjects are recruited.

10.3 Determination of Sample Size and Accrual Rate

10.3.1 Sample Size and Power Estimate

Blinatumomab has been evaluated in children with relapsed/refractory B-ALL. Among the 70 pediatric patients who received the recommended dosage, 27 (39%; 95% CI, 27% to 51%) achieved complete remission (CR) within the first two cycles, 14 (52% of 70 or 20% overall) of whom achieved complete MRD negative response. If we were to receive this response our 95% CI would be 9.8%, with 35 patients. In our patients who will be in a complete remission (< 5% blasts) at the time of receiving blinatumomab, we expect a higher response rate than what was reported in the pediatric trial for relapse/refractory patients. For 35 subjects, with the widest margin for a one-sided CI of 0.15 when the proportion is 0.5 we will have a reasonable estimate.

It is expected that the study will complete recruitment in 30 to 36 months. If there is an 80% rate of MRD negative (< 0.01%) subjects, a total of 25 evaluable subjects will be recruited. The 95% confidence interval will be (0.59,0.93) for 25 patients. If we must recruit 35 total subjects, we would expect that the proportion will be no less than 0.67 with a 95% CI of (0.47,0.83).

We expect ~40% (10 patients) will be HTS-MRD negative (undetectable MRD). With 25 evaluable subjects recruited the 95% CI would be (0.21,0.61).

10.3.2 Accrual Estimates

We expect to have 8-10 eligible subjects per year with about 6 to 8 consenting per year. Thus, the time to accrual will be 30 to 36 months.

10.4 Interim Analyses, Missing Data and Stopping Rules

A planned interim analysis will be performed upon enrolling 12 evaluable subjects. Using a Fleming 2-stage design with a target accrual goal of 25 subjects, our null hypothesis is that the response rate is less than or equal to 0.400 versus the alternative that it is greater. Success for this study will be a response rate of at least 67% MRD negativity (< 0.01%). At the first stage we have 12 evaluable subjects and the cumulative number of successes, R, will be compared to the acceptance value and rejection value numbers for that stage. If $R \leq 4$, the study committee will reevaluate the study and determine if changes to the protocol design are necessary. If $R \geq 10$, then there is a very high chance of success. Similarly, after 25 evaluable subjects are recruited, if $R < 15$ we would not have met our 60% threshold. The type I error rate would be 0.0333. The power, calculated at a response rate of 0.670, is 0.8071. The calculation is done using PASS 15.

Missing Data: The dropout pattern will be plotted and summarized. Subjects who dropout before the first cycle of blinatumomab is completed will not have an MRD assessment. Subjects that are not MRD negative (≥ 0.01%) at the end of the first cycle, proceed to a second cycle of blinatumomab, but dropout before the second cycle is completed will not have a final MRD assessment. Our primary outcome is the number of subjects who can achieve FC-MRD negativity (< 0.01%) after one or two cycles of blinatumomab. Hence the primary assessment is the proportion of subjects achieving FC-MRD negativity and completing these treatments.

However, secondary outcomes will include:

- The proportion of subjects achieving FC-MRD negativity (< 0.01%) after completing the first cycle of blinatumomab.
- The proportion of subjects achieving HTS-MRD negativity (MRD undetectable) after completing the first cycle of blinatumomab.
- The proportion of subjects achieving FC-MRD negativity (< 0.01%) out of all subjects recruited.
- The proportion of subjects achieving HTS-MRD negativity (MRD undetectable) out of all subjects recruited.

Patients who drop out or are removed from the study due to an adverse symptom profile will be reported as a safety outcome. Characteristics of these will be summarized. The occurrence of toxic death (TD) at any time during protocol therapy will be a primary endpoint for safety monitoring and a stopping rule. A population toxic death rate that exceeds p0=0.10 will be considered unacceptable. Operationally, this criterion will be satisfied if the following fractions of TDs out of total patients treated are exceeded: ≥ 1/5, ≥ 2/12, ≥ 3/20, ≥ 4/28, and so on as dictated by this rule. If this criterion is satisfied at any time the cause and circumstances of these deaths will be reviewed with the study committee and with the Data and Safety Monitoring Committee to determine whether modifications to or termination of the study is warranted.

10.5 Analyses Plans

The primary objective is to determine the efficacy of giving blinatumomab immediately prior to HCT as "bridging therapy" to eliminate MRD (as measured by flow cytometry) in children, adolescents and young adults with relapse, refractory or persistent MRD B-ALL.

10.6 Analysis Population

This will include all subjects who have completed at least one course of blinatumomab and for whom there is an assessment of MRD. **This will be the primary efficacy analysis group since we will assess the ability to proceed for HCT.**

All Enrolled Cases: This will include all subjects enrolled. If any dropout or die they will be included in the MRD positive group. This is a less enriched group and will be mainly used for assessment of feasibility of the treatment.

Per Protocol Cases: The per-protocol population will be defined as the subset of the observed cases (OC) who completed all treatments and who did not have any major protocol violations (such as lack of compliance to the study medication schedule). The definitions of these protocol violations will be finalized before the database closure and will be documented in the analysis plan. The analysis of this group will be exploratory.

10.7 Primary Analysis (or Analysis of Primary Endpoints)

10.7.1 Endpoints to be Collected

- FC-MRD: minimal residual disease measured by flow cytometry at the end of each cycle of blinatumomab.
- HTS-MRD: minimal residual disease measured by high throughput sequencing at the end of each cycle of blinatumomab.
- Severe Adverse Events: Grade 3 and 4 adverse events attributed to blinatumomab.
- Toxic death rate: deaths attributed to blinatumomab treatment prior to HCT.

10.7.2 Primary Endpoint

The proportion of subjects who are FC-MRD negative (< 0.01%) will be summarized with 95% CI.

10.7.3 Secondary Analysis (or Analysis of Secondary Endpoints)

10.7.3.1 Secondary Endpoints

- The proportion who are HTS-MRD negative (MRD undetectable) will be summarized with 95% CI.

10.7.4 Other Analyses/Assessments

We will summarize by and compare the subgroups of those who are MRD negative by Flow Cytometry AND HTS will be compared to those subjects who are MRD negative by only Flow Cytometry (HTS MRD positive) by demographics and by # of cycles (incomplete, 1 or 2). For comparison of continuous data, we will use a t-test or non-parametric Mann Whitney test, if needed due to distribution. For categorical data we will use a Fisher exact test.

10.7.5 Evaluation of Safety

Safety population: The safety population will consist of all subjects who have received any amount of blinatumomab, whether withdrawn prematurely or not.

All information on AEs and SAEs will be listed by patient and will be summarized. The SAE report will include event term(s), serious criteria, and the sponsor-investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE (Version 5.0) as a guideline whenever possible.

Frequencies will be presented for the categorical variables (e.g., race) and descriptive statistics will be presented for continuous variables (e.g., weight, age).

10.7.6 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 8.4 for reporting instructions). Adverse events of special interest for this study are as follows: Cytokine Release Syndrome (CRS) and Neurological Adverse Events.

11.0 DATA AND SAFETY MONITORING PLAN (DSMP)

Please refer to the MCWCC DSMC Charter.

11.1 Data and Safety Management Overview

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

11.1.1 Study Team

The study team minimally consists of the principal investigator, the clinical research coordinator, regulatory specialist, and the study biostatistician. While subjects are on treatment, the principal investigator will meet regularly with the research coordinator and the study biostatistician to review study status (attendees and time periods should be modified so as to make sense within the context of the study). This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for a next subject enrollment is addressed. SAE and any AEs requiring assigning of attribution are discussed and recorded via email or by physician signature on applicable documentation.

The CHW CTO DVL, Leukemia/Lymphoma, and HCT groups meet weekly to discuss upcoming protocols, SAEs, existing patients, and new patients. Individual SAEs are discussed with the attending provider as needed.

11.1.2 Quality Assurance

This protocol will be reviewed internally every six months by MCW CTSI staff. Approximately 30% of subject files will be selected randomly for review (max 5 subjects at each monitoring timepoint). Consent, eligibility and objective based data will be reviewed for those files selected. One file will be selected randomly for a comprehensive review at each quality assurance review timepoint. Regulatory will also be reviewed each time.

11.1.3 Clinical Trials Office

The MCWCC CTO provides administrative assistance and support to the DSMC.

11.1.4 DSMC

The Pediatric CTO places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at CHW includes a plan for safety and data monitoring.

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

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

- Review the clinical trial for data integrity and safety
- Review all unexpected Grade 3, and all Grade 4, and 5 adverse events (with the exception of Grade 4 hematological AEs, which can be routine reported), as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.)
- Review all DSM reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

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

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

11.2 Monitoring

The PI at each participating center is responsible for monitoring this study for accuracy of data and protocol compliance at their institution. Patient eligibility will be confirmed by Dr. Michael Burke before each patient is enrolled.

The PI, data coordinators, and research nurses are responsible for review and maintenance of all patient records at their individual institution to ensure data integrity and protocol adherence.
The site PI will permit study-related monitoring, audits, and inspections by the MCW

compliance groups, as necessary. The investigator will make available all study related documents (i.e. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (i.e. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

12.0 REGULATORY COMPLIANCE, ETHICS AND STUDY MANAGEMENT

12.1 Ethical Standard

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

12.2 Regulatory Compliance

This study will be conducted in compliance with:

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

12.3 Pre-Study Documentation

Prior to implementing this protocol at the Pediatric CTO, the protocol, informed consent form, HIPAA authorization, and any other information pertaining to participants must be approved by the CHW IRB.

The clinical investigation will not begin until the following conditions have been met, as applicable:

- The FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed
  OR
- The Investigator has received a letter from FDA stating that the study is exempt from IND requirements
  OR
- The study meets all of the following IND Exempt requirements (as applicable):
  - The drug product is lawfully marketed in the United States
  - The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug
  - In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug
  - The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the

risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii))
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50)
- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

12.4 Institutional Review Board

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the CHW IRB.

Prior to obtaining CHW approval, the protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

12.5 Informed Consent Process

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

Consent forms will be IRB-approved and the subject (and Legally Authorized Representative, if necessary) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

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

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

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Subjects that require re-consenting will be defined in the IRB approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be re-consented for continuing reviews. The Pediatric CTO will follow the

CHW IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

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

12.6 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality must be contained at all material submitted to the key sponsor contact. The following rules are to be applied:

- Subjects will be identified by a unique identification number
- Date of birth or year of birth/age at time of enrollment will be reported according with local laws and regulations

For reporting of serious adverse events, subjects will be identified by their respective subject identification number, initials and data of birth (as per their local reporting requirements for both initials and date of birth).

Per federal regulations and ICH/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, CRO, IRB/IEC and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records which includes personal information.

12.7 Protection of Human Subjects

12.7.1 Protection from Unnecessary Harm

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

12.7.2 Protection of Privacy

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

12.8 Changes in the Protocol

Once the protocol has been approved by the CHW IRB, any changes to the protocol must be

documented in the form of an amendment. The amendment must be signed by the investigator and approved by IRB prior to implementation.

If the protocol is amended, the investigators agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact.

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

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

Both CHW and the investigator reserve the right to terminate the investigators participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination and provide CHW with a copy of the correspondence.

12.9 Investigator Compliance

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

Onsite Audits/Monitoring

Auditing is essential to ensure that research conducted at the Pediatric CTO is of the highest quality and meets regulatory agency standards.

Regulatory authorities, the IRB, and/or sponsor may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

The key sponsor contact, monitors, auditors or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records assuring that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.4.

By signing the investigator agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH GCP and the audit plan, a site may be chosen for a site audit. A site audit

would include, but is not limited to, an inspection of the facility (ies), review of subject and study related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English and concomitant medications should be identified by trade names. For further details surrounding the completion of CRFs, please refer to the CRF completion guidelines.

13.0 DATA HANDLING AND RECORD KEEPING

13.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

13.2 Data Management Responsibilities

13.2.1 Principal Investigator

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

13.2.2 Research Coordinator

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

13.2.3 Research Nurse/Medical Staff

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

13.2.4 Biostatistician

The biostatistician may assist in CRF development (content and design), dataset specifications

(annotation of CRFs and record layout) and validation.

13.3 Source Documents

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities should be outlined and included in the Delegation of Authority Form.

Source documents are original documents, data and records for which the study data are collected and verified. Example of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence and death registries. Case report form entries may be considered as source data if the site of the original data collection is not available. However, use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralize filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, regulatory authorities and IRB/IECs. The filing system will include at minimum:

- Subject content including assents/consents and subject identification lists
- Protocols and protocol amendments, investigator brochure, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records and experimental product related correspondence.

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between CHW and the investigator. Should storage no longer be available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

All source documents will be written following ALCOA standards as follows:

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

ALCOA Attribute	Definition
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

13.4 Case Report Forms

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

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

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

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

13.5 Study Record Retention

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

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

Study documentation includes all CRFs, data correction forms or queries, source documents, sponsor-investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).
Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.
In accordance with FDA regulations, the investigator shall retain records for a period of two years following the date a marketing application is approved for the drug for the indication for which it

is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

The investigator will retain study records including source data, copies of case report forms, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for 10 years after the study file is closed with the IRB.

In addition, the Pediatric CTO will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient. Please contact the CTO before destroying any study related records.

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APPENDIX 1
Performance Status Criteria

Karnofsky Performance Scale For Patients 16 Years of Age and Older	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead

Lansky Performance Scale For Patients Less Than 16 Years of Age	
Lansky Score	**Play Score**
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

APPENDIX 2
Preparation of Blinatumomab

Only trained staff may prepare the blinatumomab IV solution. Blinatumomab must be prepared in an ISO Class 5 containment device, ideally in an ISO Class 7 room as described in USP <797>, but ISO Class 7 is not required. Use aseptic technique and prepare blinatumomab IV solution under a qualified biological safety cabinet.

The label on the IV bag must include the following:

- Patient name and number
- Name of the drug
- Dose (mcg/day and volume/day)
- Infusion rate
- Expiration date and time
- CAUTION: NEW DRUG – Limited by United States law to investigational use.
- Bag number
- Additional information as required by state, local, and country pharmacy regulations.

Blinatumomab must be dispensed in an acceptable IV bag. Acceptable bags include those made of polyolefin/polyethylene, ethylene vinyl acetate (EVA), or PVC non-DEHP.

The final IV solution **must** be prepared in the following sequential order (do not deviate from this order; refer to the table below for volume details):

1. Reconstitute Blinatumomab Lyophilized Powder

Blinatumomab 38.5 mcg/vial
Add 3 mL of Sterile Water for Injection (SWFI) to the vial to yield 3.08 mL of Blinatumomab at a final concentration of **12.5 mcg/mL.**

a. Rotate the vial to dissolve all powder. Do not shake.
b. The stability of the reconstituted vial is 4 hours at room temperature (22°C to 27°C) or 24 hours refrigerated at 2° to 8°C.

2. Add the appropriate amount of 0.9% NaCl into the IV bag

3. Add the IV solution stabilizer for blinatumomab to the IV bag

a. Gently mix the contents of the bag to avoid foaming. Do not shake.
b. Discard remaining IV solution stabilizer vial.

4. Add the calculated dose (mL) of blinatumomab into the solution in the IV bag

a. Rotate the IV bag to mix the solution thoroughly. Do not shake. Avoid foaming the IV bag.
b. Visually inspect for floating particles or discoloration of the IV solution. If floaters or discoloration is present, do not use the prepared solution.
c. The total volume of blinatumomab IV solution will account for the volume of the IV infusion set for the inpatient or outpatient setting.

Patients Weighing Under 22 kg

Due to the addition of bacteriostatic saline, 7-day infusion bags of Blinatumomab solution contain benzyl alcohol and are not recommended for use in any patients weighing less than 22 kg.

Prepare Blinatumomab solution for infusion with preservative-free saline in 24-hour or 48-hour infusion bags for patients weighing less than 22 kg.

Please Refer to the Current USPI for Preparation of the Infusion Bags and Volume Calculations

Blinatumomab can be infused over 24 hours (preservative-free), 48 hours (preservative-free), or 7 days (with preservative). The choice between these options for the infusion duration should be made by the treating healthcare provider considering the frequency of the infusion bag changes and the weight of the patient. The administration of Blinatumomab as a 7-day infusion is not recommended for patients weighing less than 22 kg.

Call 1-800-77-AMGEN (1-800-772-6436) if you have questions about the reconstitution and preparation of Blinatumomab.

Blinatumomab Prescribing Information can be found here:
https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/blincyto/blincyto_pi_hcp_english.pdf