NCI Protocol #: N/A

DF/HCC Protocol #: 16-118.

TITLE: A phase II study of blinatumomab for the treatment of relapsed or refractory indolent non-Hodgkin lymphoma

Coordinating Center: Massachusetts General Hospital Cancer Center

***Principal Investigator (PI):** Jeffrey Barnes M.D., Ph.D.
Center for Lymphoma, MGH Cancer Center
55 Fruit St., Boston, MA 02114
Telephone –617-643-9668
Fax –617-726-8330
jabarnes@partners.org

Statistician:

Robert Redd
Dana-Farber cancer Institute
Robert_Redd@dfci.harvard.edu

Study Coordinator:

Jeannette Van Der Velde
Center for Lymphoma, MGH Cancer Center
jvandervelde@partners.org

NCI-Supplied Agent(s): N/A
Other Agent(s): Blinatumomab, Amgen

IND #: TBD
IND Sponsor: Jeffrey Barnes

Protocol Type / Version # / Version Date: Original/ Version 1.2/ July 26, 2016

SCHEMA

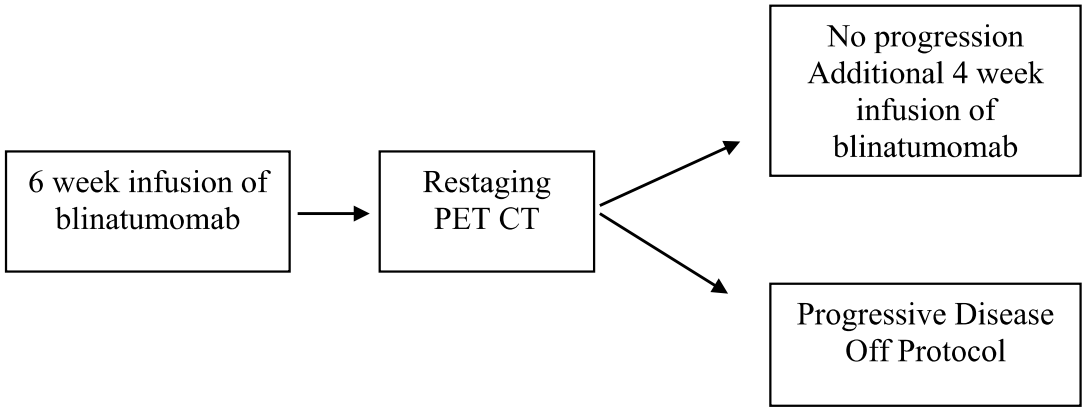

6 week infusion of blinatumomab
Restaging PET CT
No progression Additional 4 week infusion of blinatumomab
Progressive Disease Off Protocol

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This will be an open label single arm phase II study employing a Simon's optimal two stage design to assess efficacy and safety of blinatumomab in indolent NHL. Blinatumomab will be administered as a continuous IV infusion with stepwise dosing reaching a target dose of at 112mcg/d for 28 days. Subjects will start at a dose of 9 mcg/d with escalation to 28mcg/d and 112mcg/d if no toxicity at 7 day intervals. Subjects will be restaged 6 weeks after completion of the infusion by PET CT. All subjects without disease progression will receive an additional 4 week cycle. All subjects will then have an end of treatment PET CT 6 weeks after completion of the second infusion. All subjects with a response will then be followed with a CT every 6 months for 2 years then annually through 5 years or until progression.

1.2 Primary Objectives

Evaluate clinical efficacy blinatumomab in relapsed/refractory indolent NHL

1.3 Secondary Objectives

Secondary

- Determine progression-free survival and duration of response
- Evaluate safety of blinatumomab in relapsed/refractory indolent NHL subjects

Exploratory

- Evaluate the impact of baseline B:T lymphocytes ratio in peripheral blood on response and CNS toxicity

2. BACKGROUND

2.1 Indolent Non-Hodgkin Lymphoma (iNHL)

There will be approximately 72,000 new cases of Non-Hodgkin lymphoma (NHL) in the United States in 2015 with an estimated 20,000 deaths. (1) Follicular lymphoma (FL) is the most common indolent lymphoma North America and Western Europe accounting for approximately one- third of all NHLs with a slightly lower incidence in Eastern Europe and Asia. (2) Marginal zone lymphoma (MZL) including variants splenic marginal zone lymphoma, extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma), and nodal MZL represented less than 10% of all NHLs are approached similar to follicular lymphoma.(3)

Of the many effective treatment modalities for iNHL, overall survival benefits have not been demonstrated favoring one treatment approach over another, with the exception of rituximab-containing chemotherapy versus chemotherapy alone. Increased intensity regimens have been shown to improve complete response rates and progression free survivals without improvement in overall survival. Available treatment approaches currently employed in chemotherapy naïve patients include rituximab monotherapy with or without maintenance, rituximab plus bendamustine, R-CVP (cyclophosphamide, vincristine, and prednisone), R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), fludarabine-based regimens, radioimmunotherapy, and occasionally single agent oral alkylator therapy. Since no single regimen is superior over another in terms of overall survival, treatment decisions are made based on tolerability.

In a large Intergroup trial, 462 patients without indications for treatment were randomized to either observation alone, rituximab 375 mg/m2 weekly for 4 weeks, or rituximab 375mg/m2 weekly for 4 weeks followed by rituximab maintenance every 2 months for 2 years.(4) The freedom from treatment time was similar as to what was seen in previous observational studies with a median of 33 months. The authors report a benefit of improvement of time to new treatment in the rituximab arms but no difference in overall survival. The Eastern Cooperative Oncology Group RESORT (Rituximab Extended Schedule or Re-Treatment) trial of asymptomatic patients given rituximab 375 mg/m2 weekly for 4 weeks and the 274 patients that responded (70% of patient enrolled) were randomized to either maintenance as a single 375 mg/m2 dose every 3 months or observation. (5). No significant difference was seen between the groups in terms of time to treatment failure suggesting no benefit to maintenance rituximab. Rituximab does have significant single agent activity and is a reasonable approach for older patients who might tolerate chemotherapy poorly.

The combination of rituximab with chemotherapy is superior to chemotherapy alone increasing response rates and survival by approximately 15%. R-CVP administered for 8 cycles has produced comparable findings of an ORR of 81% with CRR of 30% and median TTF 27 months.(6) R-CHOP has produced ORR of 96% with CRR of 20% and TTF of 29 months in older patients and not reached in younger patients at limited follow up.(7) Recently the German Study Group Indolent Lymphoma (STiL) NHL1 trial compared RCHOP with bendamustine plus rituximab (BR). This trial of 549 patients 55% of which had FL surprisingly showed that BR was more effective than RCHOP with a median PFS of 69.5m compared to 31 m.(8) BR was also superior to RCHOP in terms of response rate with CR of 40% compared to 30%. In addition BR was better tolerated with significantly lower rates of neutropenia (11% vs. 47%), stomatitis (6% vs. 19%), and alopecia (15% all grade 1 vs. 62%). BR represents an alternative to RCVP and RCHOP with improved efficacy and tolerability.

Patients with treated FL and MZL have a median PFS survival of 27-70 months and therefore most patients require additional therapy. For patients with indications for systemic therapy, the choice of regimen is made with performance status and prior regimens in mind. Similar themes are seen as in the initial therapy with single agent rituximab having modest activity that is greatly enhanced with the combination with chemotherapy. All of the regimens detailed above have

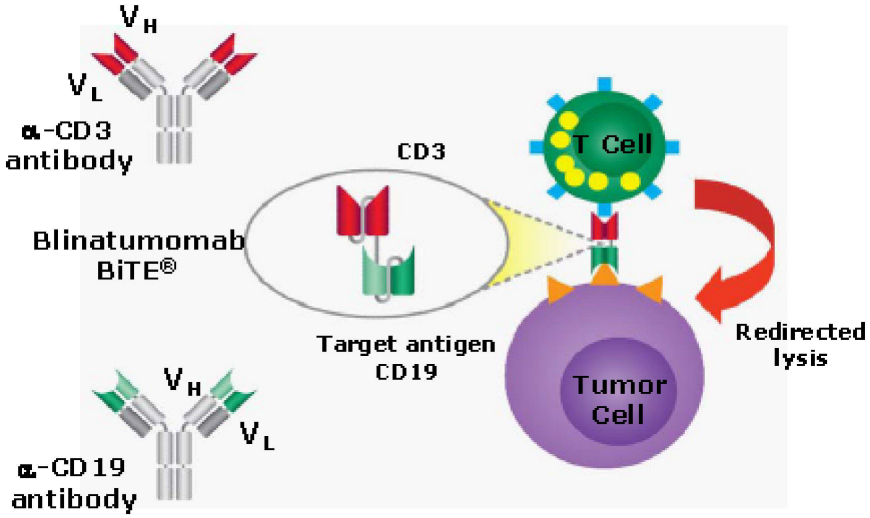
activity in the relapse setting but patient's frequently become refractory to chemotherapy or not candidates for intensive therapy due to comorbidities and this is an unmet medical need.

2.2 Blinatumomab

2.2.1 Background

Blinatumomab (AMG 103), in the literature formerly also known as MT103 or bscCD19xCD3, is a member of a novel class of T-cell-engaging bispecific single-chain antibodies designated BiTE antibodies.(9, 10) Blinatumomab is a BiTE antibody with dual binding specificities. T cells are bound by its anti-CD3 moiety, whereas B lymphoblasts are bound by the anti-CD19 moiety. This unique feature of blinatumomab allows it to transiently connect malignant cells with T cells, thereby inducing T-cell mediated killing of the bound malignant cell. In preclinical models, blinatumomab-mediated T-cell activation involves the transient release of inflammatory cytokines and proliferation of T cells. The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T-cell reaction.

Figure 2-1 T-cell-Mediated Tumor Cell Lysis Through Formation of a Cytolytic Immunological Synapse Induced by Blinatumomab



BiTE = bispecific T-cell engager.

2.2.2 Pharmacokinetics

The PK of blinatumomab was assessed over a dose range from 5 to 90 µg/m2/day following cIV in subjects with ALL and NHL. Mean Css values increased dose-proportionally over the dose range tested (Table 2-1). The Css values at a given dose were comparable in patients with NHL, MRD+ ALL and R/R ALL and comparable in pediatric and adult patients with R/R ALL. The estimated mean CL, Vz, and terminal half-life ranged from 0.94 to 1.34 L/m2/hr, 2.00 to 2.62 L/m2, and 1.47 to 2.68 hours,
respectively.

Table 2-1. Steady-State Concentration (Css) and PK Parameters of Blinatumomab

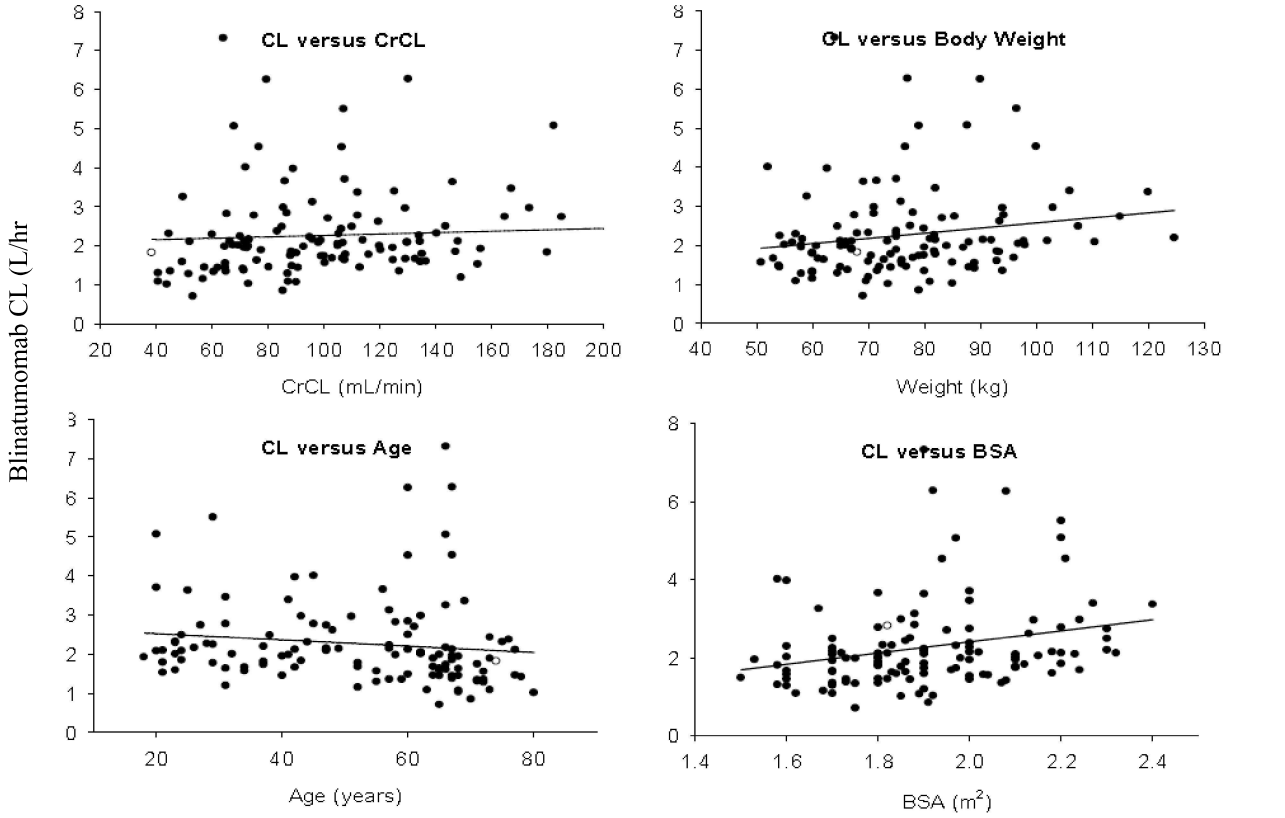
	C_{ss} (pg/mL) Mean±SD (N)					CL	V_z	$t_{½,z}$
Adult	5 µg/m^2	15 µg/m^2	30 µg/m^2	60 µg/m^2	90 µg/m^2	L/m^2/hr	L/m^2	hrs
NHL[a]	200±70.1 (34)	645±279 (36)	1030±358 (6)	2680±856 (35)	3490±904 (4)	1.18±0.587 (66)	2.62±1.61 (27)	2.68±1.70 (27)
MRD$^+$.ALL[b]		696±147 (19)				0.939±0.199 (19)	2.00±0.95 (18)	1.47±0.53 (18)
R/R ALL[c]	167±66 (31)	553±238 (34)	1180±820 (5)			1.34±0.61 (36)		
Pediatrics[d]								
R/R ALL 2-6 years	186±140 (8)	352±340 (14)	1120±1400 (5)					
R/R ALL 7-17 years	150±89.7 (9)	771±686 (12)	1190±640 (5)					

ALL = acute lymphoblastic leukemia; CL = clearance; N = number of patients; MRD = minimal residual disease; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; SD = standard deviation; $t_{1/2,z}$ = terminal half-life; Vz = volume of distribution based on terminal phase.
Sources:

a. Amgen CSR for studies MT-103-104
b. MT103-202
c. MT-103-206
d. MT-103-205, preliminary analysis.

To evaluate factors that may potentially affect the blinatumomab PK, a preliminary analysis was performed to assess the effects of body size, age and creatinine clearance (CrCl) on blinatumomab CL with data from adult patients with NHL, MRD+ ALL and R/R ALL (Figure 2-2). Results showed that within the tested range, none of these factors would have clinically meaningful effect on blinatumomab exposure.

Figure 2-2. Preliminary Analysis of Effects of Body Size, Age and Creatinine Clearance on Blinatumomab Clearance



BSA = body surface area; CL = clearance; CrCL = creatinine clearance.

2.2.3 Immunogenicity

Low immunogenicity incidence has been observed to date following cIV administration of blinatumomab. Of the 477 patients who have received blinatumomab in the clinical program, 1 patient with MRD (Patient 111-003) showed a positive immunogenicity signal at end of cycle 1 (Micromet, Report SR-GxP-0025). The patient had an objective response to blinatumomab treatment prior to the onset of the neutralizing immune response. Exposure in the first cycle was normal but was not detectable in subsequent cycles, possibly due to the onset of immunogenicity. In addition, 2 adult patients with R/R ALL (Patients 2306-018 and 2319-006) had confirmed immunogenicity results; related PK and PD assessments are under evaluation for these 2 patients.

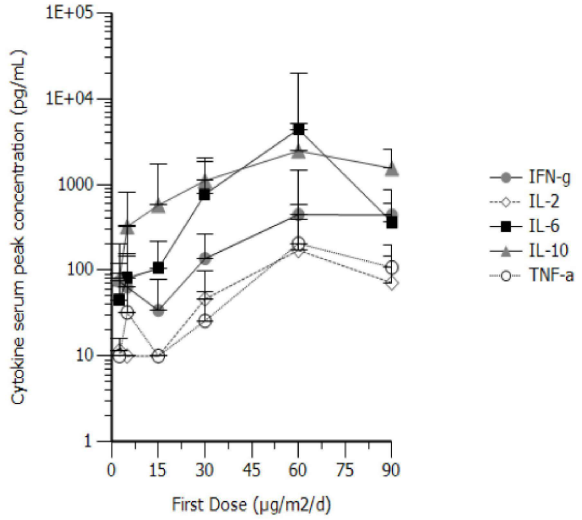
2.2.4 Pharmacodynamics

PD measures included lymphocytes subsets and cytokines. Consistent pharmacodynamic profiles were observed across clinical trials following the cIV regimen. T-cell dynamics: Following blinatumomab cIV infusion, peripheral T-cell counts initially declined within 1 to 2 days to very low levels, a phenomenon described as redistribution from periphery to tissues. After the initial decline, T-cells started to increase and reached baseline levels in about 14 days. Increase of T-cell counts above baseline was found in some patients. There was no difference between the dynamics of CD4+ and CD8+ T cells. A high inter-individual variability was observed in T-cell

baseline levels. The time to return to baseline was variable across patients (10 to 30 days). B-cell Dynamics: B-cell counts in peripheral blood decreased rapidly and become undetectable during treatment at doses ≥ 5 µg/m2/day (or 9µg/day) in the majority of patients. No recovery of B-cell counts was observed during the drug-free period between treatment cycles. Incomplete depletion of B cells was observed at doses of 0.5 and 1.5 µg/m2/day. High inter-individual variability was found in baseline B-cell
counts.

Cytokine Dynamics: The measured cytokines were TNF-α, IL-2, IL-6, IL-8, IL-10, IL-12, IL-4, and IFN-γ. Transient elevation of cytokines was observed in some patients in the first 2 days following the blinatumomab infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion period. In subsequent treatment cycles, cytokines elevation was only observed in few patients with much less intensity. The magnitude of cytokine elevation trended higher at the higher dose (Figure 2-3). The inter-subject variability in cytokine elevation was large. The mean (±SD) Cmax values for IL-10, IL-6, IFN-γ, IL-2, and TNF-α at the 60 µg/m2/day were 2459±2643 pg/mL, 4391±15182 pg/mL, 445± 1014 pg/mL, 167±227 pg/mL, 201±373 pg/mL, respectively, in Study MT103-104.

Figure 2-3. Serum Peak Cytokine Concentration (Mean+SD) Following Initiation of Blinatumomab Treatment



2.2.5 **Rationale of Clinical Dose Selection**

Since there was no clinically meaningful effect of body size on blinatumomab clearance in adults (Figure 2-1), a fixed dosing regimen (ie, starting at 9 µg/day in week 1 followed by 28 µg/day in remaining weeks) was applied to the treatment of R/R ALL in adults. The BSA based dosing regimen was found to be appropriate in pediatric patients. Five dose schemes (5, 15, 30, 15-30 and 5–15 µg/m2/day) were evaluated in the dose-finding portion of part 1 of Study MT103-205. Based on preliminary results of Study MT103-205 in pediatric subjects with ALL, the 5 µg/m2/day dose provided blinatumomab mean steady state levels from 150 to 186 pg/mL which

is within a biologically active range (blinatumomab half-maximal concentrations for in vitro target cell lysis: 10 to 100 pg/mL). Patients received between 1 and 5 cycles of blinatumomab. Following Data Review Committee/Data Safety Monitoring Board (DRC/DSMB) review of the safety, efficacy, PK, and PD data from all patients from the phase 1 cohorts, a decision was made to start with a dose lower than the maximum tolerated dose (MTD) (15μg/m²/day) for the PK expansion part of phase 1. An initial dose of 5 μg/m²/day was selected in order to prevent cytokine release syndrome, which was the major toxicity observed. This dosing regimen includes 5 μg/m2/day for the first week of treatment of the first cycle, increased to 15 μg/m2/day at the end of the first week of the first cycle. For consolidation, starting from cycle 2, a constant dose of 15 μg/m2/day is given. With this step dosing the pediatric dosing is comparable to the respective non-BSA based dosing in adult R/R ALL (9 μg/day, followed by 28 μg/day)

The effective dose for NHL is expected to be higher than that for the R/R ALL. Based on data from the phase 1 dose-finding Study MT103-104, objective clinical responses were observed starting at 15 μg/m2/d and peaked at 60 μg/m2/d. PK/PD analysis suggested the reduction of tumor size was dependent on systemic blinatumomab exposure and treatment duration. Comprehensive analysis is ongoing to further evaluate the optimal doses for the NHL treatment. The dose of 60 μg/m2/d was established in the NHL phase 1 study as the target dose and was also used in the phase 2 DLBCL study (MT103-208) as the BSA-independent dose of 112 μg/d.

2.2.6 **Clinical Safety**

As of the safety data cut-off date (10 October 2013), 477 patients (436 adult patients and 41 pediatric patients) have received treatment in the cIV infusion studies in the blinatumomab clinical development program in B lineage ALL and NHL; all patients have received blinatumomab since the beginning of the program. Patients have been treated with blinatumomab at doses ranging from 0.5 μg/m²/day to 90 μg/m²/day for initial periods between 2 and 288 days.

Table 2-2 provides an overview of the adverse event data by indication. Treatment-emergent adverse events (TEAEs) were reported for similar percentages of patients across the R/R ALL (MT103-206, MT103-211, and MT103-205), MRD ALL (MT103-202 and MT103-203), and NHL (MT103-104 and MT103-208) studies. Treatment-related TEAEs were reported for approximately 10% fewer patients in the R/R ALL studies as compared to the NHL and MRD studies. Fatal adverse events (that occurred up to 30 days after the last dose) were reported for45 patients during the cIV infusion studies. Seven of the deaths (3 due to sepsis [sepsis,bacterial sepsis, *Escherichia* sepsis], 1 due to pneumocystis jirovecii pneumonia, 1 due to invasive fungal infection [central nervous system infection], 1 due to respiratory failure, and 1 due to candidiasis [fungemia]) were considered by the investigator to be possibly related to blinatumomab; however, the patients' underlying disease and concomitant treatment with steroids confound causal assessments of these cases.

Table 2-2. Overview of Adverse Events Reported in Patients Treated With Blinatumomab as of 10 October 2013

	All Studies				
	NHL Studies (N=95) n (%)	Adult R/R ALL Studies (N=232) n (%)	Ped R/R ALL Study (N=41) n (%)	MRD ALL Studies (N=109) n (%)	Pooled (N=477) n (%)
All Treatment-emergent Adverse Events	95 (100.0)	231 (99.6)	41 (100.0)	106 (97.2)	473 (99.2)
All Treatment-emergent Adverse Events with worst grade ≥ 3	88 (92.6)	184 (79.3)	37 (90.2)	72 (66.1)	381 (79.9)
Serious Adverse Events	76 (80.0)	150 (64.7)	23 (56.1)	64 (58.7)	313 (65.6)
Treatment-Related Adverse Events	92 (96.8)	201 (86.6)	34 (82.9)	105 (96.3)	432 (90.6)
Treatment-Related Adverse Events with worst grade ≥ 3	76 (80.0)	128 (55.2)	26 (63.4)	60 (55.0)	290 (60.8)
Treatment-Related Serious Adverse Events	63 (66.3)	89 (38.4)	11 (26.8)	55 (50.5)	218 (45.7)
Adverse Events Leading to Interruption of Study Drug	23 (24.2)	74 (31.9)	6 (14.6)	33 (30.3)	136 (28.5)
Adverse Events Leading to Discontinuation of Study Drug	34 (35.8)	45 (19.4)	8 (19.5)	19 (17.4)	106 (22.2)
Serious Adverse Events Leading to Discontinuation of Study Drug	24 (25.3)	38 (16.4)	8 (19.5)	15 (13.8)	85 (17.8)
Fatal Adverse Event	4 (4.2)[a]	32 (13.8)	8 (19.5)	2 (1.8)	46 (9.6)
Treatment-Related Fatal Adverse Events	2 (2.1)	4 (1.7)	1 (2.5)	0	7 (1.5)

ALL = acute lymphoblastic leukemia; MRD = minimal residual disease; n = number of patients with at least 1 event; N = number of patients treated with blinatumomab; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event.
Safety Analysis Set includes all subjects who received at least one dose of AMG103.
TEAEs include adverse events that began between the first administration of AMG 103 and 30 days after the last administration of AMG 103.
AMG 103 studies cut-off date (study): 04/22/2010 (202), 06/22/2012 (104), and 10/10/2013 (203,205,206,208,211)

Table 2-3 provides a summary of all TEAEs reported in ≥ 10% of patients overall in the blinatumomab cIV infusion studies. The most frequently reported TEAEs were in the System Order Classes (SOCs) of General disorders and administration site conditions, Nervous system disorders, Investigations, and Gastrointestinal disorders. Across studies, the most frequently reported (those reported in ≥ 20% of patients overall) TEAEs were pyrexia (70%), headache (36%), fatigue (26%), nausea (23%), hypokalemia (23%), tremor (22%), and diarrhea (21%). In the NHL population, the incidence of the following TEAEs was approximately 2-fold higher than in the other indications: lymphopenia, leukopenia, thrombocytopenia, fatigue, C-reactive protein increased, hyperglycemia, and weight increased. Of note, in the MRD ALL and R/R ALL studies, patients usually received a target blinatumomab dose of 15 µg/m2/day (or 28 µg/day), whereas in the phase 1, dose-finding, NHL study (MT103-104), some patients received blinatumomab doses of up to 90 µg/m2/day, and in the ongoing study 208 in DLBCL patients receive a target dose of 112 µg/day. Given the phase 1 nature of the larger NHL Study MT103-104, investigators on that study were required to report all lab changes as adverse events and all Common Terminology Criteria for Adverse Events (CTCAE) grade 4 lab changes as serious adverse events (SAEs) regardless of clinical relevance.

In general, the probability of patients experiencing TEAEs was greatest within 0 to 3 days of blinatumomab treatment. Across studies, 91% of patients had TEAEs that were considered by the investigator to be related to treatment. The most frequently reported (those reported in ≥ 20% of patients overall) treatment-related TEAEs were pyrexia (59%), headache (23%), and tremor (20%).

Table 2-3. Summary of Treatment-Emergent Adverse Events Reported in ≥ 10% of Patients Overall Treated with Blinatumomab as of 10 October 2013

	ALL Studies				
Preferred Term	NHL Studies (N=95) n (%)	Adult R/R ALL Studies (N=232) n (%)	R/R ALL Ped Study (N=41) n (%)	MRD ALL Studies (N=109) n (%)	Pooled (N=477) n (%)
Number of subjects reporting treatment-emergent adverse events	95 (100.0)	231 (99.6)	41 (100.0)	106 (97.2)	473 (99.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	74 (77.9)	135 (58.2)	22 (53.7)	38 (34.9)	269 (56.4)
Leukopenia	37 (38.9)	25 (10.8)	3 (7.3)	14 (12.8)	79 (16.6)
Anaemia	18 (18.9)	41 (17.7)	12 (29.3)	7 (6.4)	78 (16.4)
Lymphopenia	61 (64.2)	5 (2.2)	2 (4.9)	9 (8.3)	77 (16.1)
Thrombocytopenia	31 (32.6)	28 (12.1)	3 (7.3)	10 (9.2)	72 (15.1)
Neutropenia	20 (21.1)	28 (12.1)	4 (9.8)	16 (14.7)	68 (14.3)
Febrile neutropenia	2 (2.1)	55 (23.7)	6 (14.6)	2 (1.8)	65 (13.6)
GASTROINTESTINAL DISORDERS	56 (58.9)	143 (61.6)	24 (58.5)	62 (56.9)	285 (59.7)
Nausea	18 (18.9)	53 (22.8)	10 (24.4)	28 (25.7)	109 (22.9)
Diarrhoea	25 (26.3)	45 (19.4)	5 (12.2)	23 (21.1)	98 (20.5)
Constipation	11 (11.6)	48 (20.7)	3 (7.3)	16 (14.7)	78 (16.4)
Vomiting	14 (14.7)	29 (12.5)	9 (22.0)	26 (23.9)	78 (16.4)
Abdominal pain	9 (9.5)	36 (15.5)	11 (26.8)	4 (3.7)	60 (12.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	85 (89.5)	197 (84.9)	35 (85.4)	101 (92.7)	418 (87.6)
Pyrexia	67 (70.5)	141 (60.8)	29 (70.7)	94 (86.2)	331 (69.4)
Fatigue	41 (43.2)	47 (20.3)	8 (19.5)	29 (26.6)	125 (26.2)
Chills	23 (24.2)	32 (13.8)	1 (2.4)	33 (30.3)	89 (18.7)
Oedema peripheral	15 (15.8)	60 (25.9)	2 (4.9)	11 (10.1)	88 (18.4)
INFECTIONS AND INFESTATIONS	48 (50.5)	146 (62.9)	20 (48.8)	55 (50.5)	269 (56.4)
Nasopharyngitis	13 (13.7)	12 (5.2)	2 (4.9)	13 (11.9)	40 (8.4)
INVESTIGATIONS	79 (83.2)	130 (56.0)	32 (78.0)	53 (48.6)	294 (61.6)
C-reactive protein increased	40 (42.1)	22 (9.5)	0 (0.0)	15 (13.8)	77 (16.1)
Weight increased	33 (34.7)	28 (12.1)	5 (12.2)	10 (9.2)	76 (15.9)
Alanine aminotransferase increased	25 (26.3)	30 (12.9)	8 (19.5)	8 (7.3)	71 (14.9)
Aspartate aminotransferase increased	16 (16.8)	27 (11.6)	9 (22.0)	5 (4.6)	57 (11.9)
METABOLISM AND NUTRITION DISORDERS	66 (69.5)	121 (52.2)	20 (48.8)	37 (33.9)	244 (51.2)
Hypokalaemia	18 (18.9)	53 (22.8)	10 (24.4)	27 (24.8)	108 (22.6)
Hyperglycaemia	34 (35.8)	30 (12.9)	4 (9.8)	6 (5.5)	74 (15.5)

Table 2-3. Summary of Treatment-Emergent Adverse Events Reported in ≥ 10% of Patients Overall Treated with Blinatumomab as of 10 October 2013 Continued

	ALL Studies				
Preferred Term	NHL Studies (N=95) n (%)	Adult R/R ALL Studies (N=232) n (%)	R/R ALL Ped Study (N=41) n (%)	MRD ALL Studies (N=109) n (%)	Pooled (N=477) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	41 (43.2)	115 (49.6)	18 (43.9)	42 (38.5)	216 (45.3)
Back pain	17 (17.9)	30 (12.9)	8 (19.5)	15 (13.8)	70 (14.7)
Pain in extremity	8 (8.4)	23 (9.9)	11 (26.8)	9 (8.3)	51 (10.7)
NERVOUS SYSTEM DISORDERS	64 (67.4)	146 (62.9)	25 (61.0)	73 (67.0)	308 (64.6)
Headache	32 (33.7)	80 (34.5)	15 (36.6)	45 (41.3)	172 (36.1)
Tremor	23 (24.2)	47 (20.3)	4 (9.8)	31 (28.4)	105 (22.0)
Dizziness	15 (15.8)	27 (11.6)	2 (4.9)	11 (10.1)	55 (11.5)
PSYCHIATRIC DISORDERS	26 (27.4)	73 (31.5)	6 (14.6)	31 (28.4)	136 (28.5)
Insomnia	8 (8.4)	32 (13.8)	0 (0.0)	21 (19.3)	61 (12.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	43 (45.3)	94 (40.5)	20 (48.8)	25 (22.9)	182 (38.2)
Cough	16 (16.8)	38 (16.4)	8 (19.5)	14 (12.8)	76 (15.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	44 (46.3)	92 (39.7)	10 (24.4)	37 (33.9)	183 (38.4)
Rash	6 (6.3)	29 (12.5)	3 (7.3)	16 (14.7)	54 (11.3)
VASCULAR DISORDERS	31 (32.6)	71 (30.6)	19 (46.3)	29 (26.6)	150 (31.4)
Hypotension	9 (9.5)	25 (10.8)	8 (19.5)	16 (14.7)	58 (12.2)
Hypertension	7 (7.4)	20 (8.6)	13 (31.7)	8 (7.3)	48 (10.1)

Table 2-4 provides a summary of all TEAEs of grade ≥ 3 reported by 10 or more (ie, > 2%) patients overall. The most frequently reported TEAEs of grade ≥ 3 were those in the SOCs of Blood and lymphatic system disorders, Investigations, and Infections and infestations. The incidence of grade ≥ 3 lymphopenia, leukopenia, thrombocytopenia, CRP increased, and hyperglycemia was higher in the NHL population than in the other indications. This may be due in part to the protocol requirement in study MT103-104 to report all laboratory abnormalities as adverse events regardless of clinical relevance. Across studies, 61% of patients had TEAEs of grade ≥ 3 that were considered by the investigator to be related to treatment. The most frequently reported treatment-related events of grade ≥ 3 were lymphopenia (15%), neutropenia (10%), leukopenia (8%), and febrile neutropenia (7%).

Table 2-4. Summary of Treatment-Emergent Adverse Events With CTC Grade 3 or Higher Reported in 10 or More (> 2%) Patients Overall Treated With Blinatumomab (Pooled Data) as of 10 October 2013

		ALL Studies			
Preferred Term	NHL Studies (N=95) n (%)	Adult R/R ALL Studies (N=232) n (%)	R/R ALL Ped Study (N=41) n (%)	MRD ALL Studies (N=109) n (%)	Pooled (N=477) n (%)
Number of subjects reporting treatment-emergent adverse events of grade ≥3	88 (92.6)	184 (79.3)	37 (90.2)	72 (66.1)	381 (79.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	67 (70.5)	106 (45.7)	16 (39.0)	29 (26.6)	218 (45.7)
Lymphopenia	60 (63.2)	4 (1.7)	2 (4.9)	9 (8.3)	75 (15.7)
Neutropenia	12 (12.6)	26 (11.2)	4 (9.8)	15 (13.8)	57 (11.9)
Febrile neutropenia	2 (2.1)	48 (20.7)	5 (12.2)	2 (1.8)	57 (11.9)
Leukopenia	17 (17.9)	19 (8.2)	3 (7.3)	8 (7.3)	47 (9.9)
Anaemia	5 (5.3)	27 (11.6)	10 (24.4)	2 (1.8)	44 (9.2)
Thrombocytopenia	11 (11.6)	18 (7.8)	3 (7.3)	4 (3.7)	36 (7.5)
GASTROINTESTINAL DISORDERS	5 (5.3)	19 (8.2)	5 (12.2)	2 (1.8)	31 (6.5)
Abdominal pain	3 (3.2)	6 (2.6)	2 (4.9)	0 (0.0)	11 (2.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (10.5)	35 (15.1)	10 (24.4)	13 (11.9)	68 (14.3)
Pyrexia	4 (4.2)	14 (6.0)	8 (19.5)	6 (5.5)	32 (6.7)
IMMUNE SYSTEM DISORDERS	0 (0.0)	11 (4.7)	6 (14.6)	5 (4.6)	22 (4.6)
Cytokine release syndrome	0 (0.0)	4 (1.7)	5 (12.2)	2 (1.8)	11 (2.3)
INFECTIONS AND INFESTATIONS	16 (16.8)	76 (32.8)	12 (29.3)	14 (12.8)	118 (24.7)
Pneumonia	3 (3.2)	19 (8.2)	0 (0.0)	1 (0.9)	23 (4.8)
Sepsis	1 (1.1)	12 (5.2)	2 (4.9)	1 (0.9)	16 (3.4)
Device related infection	2 (2.1)	7 (3.0)	2 (4.9)	3 (2.8)	14 (2.9)
INVESTIGATIONS	39 (41.1)	63 (27.2)	21 (51.2)	23 (21.1)	146 (30.6)
Alanine aminotransferase increased	0 (0.0)	14 (6.0)	8 (19.5)	5 (4.6)	27 (5.7)
C-reactive protein increased	17 (17.9)	5 (2.2)	0 (0.0)	1 (0.9)	23 (4.8)
White blood cell count decreased	3 (3.2)	12 (5.2)	6 (14.6)	2 (1.8)	23 (4.8)
Aspartate aminotransferase increased	0 (0.0)	8 (3.4)	6 (14.6)	4 (3.7)	18 (3.8)
Neutrophil count decreased	3 (3.2)	9 (3.9)	5 (12.2)	1 (0.9)	18 (3.8)
Blood immunoglobulin G decreased	3 (3.2)	4 (1.7)	2 (4.9)	5 (4.6)	14 (2.9)
Gamma-glutamyltransferase increased	7 (7.4)	6 (2.6)	0 (0.0)	1 (0.9)	14 (2.9)
Blood bilirubin increased	1 (1.1)	8 (3.4)	4 (9.8)	0 (0.0)	13 (2.7)
Platelet count decreased	2 (2.1)	6 (2.6)	3 (7.3)	2 (1.8)	13 (2.7)
Fibrin D dimer increased	7 (7.4)	5 (2.2)	0 (0.0)	0 (0.0)	12 (2.5)
Blood immunoglobulin A decreased	4 (4.2)	3 (1.3)	0 (0.0)	3 (2.8)	10 (2.1)
Lymphocyte count decreased	4 (4.2)	3 (1.3)	3 (7.3)	0 (0.0)	10 (2.1)

Table 2-4. Summary of Treatment-Emergent Adverse Events With CTC Grade 3 or Higher Reported in 10 or More (> 2%) Patients Overall Treated With Blinatumomab (Pooled Data) as of 10 October 2013 Continued

METABOLISM AND NUTRITION DISORDERS	22 (23.2)	54 (23.3)	14 (34.1)	7 (6.4)	97 (20.3)
Hypokalaemia	5 (5.3)	15 (6.5)	7 (17.1)	3 (2.8)	30 (6.3)
Hyperglycaemia	10 (10.5)	15 (6.5)	2 (4.9)	2 (1.8)	29 (6.1)
Hypophosphataemia	1 (1.1)	11 (4.7)	3 (7.3)	1 (0.9)	16 (3.4)
NERVOUS SYSTEM DISORDERS	22 (23.2)	38 (16.4)	4 (9.8)	18 (16.5)	82 (17.2)
Encephalopathy	7 (7.4)	9 (3.9)	0 (0.0)	5 (4.6)	21 (4.4)
Headache	3 (3.2)	9 (3.9)	0 (0.0)	5 (4.6)	17 (3.6)
Tremor	3 (3.2)	4 (1.7)	0 (0.0)	6 (5.5)	13 (2.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	10 (10.5)	15 (6.5)	10 (24.4)	2 (1.8)	37 (7.8)
Respiratory failure	1 (1.1)	7 (3.0)	4 (9.8)	0 (0.0)	12 (2.5)
Dyspnoea	5 (5.3)	5 (2.2)	1 (2.4)	0 (0.0)	11 (2.3)
VASCULAR DISORDERS	5 (5.3)	21 (9.1)	6 (14.6)	4 (3.7)	36 (7.5)
Hypertension	1 (1.1)	10 (4.3)	2 (4.9)	1 (0.9)	14 (2.9)
Hypotension	1 (1.1)	5 (2.2)	3 (7.3)	1 (0.9)	10 (2.1)

Table 2-5 provides a summary by SOC of all treatment-emergent SAEs reported by 10 or more (ie, >2%) patients overall. The most frequently reported treatment-emergent SAEs were in the SOCs of Infections and infestations, Blood and lymphatic disorders, and Nervous system disorders. A greater percentage of patients in the NHL study MT103-104 reported treatment emergent SAEs compared with patients in the MRD ALL and R/R ALL studies. As noted previously, in the MRD ALL and R/R ALL studies, patients usually received a target blinatumomab dose of 15 µg/m2/day (or 28 µg/day), whereas in the phase 1, dose-finding, NHL study, 51 of 76 patients (67%) received blinatumomab doses of 30 to 90 µg/m2/day. Additionally, in the NHL study, all grade 4 laboratory abnormalities that occurred during or after administration of blinatumomab were to be reported as SAEs. Because of these differences, the higher percentage of treatment-emergent SAEs reported in the NHL study is not unexpected. Across studies, 46% of patients had SAEs that were considered by the investigator to be related to treatment. The most common treatment-related SAEs overall were lymphopenia (10%), pyrexia (5%), encephalopathy (4%), and tremor (4%). The incidence of treatment-related SAEs of lymphopenia, neutropenia, and leukopenia was approximately 2-fold higher in the NHL population than in the other indications. Of note, 47% of patients in the NHL study MT103-104 received blinatumomab doses of 60 to 90 µg/m2/day.

Table 2-5. Summary of Treatment-Emergent Serious Adverse Events Reported in 10 or More Patients Overall Treated With Blinatumomab as of 10 October 2013

		ALL Studies			
Preferred Term	NHL Studies (N=95) n (%)	Adult R/R ALL Studies (N=232) n (%)	R/R ALL Ped Study (N=41) n (%)	MRD ALL Studies (N=109) n (%)	Pooled (N=477) n (%)
Number of subjects reporting treatment emergent serious adverse events	76 (80.0)	150 (64.7)	23 (56.1)	64 (58.7)	313 (65.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	50 (52.6)	34 (14.7)	2 (4.9)	11 (10.1)	97 (20.3)
Lymphopenia	42 (44.2)	1 (0.4)	0 (0.0)	6 (5.5)	49 (10.3)
Febrile neutropenia	1 (1.1)	17 (7.3)	1 (2.4)	1 (0.9)	20 (4.2)
Neutropenia	7 (7.4)	6 (2.6)	0 (0.0)	4 (3.7)	17 (3.6)
Leukopenia	7 (7.4)	1 (0.4)	0 (0.0)	2 (1.8)	10 (2.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	11 (11.6)	32 (13.8)	4 (9.8)	20 (18.3)	67 (14.0)
Pyrexia	11 (11.6)	14 (6.0)	2 (4.9)	11 (10.1)	38 (8.0)
INFECTIONS AND INFESTATIONS	24 (25.3)	71 (30.6)	9 (22.0)	14 (12.8)	118 (24.7)
Pneumonia	6 (6.3)	11 (4.7)	0 (0.0)	0 (0.0)	17 (3.6)
Sepsis	2 (2.1)	9 (3.9)	2 (4.9)	1 (0.9)	14 (2.9)
Device related infection	4 (4.2)	6 (2.6)	1 (2.4)	2 (1.8)	13 (2.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	7 (7.4)	13 (5.6)	2 (4.9)	9 (8.3)	31 (6.5)
Overdose	4 (4.2)	5 (2.2)	2 (4.9)	6 (5.5)	17 (3.6)
NERVOUS SYSTEM DISORDERS	21 (22.1)	36 (15.5)	7 (17.1)	24 (22.0)	88 (18.4)
Encephalopathy	7 (7.4)	8 (3.4)	0 (0.0)	6 (5.5)	21 (4.4)
Tremor	2 (2.1)	8 (3.4)	0 (0.0)	7 (6.4)	17 (3.6)
Aphasia	5 (5.3)	3 (1.3)	0 (0.0)	5 (4.6)	13 (2.7)
Convulsion	2 (2.1)	4 (1.7)	2 (4.9)	4 (3.7)	12 (2.5)

2.2.7 **Clinical Efficacy**

Study MT103-104- Study Design and Population

Study MT103-104 was an open-label, dose-escalation, multicenter, phase 1 study in Germany to investigate the tolerability and safety of blinatumomab given as cIV infusion over 4 or 8 weeks in adult patients with relapsed NHL. This study has been completed. Blinatumomab was administered to 76 patients. The distribution of histologic subtypes in the study population was FL in 37%, other subtypes of indolent lymphoma in 13%, MCL in 32%, and DLBCL in 18%. Among treated patients, the median number of prior treatment regimens was 3, the average age was 60 years (range 20-80 years), and the majority of patients (75%) were men.

In Study MT103-104, the antitumor activity of blinatumomab in terms of objective response was assessed using Cheson criteria(11), and all CT scans were centrally reviewed by an independent radiologist. Table 2-6 shows the response rates at different dose levels in Study MT103-104. The efficacy of blinatumomab was dose-dependent, with objective responses starting at a blinatumomab dose of 15 µg/m²/day. At a dose of 5 µg/m²/day, biological activity in terms of compete depletion of peripheral B cells was observed. Three responses (2 partial responses [PRs], 1 CR) were observed in 15 patients treated with blinatumomab maximal 15 µg/m²/day. In patients receiving blinatumomab maximal 60 µg/m²/day (either reached by step-wise dose escalation or by directly starting at this dose), a 69% objective response rate (24/35 patients: CR/unconfirmed CR [CRu] in 13 patients and PR in 11 patients) was observed. The mean duration of response was 15.4 months (95% confidence interval = 6.8, 37.1) (transplant not counted as progression). At blinatumomab maximal 90 µg/m²/day, 1 of the 4 patients showed a CR and 1 showed a PR. One of the 4 patients could not be evaluated due to early treatment discontinuations due to dose-limiting toxicity (DLT) (2 DLTs of encephalopathy).

Table 2-6. Responses by Maximal Dose Received in Study MT103-104 for All NHL Entities

Blinatumomab Dose Level[a]	Patients (N=76)	Complete Response[b]	Partial Response	Total Responses[c]	Overall Response Rate
<5 µg/m²/day	9	0	0	0/9	0.0%
5 µg/m²/day	7	0	0	0/7	0%
15 µg/m²/day	15	1	2	3/15	20.0%
30 µg/m²/day	6	1	0	1/5	20.0%
60 µg/m²/day	35	8	11	24/35	69.0%
90 µg/m²/day	4	1	1	2/4	50.0%

[a] Dose level based on maximal dose reached.
[b] Includes CRu (unconfirmed complete response).
[c] Complete response + partial response. Only includes patients who reached the highest target dose.

2.3 Rationale

Indolent B-cell lymphomas remain incurable diseases in the modern era. Despite numerous available therapies, subjects typically display a pattern of ongoing relapse during their lives, and additional therapies are still needed, particularly those that are not chemotherapy-based.

Blinatumomab is a bispecific antibody targeting CD19 and CD3 with activity in B cell acute lymphoblastic leukemia and NHL. In a phase I study including indolent NHL, 8 of 9 subjects treated at a constant dose exceeding 60ug/m2/d had an objective response with a median duration of response of 26 months. (12) Treatment was well tolerated with the most common AEs being transient/reversible fever, headache and fatigue. Out of 52 subjects, 9 discontinued treatment due to CNS toxicity including kinetic tremor, speech impairment, disorientation, apraxia and seizure which resolved upon stopping study drug. A baseline B cell to T cell (B:T) ratio in peripheral blood at or below 1:10 has been identified as a predictive factor for occurrence of neurological AEs.(13) Neurologic events were reversible. Given the significant signal of activity of blinatumomab in indolent B-cell NHL and the overall favorable safety profile, we propose a phase 2 study of blinatumomab in relapsed/refractory indolent NHL.

2.4 Correlative Studies Background

2.4.1 Neurologic toxicity

Patients receiving blinatumomab may experience a spectrum of neurologic events, the most clinically relevant being encephalopathy, confusional and cognitive disorders, memory impairment, disorientation, convulsions (convulsion, grand mal seizure, and epilepsy), speech disorders (aphasia, speech disorder, and dysarthria), cerebellar syndrome, tremor, and hallucinations. Across all indications/studies, the incidence of patients experiencing neurologic events is greatest within the first few days of blinatumomab treatment. Most of these events are clinically manageable after interruption or permanent discontinuation of blinatumomab. Of the 477 subjects enrolled across the program as of 10 October 2013, 243 patients (51%) have experienced neurologic TEAEs, and 197 (41%) were considered by the investigator as related to treatment. The majority of TEAEs occurred within the first week of the first cycle of blinatumomab treatment. Overall, the types of events observed in the R/R ALL population were similar to those in the MRD-positive and R/R NHL populations, with no major differences in the frequencies of events between indications. Serious neurologic events were observed at blinatumomab doses ranging from 5 to 90 μg/m2/day, with higher doses (60 and 90 μg/m2/day) associated with an increased severity of events in the NHL studies. Prodromal symptoms included tremor and disorientation. No specific pattern was observed in medical histories or concomitant medications. A baseline B cell to T cell (B:T) ratio in peripheral blood at or below 1:10 has been identified as a predictive factor for occurrence of neurological AEs.(13) We will correlate baseline B cell to T cell (B:T) ratio in peripheral blood measured by flow cytometry with neurologic events in a descriptive manner.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Subjects must have histologically determined B cell NHL that is relapsed or primary refractory after initial therapy.

- Follicular Lymphoma of any grade
- Marginal zone lymphoma (extranodal, nodal, or splenic). Patients with gastric MALT must have progressed after H. Pylori therapy and radiation. Patients with splenic MZL must have prior splenectomy.

3.1.2 At least 1 prior line of chemoimmunotherapy if primary refractory or relapsed with in one year. Subjects who respond to initial therapy for greater than one year must have had at least 2 prior lines of therapy including one line with chemoimmunotherapy including an anti-CD20 monoclonal antibody

3.1.3 Measurable disease that has not been previously irradiated on PET-CT of at least 1.5cm,

3.1.4 Age ≥18 years.

3.1.5 ECOG performance status ≤2 (see Appendix A)

3.1.6 Participants must have adequate organ and marrow function as defined below:

- absolute neutrophil count ≥750/mcL
- platelets ≥75,000/mcL
- total bilirubin < 2.0 x upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal or ≤ 5 X ULN
  - if due to lymphoma infiltration
- creatinine ≤ 2.0 X ULN

OR

- creatinine clearance ≥50 mL/min/1.73 m^2 for participants with creatinine levels above 2.0 X ULN .

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Participants who have had chemotherapy within 3 weeks, rituximab or obinutuzumab within 4 weeks, or radioimmunotherapy within 6 weeks prior to entering the study, or those who have not recovered from adverse events due to agents administered more than 3 weeks earlier. Subjects actively progressing within that window who have recovered from toxicities of prior therapy are also eligible.

3.2.2 Autologous stem cell transplantation within 12 weeks prior to study entry

3.2.3 Prior allogeneic transplant

3.2.4 Therapeutic doses of corticosteroids within 14 days prior to study entry, defined as >20mg/day pf prednisone, or equivalent. Topical and/or inhaled steroids are permitted.

3.2.5 Participants who are receiving any other investigational agents.

3.2.6 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to blinatumomab

3.2.8 Subjects with known HIV infection

3.2.9 Pregnant or lactating subjects.

3.2.10 Chronic infection with hepatitis B or hepatitis C virus

3.2.11 History of or current relevant CNS pathology such as epilepsy, seizure, paresis,aphasia, apoplexia, severe brain injuries, cerebellar disease, organic brain syndrome, psychosis

3.2.12 Prior history of another malignancy (except for non-melanoma skin cancer, *in situ* cervical or breast cancer, or localized prostate cancer) unless disease free for at least one year and felt at low risk of relapse by treating physician.

3.2.13 Uncontrolled intercurrent illness including, but not limited to, ongoing or uncontrolled systemic fungal, bacterial, viral, or other infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

N/A

4.4 Registration Process for Other Investigative Sites

N/A

5. TREATMENT PLAN

5.1 Treatment Regimen

This will be an open label single arm phase II study employing a Simon's optimal two stage design to assess efficacy and safety of blinatumomab in indolent NHL. Blinatumomab will be administered as a continuous IV infusion through a central venous catheter for a 42 day cycle. Blinatumomab will start with a 7 day infusion at 9mcg/d. If no dose limiting toxicity (table 6.1)

after 7 days, the dose will be escalated to 28 mcg/d for 7 additional days. If no dose limiting toxicity (table 6.1) after 14 days, blinatumomab will be infused at a target dose of at 112mcg/d for 28 days. The first 5 patients enrolled on study will be admitted for 3 days during each dose escalation as well as the first 3 days of cycle 2 to monitor for cytokine release syndrome as well as neurotoxicity. If no grade 4 toxicities are seen, future patients enrolled on study will begin therapy as an outpatient. Subjects will be restaged after a 6 week treatment free period by PET CT. All subjects without disease progression will receive an additional 4 week cycle starting at the target dose of 112 mcg/d. All subjects will then have an end of treatment PET CT 6 weeks after completion of the second infusion. All subjects with a response will then be followed with a CT every 6 months for the first 2 years and then annually for 5 years or until progression.

5.2 Blinatumomab Administration

Subjects will receive premedication with dexamethasone 20 mg (or equivalent) intravenously 1 hour (+/- 30 minutes) prior to the first dose of blinatumomab of each cycle, prior to a step dose (such as Cycle 1 day 8), or when restarting an infusion after an interruption of 4 or more hours. Blinatumomab will be administered as a continuous IV infusion through a central venous catheter at a constant flow rate using an infusion pump for a 42 day cycle with cycle 1 and a 28 day cycle with cycle 2. Blinatumomab will start with a 7 day infusion at 9mcg/d. If no grade 3 toxicity after 7 days, the dose will be escalated to 28 mcg/d for 7 additional days. If no grade 3 toxicity after 14 days, blinatumomab will be infused at a target dose of at 112mcg/d for 28 days.

5.3 General Concomitant Medication and Supportive Care Guidelines

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug.

All Concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded.

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medication should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Growth factors (e.g.G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) may be used at the discretion of the treating investigator.
- No chronic treatment with systemic steroids at >20mg/day of prednisone, or equivalent, or another immunosuppressive agents. Topical or inhaled

corticosteroids are allowed. Musculoskeletal injections of steroids are allowed.

- No formal drug interaction studies have been conducted with blinatumomab. Initiation of blinatumomab treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug drug interaction risk is during the first 9 days of the cycle and in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (eg, warfarin) or drug concentrations (eg, cyclosporine).

5.4 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for 2 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Jeffrey Barnes M.D., Ph.D. at 617-724-4000.

5.5 Duration of Follow Up

Participants removed from study due to criteria in section 5.4 will be followed for survival for 5 years or until death. . Participants removed from protocol therapy for unacceptable adverse event(s) will be followed monthly until resolution or stabilization of the adverse event.

5.6 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Toxicity Management/ Dosage Adjustments

Table 6-1 Criteria for dosing delays and re-initiation of treatment for toxicity definitely or possibly related to study drug. Based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Toxicity	Grade	Action
Cytokine Release Syndrome (CRS)	Grade 3	Withhold blinatumomab until resolved to ≤ grade 1, then restart blinatumomab at 9 mcg/day with dexamehtasone 8mg TID for three days. Dexamethasone will then be decreased by 25% per day until discontinued. Escalate to 28 mcg/day after 7 days and then to 112 mcg/d after an additional 7 days if the toxicity does not recur.
	Grade 4	Remove from study
Neurologic toxicity	Seizure	Discontinue blinatumomab permanently if more than one seizure occurs despite antiepileptics.
	Grade 3	Withhold blinatumomab until ≤ grade 1, (mild), then restart blinatumomab at 9 mcg/day with dexamethasone (or equivalent) 20mg iv within 1 hour of start of retreatment. Dexamethasone will then be decreased by 25% per day until discontinued. Escalate to 28 mcg/day after 7 days and then to 112 mcg/d after an additional 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
	Grade 4	Remove from study
Other clinically relevant adverse reactions	Grade 3	Withhold blinatumomab until ≤ grade 1 (mild), then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days and then to 112 mcg/d after an additional 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
	Grade 4	Remove from study

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Cytokine Release Syndrome

Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving blinatumomab.

Infusion reactions have occurred with the blinatumomab infusion and may be clinically indistinguishable from manifestations of CRS.

Serious adverse events that may be associated with CRS included pyrexia, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, and increased total bilirubin; these events infrequently led to blinatumomab discontinuation. Life-threatening or fatal CRS was infrequently reported in patients receiving blinatumomab. In some cases, disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS.

Subjects will be closely monitored for signs or symptoms of these events. Management of these events will require either temporary interruption or discontinuation of blinatumomab (see table 6-1).

7.1.2 Neurological Toxicities

In patients receiving blinatumomab in clinical trials, neurological toxicities have occurred in approximately 50% of patients. The median time to onset of any neurological toxicity was 7 days. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of blinatumomab administration occurred in approximately 15% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The majority of events resolved following interruption of blinatumomab, but some resulted in treatment discontinuation.

Subjects will be closely monitored for signs and symptoms of neurological toxicities, and interrupt or discontinue blinatumomab (see table 6-1).

7.1.3 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), which may be life-threatening or fatal, has been observed in patients receiving blinatumomab. Subjects with bulky disease defined as adenopathy >10cm on CT imaging or circulating disease ≥ 15,000 circulating malignant cells/ mm^3 will receive allopurinol 300mg BID begining 24 hours prior to first infusion and for 30 days follwoing begining of treatment for prophylaxis of tumor lysis syndrome.

7.1.4 Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including seizures, patients receiving blinatumomab are at risk for loss of consciousness . Subjects will be advised to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while blinatumomab is being administered.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Sections 2.2.6 and 7.1.

8.1 Blinatumomab

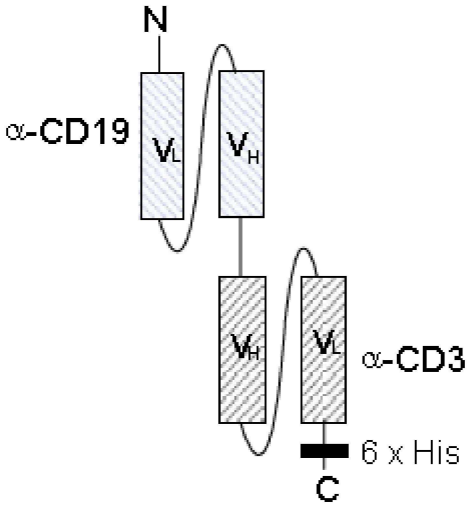
8.1.1 Description

Blinatumomab is a novel single-chain antibody derivative of the BiTE□ class. It is designed to target CD19 expressed on malignant B cells. It was developed by genetic engineering from 2 distinct parental murine monoclonal antibodies (mAbs): HD37, which recognizes the pan-B cell antigen CD19; and L2K-07, which specifically binds the T-cell receptor (TCR)-associated

complex, CD3. The single-chain variable fragments (scFv) of these antibodies are linked to form 1 single polypeptide chain.

Blinatumomab is a recombinant non-glycosylated protein, consisting of 504 amino acids with a molecular weight of approximately 55 kDa. The CD19-binding region of blinatumomab is positioned at the amino terminus, while the CD3-binding region is at the carboxy terminus. The 2 scFv are joined by a flexible linker consisting of glycine/serine amino acid residues. The domain structure of blinatumomab is shown in Figure 8-1.

Figure 8-1. Domain Structure of Blinatumomab (AMG 103)



8.1.2 **Form**

Blinatumomab is supplied in 4 mL single-use glass injection vials as a sterile, preservative-free, white to off-white lyophilized powder for reconstitution and administration by IV infusion. The lyophilized product is manufactured in 38.5 mcg vials of blinatumomab. Each vial contains the additional excipients and buffers listed below, pH 7.0:

Lyophilized Vial Presentations		
Blinatumomab content		38.5 mcg
Citric acid monohydrate		3.68 mg
Lysine hydrochloride		25.55 mg
Trehalose dihydrate		105.0 mg
Polysorbate 80		0.70 mg

8.1.3 **Storage and Stability**

Both the blinatumomab lyophilized Drug Product and IV Solution Stabilizer vials must be stored at 2°C to 8°C (36°F to 46°F) in their original outer package to maintain product integrity and prevent exposure to light.

Reconstituted vials should not be stored for longer than 4 hours between 22°C and 27°C (72°F and 81°F) or longer than 24 hours between 2°C and 8°C (36°F and 46°F).

Blinatumomab solution for infusion must be administered at ambient temperature and must not be kept at ambient temperature more than 48 hours. 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.

8.1.4 **Compatibility**

Blinatumomab will run through a dedicated central line and will not be combined with any additional agents.

8.1.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 **Availability**

Blinatumomab is an investigational agent and will be supplied free-of-charge from Amgen.
.

8.1.7 **Preparation**

To prepare blinatumomab for intravenous administration, the lyophilized powder is reconstituted with sterile Water for Injection (sWFI). The reconstituted solution is added to an infusion bag containing 0.9% NaCl primed with a product-specific stabilizer (IV Solution Stabilizer). The IV Solution Stabilizer functions to prevent adsorption of blinatumomab to surfaces of the infusion components.

The IV Solution Stabilizer is supplied in 10 mL single-use glass injection vials as a sterile, preservative-free, clear, colorless-to-slightly-yellow liquid concentrate. It consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride, and 0.1% (weight/volume [w/v]) polysorbate 80, pH 7. Following dilution in 0.9% NaCl, the ingredient concentrations are 25 mM L-lysine hydrochloride, 0.002% (w/v) polysorbate 80, and 0.5 mM citric acid monohydrate..

8.1.8 **Administration**

Subjects will receive premedication with dexamethasone 20 mg (or equivalent) intravenously 1 hour prior to the first dose of blinatumomab of each cycle, prior to a step dose (such as Cycle 1 day 8), or when restarting an infusion after an interruption of 4 or more hours. Blinatumomab will be administered as a continuous IV infusion through a central venous catheter at a constant flow rate using an infusion pump for a 42 day cycle. Blinatumomab will start with a 7 day infusion at 9mcg/d. If no dose limiting toxicity (table 6.1) after 7 days, the dose will be escalated to 28 mcg/d for 7 additional days. If no dose limiting toxicity (table 6.1) after 14 days, blinatumomab will be infused at a target dose of at 112mcg/d for 28 days.

Blinatumomab solution for infusion may be administered using IV bags and infusion lines made of polyolefin/polyethylene, ethylene vinyl acetate (EVA), or PVC non-DEHP. Infusion lines with an in-line 0.2 μm filter should be used.

8.1.9 **Ordering**

Blinatumomab will be provided by Amgen.

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 **Destruction and Return**

At the end of the study, unused supplies of blinatumomab should be returned to Amgen or destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Correlation of Response and CNS Toxicity With B:T Lymphocytes Ratio In Peripheral Blood Collection of Specimen(S).

A baseline B cell to T cell (B:T) ratio in peripheral blood at or below 1:10 has been identified as a predictive factor for occurrence of neurological AEs.(13) We will correlate baseline B cell to T cell (B:T) ratio in peripheral blood measured by flow cytometry with neurologic events in a descriptive manner. Flow cytometry will be performed at the enrolling institution per standard protocol.

10. STUDY CALENDAR

10.1 Pre-Treatment Evaluations -within 45 days of the start of protocol therapy, unless otherwise noted

- Signed inform consent document
- Vital signs, including height, weight, temperature, pulse, blood pressure, respiratory rate, and oxygen saturation
- Complete physical examination
- Medical history: Detailed documentation of disease and treatment history with outcomes.
- ECOG performance status
- Concurrent medical conditions.
- Concurrent medications within 30 days of C1D1
- CBC with differential.
- Serum chemistries: Electrolytes (sodium, potassium, chloride, and bicarbonate), calcium, magnesium, phosphate, blood urea nitrogen (BUN), creatinine, glucose, beta-2 microglobulin, lactate dehydrogenase (LDH) and liver function tests (aspartate aminotransferase (AST) and alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein, albumin, and total bilirubin.
- Coagulation studies including prothrombin time and partial thromboplastin time
- HBsAg, HBsAb, HBcAb, and HCV Ab. HBV DNA PCR in patients who are HbsAg negative but who are HBcAb positive. *Hepatitis serologies may have been performed any time within one year of protocol enrollment.*
- Full body CT (neck, chest, abdomen/pelvis) and full body PET scan (or preferably a single combined-modality PET-CT scan). Bi-dimensional measurement of up to 3 of the largest target lesions. *Scans must be performed within 30 days of initiation of therapy.*
- Measurements will be made by the DF/HCC tumor imaging metric core (TIMC)
- Paraffin-embedded tissue block from diagnostic biopsy specimen will be obtained when available for performance of correlative testing. If the paraffin embedded block cannot be obtained, then 6 unstained slides will be obtained, if available. Patients without available specimens will still be eligible for study.
- Serum pregnancy test –All females of childbearing potential should complete a serum pregnancy test within 7 days prior to the administration of blinatumomab on day 1 of cycle 1. The test will be repeated on day 1 of cycle 2.
- Baseline flow cytomety for B:T cell ratio

10.2 Evaluations During Treatment

10.2.1 The following laboratory assessments will be performed weekly during the first cycle and second cycle

- Hematology: CBC with differential
- Serum chemistries: Na, K, Cl, HCO3, glucose, blood urea nitrogen (BUN), creatinine, calcium, magnesium, phosphate, total bilirubin, AST, ALT, alkaline phosphatase, albumin, and total protein.
- Peripheral blood sample for flow cytomtery for B:T cell ration will be drawn on cycle 1 day 8
- Serum pregnancy test –All females of childbearing potential should complete a serum pregnancy test within 7 days prior to the administration of blinatumomab on day 1 of cycle 1. The test will be repeated on day 1 of cycle 2.

10.2.2 The following clinical assessments are to be performed on weekly every cycle (± 3 days). Procedures and examinations may be performed more frequently if clinically indicated:

- Brief physical examination
- Vital signs, including weight, temperature, pulse, blood pressure, respiratory rate, and oxygen saturation
- ECOG Performance Status;
- Recording of AEs (patients and/or family members will be instructed to telephone the site with any changes in mental or physical status or with any questions regarding treatment)
- Recording of concomitant medications.

10.2.3 The following objective disease assessments are to be performed within the 7 days prior to beginning cycle 2.

- Full body CT and PET scans (or preferably a single combined-modality PET-CT scan). Neck imaging is only required if baseline neck imaging showed lymphoma involvement.
- Bi-dimensional measurement of up to 3 of the largest target lesions.
- Measurements will be made by the DF/HCC tumor imaging metric core (TIMC).

10.3 Post Treatment Evaluations

- Subjects without progression will be seen every 3 months for the first 2 years with CT scans every 6 months. After 2 years, subjects will be seen every 6 months with CT scans annually through 5 years.

- Hematology: CBC with differential
- Serum chemistries: Na, K, Cl, HCO3, glucose, blood urea nitrogen (BUN), creatinine, calcium, magnesium, phosphate, total bilirubin, AST, ALT, alkaline phosphatase, albumin, and total protein.
- Brief physical examination
- Vital signs, including weight, temperature pulse, blood pressure, respiratory rate, and oxygen saturation
- ECOG Performance Status;
- Recording of AEs (patients and/or family members will be instructed to telephone the site with any changes in mental or physical status or with any questions regarding treatment)
- Recording of concomitant medications.
- Contrast enhanced CT scan of the chest, abdomen, and pelvis with tumor measurements will be performed every 6 months (+/- 7 days) beginning 6 months following the end of treatment restaging scan for two years and then annually through 5 years or until disease progression

10.4 End of study evaluations

When a patient is removed from study, end of study assessments are to be performed within 30 days (+/- 2 days). If the patient is not available, the reason for not completing the end of study assessments must be recorded in the patient's source documents.

The following clinical assessments will be performed:

- Full physical examination
- Weight and vital signs (blood pressure, pulse rate, respiratory rate, oxygen saturation, and temperature)
- ECOG Performance Status
- Recording of AEs
- Recording of concomitant medications

The following laboratory assessments will be performed:

- CBC with differential and platelet count
- Serum chemistries: Na, K, Cl, HCO3, glucose, blood urea nitrogen (BUN), creatinine, calcium, magnesium, phosphate, total bilirubin, AST, ALT, alkaline phosphatase, albumin, and total protein

Patients will be followed for 1 year after the last cycle of therapy for toxicity and duration of response (if applicable). The following procedures will be completed:

- Recording of AEs (patients and/or family members will be instructed to telephone the site with any changes in mental or physical status) for 90 days following their last dose of blinatumomab.

Visit evaluation schedule

	Baseline[1]	**Cycle 1**								**Cycle 2**						**Follow up visits**[12]	**End of study**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**14-24**	**25**
Day of cycle	**-45 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D85 (+/- 7)**	**D1**	**D8**	**D15**	**D22**	**D28**	**70 (+/- 7)**		
Demography/informed consent, Inclusion/exclusion criteria	X																
Relevant medical history/current medical conditions	X															X	X
Diagnosis and iNHL History including prior cancer therapy	X																
Vital signs, weight and physical examination[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (only at baseline)[2]	X																
ECOG performance status[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Staging[4]	X															X	X
Hematology and Biochemistry tests[5,7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation[6]	X																
Peripheral blood flow cytometry[8]	X		X														
Serum pregnancy test[9]	X									X							
Blinatumomab dosing		6 week continuous infusion								4 week continuous infusion							
Prior/concomitant medications[10]	Continuous																
Adverse events [11]	Continuous																

1. Baseline evaluations must be performed ≤ 45 days prior to cycle 1 administration of blinatumomab, unless otherwise stated.
2. Physical examination, vital signs, weight, height – Physical examinations, vital signs, and weight will be performed on the scheduled day, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated. If these baseline examinations were performed ≤ 72 hours prior to the first dose of blinatumomab, they need not be repeated on day 1 of cycle 1. Vital signs (weight, temperature, respiratory rate, oxygen saturation, sitting blood pressure, and sitting pulse) should be performed weekly unless otherwise indicated. .
3. ECOG performance status –Assessment of ECOG Performance Status will be performed on the scheduled day, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated. If the baseline assessment was performed ≤ 72 hours prior to the first dose of blinatumomab, then it does not need to be repeated on day 1 of cycle 1.
4. PET/CT Scan will be performed at baseline, 6 weeks after completion of the first cycle, and 6 weeks after completion of the second cycle. Staging will then be performed with CT scans of the chest, abdomen, and pelvis every 6 months for the first 2 years and then annually for 5 years or until progression. Neck CT after baseline study is only required if neck was involved on baseline imaging.
5. Hematology –Hematology should be performed at baseline, weekly during cycle 1and 2, every 3 months during follow up, and at the time of study treatment completion
6. Coagulation –The coagulation profile must be performed at baseline only and repeated only as clinically indicated
7. Biochemistry –Biochemistry should be performed at baseline, weekly during cycle 1and 2, every 3 months during follow up, and at the time of study treatment completion. Subjects will have hepatitis serologies, LDH, and beta-2 microglobulin drawn at baseline.
8. Peripheral blood flow cytometry for calculation of absolute b and t lymphocytes should be performed at baseline and on day 8 of cycle 1.
9. Serum pregnancy test –All females of childbearing potential should complete a serum pregnancy test within 7 days prior to the administration of blinatumomab on day 1 of cycle 1. The test will be repeated on day 1 of cycle 2.

10. Prior/concomitant medications –Record all medications administered ≤ 30 days prior to the administration of blinatumomab. Record all medications taken during the study on the Concomitant Medications eCRF.
11. Adverse events –. Subjects must be instructed to notify the investigator concerning any undesirable symptoms or side-effects while on study. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment. Antineoplastic therapies since discontinuation of study drug – All cancer medications/therapies given to a subject after the last dose of study drug must be recorded in the Antineoplastic therapies since discontinuation of study drug eCRF. This should be done monthly for the first 6 months, then once every 3 monthly thereafter until disease progression or subject receives new antineoplastic therapies whichever happens first.

12. Subjects without progression will be seen every 3 months for the first 2 years with CT scans every 6 months. After 2 years, subjects will be seen every 6 months with CT scans annually through 5 years.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effects

Response and progression will be evaluated in this study using the modified Cheson criteria for lymphoma response.(14)

- Patients will be assessed for response at 6 weeks after the conclusion of cycle 1 (within 7 days of day 84) using a CT scan of the chest, abdomen and pelvis, as well as a full body PET scan (preferably a combined modality PET-CT scan will be used). Neck CT only required if involved on baseline imaging.

- Patients who continue on study (non-progressors) will be re-evaluated at 6 weeks after the conclusion of cycle 2 (within 7 days of day 168) using a CT scan of the chest, abdomen and pelvis, as well as a full body PET scan (preferably a combined modality PET-CT scan will be used). Neck CT only required if involved on baseline imaging.

- Patients who continue on study (non-progressors) after 2 cycles will be assessed using a CT scan of the chest, abdomen and pelvis every 6 months for 2 years and then annually for 5 years or until progression. Neck CT only required if involved on baseline imaging.

11.2 Definitions

Evaluable for toxicity. All patients who receive at least one dose of study drug will be evaluable for toxicity.

Evaluable for objective response. Only those patients who have received at least one complete cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. Subjects removed from study for disease progression prior to a full cycle of therapy will also be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

11.3 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques (CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

11.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

CT and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

11.5 Response Criteria

11.5.1 Complete Response (CR)

CR requires **all** of the following:

1. PET positive prior to therapy: mass of any size permitted if PET negative with a score of 3 or less on the Deauville five point scale.

   1-no uptake or no residual uptake

   2-slight uptake, but below mediastinal blood pool

   3-uptake above mediastinal, but below or equal to uptake in the liver

   4-uptake slightly to moderately higher than liver

   5-markedly increased uptake or any new lesion

New sites of FDG-avidity felt unrelated to lymphoma (Deauville 3 or less) will be considered CR but imaging should be repeated 6-8 weeks later to insure resolution of inflamamtory changes.

2. Variably FDG-avid or PET negative prior to therapy: regression to normal size on CT (≤ 1.5 cm in their greatest transverse diameter for nodes ≥ 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to <1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination.

11.5.2 Partial Response (PR)

1. ≥50% decrease in SPD of up to 6 largest dominant masses
   a. FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved site with a Deauville score >3
   b. Variably FDG-avid or PET negative: regression on CT

2. No new sites of disease or increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by at least 50% in the SPD.

11.5.3 Stable Disease (SD)

Stable disease is defined as less than a PR (see above) but is not progressive or relapsed disease FDG-avid or PET positive prior to therapy: PET positive at prior sites of disease and no new sites on CT or PET. Variably FDG-avid or PET negative: no change in size of previous lesions on CT

11.5.4 Progressive Disease (PD) or Relapsed Disease (RD):

1. Appearance of a new PET positive (Deauville 4 or 5) lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node > 1 cm in short axis..
2. >50% increase from nadir in the SPD of any previous lesions

New sites of FDG-avidity felt unrelated to lymphoma (Deauville 3 or less) not be considered PD or ED, but imaging should be repeated 6-8 weeks later to insure resolution of inflamamtory changes.

11.6 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.7 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of documentation of progression or death.

11.8 Time to relapse (TTR) -

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Primary
- Overall Response Rate by the revised response criteria for malignant lymphoma (2014)

Secondary
- Clinical: Duration of response, time to response, progression-free survival, and overall survival
- Safety: Discontinuation of drug due to toxicity, adverse events

Exploratory
- Association of response and CNS toxicity with B:T lymphocytes ratio in peripheral blood
- Association of MRD status with progression free and overall survival

13.2 Sample Size, Accrual Rate and Study Duration

We will use a Simon two-stage design to assess whether the results of this regimen are consistent

with an overall response rate of 65%, which serves as our alternative hypothesis. We have identified an ORR of 40% as the null hypothesis. We will initially enroll 13 subjects. If 6 or more subjects achieve a response, we will enroll an additional 15 subjects. If 15 or more subjects of 28 achieve a response, we will consider the regimen worthy of further study. The probability that we observe 15 or more responses if the true but unknown response rate is 40% is 0.093; this serves as the significance level of the test. The probability that we observe 15 or more responses if the true but unknown ORR rate is 65% is 0.904, which serves as the power of the test. The study will stop early under the null hypothesis of 40% with probability 0.57 and under the alternative hypothesis of 65% with probability 0.05. It is anticipated that a minimum of 8-10 subjects will enroll per year with enrollment completing with in 3 years. Subjects without progressive disease will be followed for a total of 5 years with an anticipated study duration of 8 years.

13.3 Reporting and Exclusions

13.3.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with study drug.

13.3.2 Evaluation of the Primary Efficacy Endpoint

Only those subjects who have measurable disease and have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. Subjects who exhibit objective disease progression prior to removal from study will also be considered evaluable.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

REFERENCES

1. American Cancer Society. Cancer facts and figures 2012. . 2012.

2. Anderson JR, Armitage JO, Weisenburger DD, for the Non-Hodgkin's Lymphoma Classification Project. Epidemiology of the non-Hodgkin's lymphomas: Distributions of the major subtypes differ by geographic locations. Annals of Oncology. 1998 July 01;9(7):717-20.

3. Swerdlow S, Campo E, Harris NL, Jaffe ES, Pileri S, Stein H, et al, editors. WHO Classification of Tumours of Haematopoetic and Lymphoid Tissue. Lyon: IARC; 2008.

4. Ardeshna KM, Qian W, Smith P, Warden J, Stevens L, Pocock CF, et al. An Intergroup Randomised Trial of Rituximab Versus a Watch and Wait Strategy In Patients with Stage II, III, IV, Asymptomatic, Non-Bulky Follicular Lymphoma (Grades 1, 2 and 3a). A Preliminary Analysis. ASH Annual Meeting Abstracts. 2010 November 19;116(21):6.

5. Kahl BS, Hong F, Williams ME, Gascoyne RD, Wagner LI, Krauss JC, et al. Results of Eastern Cooperative Oncology Group Protocol E4402 (RESORT): A Randomized Phase III Study Comparing Two Different Rituximab Dosing Strategies for Low Tumor Burden Follicular Lymphoma. ASH Annual Meeting Abstracts. 2011 November 18;118(21):LBA-6.

6. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood. 2005 Feb 15;105(4):1417-23.

7. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma. N Engl J Med. 2002 January 24;346(4):235-42.

8. Rummel MJ, Niederle N, Maschmeyer G, Banat AG, von Gruenhagen U, Losem C, et al. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent and mantle cell lymphomas (MCL): Updated results from the StiL NHL1 study. ASCO Meeting Abstracts. 2012 June 21;30(18_suppl):3.

9. Schlereth B, Quadt C, Dreier T, Kufer P, Lorenczewski G, Prang N, et al. T-cell activation and B-cell depletion in chimpanzees treated with a bispecific anti-CD19/anti-CD3 single-chain antibody construct. Cancer Immunol Immunother. 2006 May;55(5):503-14.

10. Dreier T, Baeuerle PA, Fichtner I, Grun M, Schlereth B, Lorenczewski G, et al. T cell costimulus-independent and very efficacious inhibition of tumor growth in mice bearing subcutaneous or leukemic human B cell lymphoma xenografts by a CD19-/CD3- bispecific single-chain antibody construct. J Immunol. 2003 Apr 15;170(8):4397-402.

11. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. J Clin Oncol. 1999 April 1;17(4):1244.

12. Viardot A, Goebeler M, Scheele JS, Zugmaier G, Noppeney R, Knop S, et al. Treatment of Patients with Non-Hodgkin Lymphoma (NHL) with CD19/CD3 Bispecific Antibody Blinatumomab (MT103): Double-Step Dose Increase to Continuous Infusion of 60 {micro}g/m2/d Is Tolerable and Highly Effective. ASH Annual Meeting Abstracts. 2010 November 19;116(21):2880.

13. Zugmaier G, Nagorsen D, Klinger M, Bargou RC, Goebeler M, Viardot A, et al. Identification of a Predictive Factor for Reversible Neurological Adverse Events in a Subset of Non-Hodgkin Lymphoma Patients Treated with CD19-Specific BiTE (R) Antibody Blinatumomab. ASH Annual Meeting Abstracts. 2009 November 20;114(22):4793.

14. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

APPENDIX A PERFORMANCE STATUS CRITERIA

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

Appendix B – Amgen recomendations for notification of adverse events

Table 1- For Interventional studies with Amgen IMP*:

Safety Data	Timeframe for Submission to Amgen
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Sent to Amgen at time of regulatory submission
Serious Adverse Events (SAEs)	Cumulative line listing every 6 months
Adverse Events not meeting serious criteria	Not required, unless contractually specified per study
Events of Interest	Not required, unless contractually specified per study
Pregnancy/Lactation	Within 10 days of Sponsor awareness
Event listing for reconciliation	As specified per contract, at study close-out at a minimum

*Specific requirements are to be outlined in the Research Agreement

Table 2 - For all studies – aggregate reports*:

Safety Data	Timeframe for submission to Amgen
Annual Safety Report (eg, EU Clinical Trial Directive [CTD] Annual Safety Report, and US IND Annual Report)	**Annually**
Other Aggregate Analyses (any report containing safety data generated during the course of a study)	**At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc)
Final (End of Study Report, including: • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	**At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc) but not later than 1 calendar year of study completion

*Specific requirements are to be outlined in the Research Agreement