

A Pivotal Multicenter Trial of Moxetumomab Pasudotox in Relapsed/Refractory Hairy Cell Leukemia

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PRÉCIS

Background:

- Hairy cell leukemia (HCL) is an indolent B-cell leukemia comprising 2% of all leukemias ([Bouroncle, 1994](#); [Kreitman and Cheson, 1999](#)), or approximately 900 of the 44,000 new cases of leukemia/year in the US ([Jemal et al, 2007](#)).
- Over the last two decades, immunotoxin research has accumulated to support a role for CD22-targeted therapy in the treatment of HCL.
- Moxetumomab pasudotox is a recombinant immunotoxin containing a variable domain (Fv) fragment of an anti-CD22 monoclonal antibody and truncated *Pseudomonas* exotoxin.
- Moxetumomab pasudotox has demonstrated a high complete response (CR) rate in patients with chemoresistant HCL and has shown activity in pediatric acute lymphoblastic leukemia as well.
- Modification of the structure of moxetumomab pasudotox has greatly improved binding and cytotoxicity toward CD22 expressing malignant cells compared to the precursor molecule. Preclinical and clinical studies have demonstrated that this increase in binding affinity results in improved antitumor activity and tolerability.
- At the time of study start, 114 patients have been treated with moxetumomab pasudotox, including 48 with HCL. Moxetumomab pasudotox was generally well tolerated in HCL patients with no maximum tolerated dose (MTD) defined and some patients treated for over a year.
- Currently there are no approved agents with significant efficacy for HCL patients after failure of standard therapy.

Objectives:

- The primary objective of this study is to determine the rate of durable complete response (CR) in multiply relapsed HCL with moxetumomab pasudotox. To meet the primary endpoint, patients will need to meet standard criteria for CR by analysis of blood, bone marrow and imaging, and maintain a hematologic remission (HR), namely the blood counts needed for CR, for >180 days.
- Secondary objectives include determining the overall response rate (ORR), progression-free survival (PFS), time to treatment failure (TTF), duration of responses (CR and partial response [PR]), confirming tolerability and safety, and evaluating immunogenicity and pharmacokinetics of moxetumomab pasudotox.

Eligibility:

- Histologically confirmed, immunotoxin-naïve HCL or HCL variant with a need for therapy based on at least one of the following criteria:
 - neutrophils $< 1.0 \times 10^9/L$
 - platelets $< 100 \times 10^9/L$
 - hemoglobin $< 10 \text{ g/dL}$
 - symptomatic splenomegaly.
- Have had at least 2 prior systemic therapies, including 2 courses of a purine nucleoside analog (PNA), or 1 course of either rituximab or BRAF inhibitor following a single prior course of PNA.
- Age ≥ 18 years.

Design:

- This is a multicenter, single-arm study of moxetumomab pasudotox in patients with relapsed or refractory HCL.
- Seventy- seven patients will be enrolled to receive $40 \mu\text{g/kg}$ moxetumomab pasudotox, intravenous (IV) on Days 1, 3 and 5 of each 28 day cycle for a maximum of 6 cycles or until disease progression, unacceptable toxicity occurs, the subject begins alternate therapy, or documented CR (for subjects who have no assessable minimal residual disease and not to exceed 6 cycles). If ≤ 2 of the first 25 patients do not achieve durable CR, no additional patients will be accrued.
- The primary endpoint is to determine the durable complete response (CR) rate of moxetumomab pasudotox with a minimum duration of >180 days. A durable CR will be defined as one in which HR, namely the blood counts required for CR, are maintained for >180 days. Disease assessments for determining CR include bone marrow examination, cross-sectional imaging, and peripheral blood evaluation. Recurrent sustained (non-transient) cytopenias, particularly during the first 6 months of CR, will prompt a repeat bone marrow study to confirm relapse. The durable CR rate and its 95% confidence interval (CI) will be constructed using the exact probability method (Clopper-Pearson exact interval) in the Intent-to-Treat population. With 77 patients enrolled, there will be 90% power to detect a difference between 28% and 13% (expected CR rate from best alternative non-chemotherapy treatment, rituximab) durable CR rates using a 2-sided significance level of 0.05.
- The overall estimated accrual is 80 to allow for a small screen-failure rate.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	antidrug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CK	creatinine kinase
CLS	capillary leak syndrome
CR	complete response
eCRF	electronic case report form
CRP	C reactive protein
CT	computed tomography
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ft4	free thyroxine
Fv	variable domain
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBcAg	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCL	hairy cell leukemia
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPF	high power field
HR	hematologic remission
HUS	hemolytic uremic syndrome
INR	international normalized ratio
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin

Abbreviation or Specialized Term	Definition
IRB	Institutional Review Board
IV	Intravenous(ly)
LDH	lactate dehydrogenase
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAb	neutralizing antidrug antibodies
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NSAIDs	non-steroidal anti-inflammatory medications
ORR	overall response rate
PD	progressive disease
PFS	progression-free survival
PFT	pulmonary function test
PI	principal investigator
PK	pharmacokinetics
PNA	purine nucleoside analog
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
SAE	serious adverse event
SD	stable disease
SID	subject identification
sIg	surface immunoglobulin
TLS	tumor lysis syndrome
TSH	thyroid stimulating hormone
TTF	time to treatment failure
ULN	upper limit of normal
US	United States

1 OBJECTIVES

1.1 Primary Objectives

- The primary objective of this study is to determine the rate of durable complete response (CR) in multiply relapsed hairy cell leukemia (HCL) with moxetumomab pasudotox. To meet the primary endpoint, patients will need to meet standard criteria for CR by analysis of blood, bone marrow and imaging, and maintain a hematologic remission (HR), the blood counts needed for CR, for >180 days.

1.2 Secondary Objectives

- Determine the overall response rate (ORR), progression-free survival (PFS), time to treatment failure (TTF), and duration of responses (CR and partial response [PR]).
- Confirm the tolerability and safety of moxetumomab pasudotox in patients with HCL.
- Evaluate immunogenicity and pharmacokinetics (PK) of moxetumomab pasudotox.

2 BACKGROUND

2.1 Hairy Cell Leukemia

HCL is an indolent B-cell leukemia comprising 2% of all leukemias ([Bouroncle, 1994](#); [Kreitman and Cheson, 1999](#)), or approximately 900 of the 44,000 new cases of leukemia/year in the United States (US) ([Jemal et al, 2007](#)). Patients present with pancytopenia and splenomegaly, and the malignant cells have cytoplasmic projections resembling hairs ([Sharpe and Bethel, 2006](#); [Cawley, 2006](#)). By flow cytometry, B-cell antigens FMC7, cluster of differentiation (CD) 11c, CD20, CD22 and surface immunoglobulin (sIg) are strongly positive, and in the typical or classic form, CD103, CD25 and CD123 are also positive ([Robbins et al, 1993](#); [Matutes, 2006](#); [Matutes et al, 2008](#)). The median survival of HCL without effective treatment is about 4 years ([Golomb et al, 1978](#)), and early treatments including splenectomy and interferon were of modest benefit ([Habermann, 2006](#)). Treatment of HCL was revolutionized with the advent of purine nucleoside analog (PNA) therapy in the late 1980s. Response rates for PNA averaged 70% in the primary setting and ranged from 70-90% among patients that relapsed ([Cheson et al, 1998](#); [Piro et al, 1990](#); [Quesada et al, 1984](#); [Rai et al, 1995](#); [Ratain et al, 1995](#); [Saven et al, 1998](#); [Tallman et al, 1996](#)). However, the responses were less durable in the relapse setting. Furthermore, side effects including bone marrow aplasia, persistent CD4 lymphopenia, infections and neurotoxicity ([Cheson et al, 1998](#); [Betticher et al, 1994](#); [Cheson, 1995](#); [Legrand et al, 1997](#); [Seymour et al, 1994](#)) associated with the repetitive administration of PNA signify a need for

the development of new treatments for patients who have relapsed following PNA therapy or who are refractory to PNA treatment.

2.2 IND Agent - Moxetumomab pasudotox

Over the last two decades, developments in immunotoxin research have accumulated to support a role for CD22-targeted therapy in the treatment of HCL. An initial construct, BL22 (CAT-3888), is a recombinant immunotoxin containing a variable domain (Fv) fragment of an anti-CD22 monoclonal antibody and truncated *Pseudomonas* exotoxin. In Phase 1 and 2 trials, BL22 had 47-61% CR rates and 72-81% ORR in chemoresistant HCL ([Kreitman et al 2001](#); [Kreitman et al, 2005](#); [Kreitman et al, 2009](#)).

Moxetumomab pasudotox (HA22, CAT-8015), is a high affinity (14-fold improved) mutant of BL22, differing by 3 amino acids ([Salvatore et al, 2002](#)). [REDACTED]

[REDACTED] In HCL, the agent was tested in a Phase 1 trial in multiply relapsed patients. The results of the Phase 1 trial in the first 28 patients were published in the *Journal of Clinical Oncology* ([Kreitman et al, 2012](#)). [REDACTED]

[REDACTED]

[REDACTED]

Benefit in HCL therapy is not limited to CR. Patients with advanced HCL are at risk of dying of cytopenias due to bleeding or infection, due to thrombocytopenia or neutropenia. Symptoms may include abdominal pain and weight loss due to splenomegaly, and fatigue from anemia. Lymphocytosis and adenopathy are associated with more advanced disease and worse outcome ([Mercieca et al, 1992](#); [Mercieca et al, 1994](#); [Mercieca et al, 1996](#); [Robak et al, 1999](#)). Therefore achievement of durable PR, which requires improvement or resolution of cytopenias, lymphocytosis, splenomegaly and adenopathy, is considered beneficial in HCL. Conversely, the difference between achievement of PR and CR is limited to the presence and absence of marrow disease assessed by bone marrow biopsy, and the achievement of CR may be associated with a longer TTF than achievement of PR.

[REDACTED]

Given the efficacy and safety profile associated with moxetumomab pasudotox, this pivotal trial will determine the durable CR rate of the experimental agent in the setting of multiply-relapsed or PNA refractory HCL.

2.3 Rationale

Standard first- and second-line treatment for HCL. Starting at the time HCL was initially described 54 years ago up until the 1980s, the outcome for patients with the disease was poor with a median survival of 4 years ([Golomb et al, 1978](#)). In the early 1980s, splenectomy and alpha interferon were noted to have efficacy in inducing remissions, mostly partial, in a significant percent of patients ([Habermann, 2006](#)). However these treatments are now mainly of historical interest because of the effectiveness of PNA, demonstrated in the late 1980s and early 1990s. Purine analogs cladribine and pentostatin each showed durable CR rates of 72-89% in first line therapy ([Cheson et al, 1998](#)), with most of these patients remaining in CR after 4-8 years of follow-up. In a randomized trial, pentostatin was found to be far superior to interferon, with CR rates of 79% vs 11%, and no patient responded after crossing over from pentostatin to interferon ([Grever et al, 1995](#)). Today, PNA remains the accepted standard HCL treatment not only in 1st line, but also in 2nd line, since 62-69% of patients achieve CR with PNA in second line ([Saven et al, 1998](#)).

Purine analogs for multiply relapsed HCL.

Data from small groups of patients suggest 50% or less of patients may achieve CR from repeated courses of PNA in > 2second line ([Else, et al, 2009](#); [Saven et al, 1998](#)), and these retrospective data contains a strong selection bias because patients having more durable remissions in second line are more likely to receive PNA in third or later lines. Anecdotally, responses to 1 PNA are reported after failure of the other ([Saven and Piro, 1993](#); [Chadha et al, 2005](#)), but overall, the lower response rate observed in repeated courses of PNA is not improved if a different PNA is used ([Else, et al, 2009](#)).

Moreover, the toxicity of multiple courses of PNA can be both substantial and long-lasting. Even 1 course of either cladribine or pentostatin is reported to result in decreases in CD4+ lymphocytes lasting up to 4 years ([Seymour et al, 1994](#); [Seymour et al, 1997](#)), and damage to stem cells may be irreversible and lead to myelodysplasia ([Kroft et al, 1997](#); [Leleu et al, 2009](#);

[Todd et al, 2002](#)). Still further, PNA cause neuropathy in about 15% of patients after a single course ([Cheson et al, 1994](#)). These long-lasting toxicities of PNA accumulate with multiple courses and thus, decreasing efficacy combined with increased toxicity, argue against their repeated use in most situations. Rather, multiply relapsed HCL patients are in particular need of effective non-chemotherapy options.

Rituximab for HCL depending on extent of cytopenias and prior therapy. Though not approved for HCL by the US Food and Drug Administration, the most widely used non-chemotherapy option at this time for HCL is rituximab, which binds to and kills CD20+ cells by inducing apoptosis or by mediating complement and antibody dependent cytotoxicity (CDC and ADCC, respectively) ([Villamor et al, 2003](#)). CR rates among the 6 reported rituximab studies in HCL (10-25 patients each, total 97) vary from 10 to 54% ([Hagberg and Lundholm, 2001](#); [Lauria et al, 2001](#); [Nieva et al, 2003](#); [Thomas et al, 2003](#); [Angelopoulou et al, 2008](#); [Zenhausern et al, 2008](#)).

[REDACTED]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[REDACTED]

[REDACTED]

Subjects will be treated for up to a total of 6 cycles in the study. [REDACTED]

[REDACTED]

[REDACTED] The study design also allows subjects maintaining blood counts needed for CR for at least 4 weeks to have an interim disease assessment. If this assessment shows CR without detectable MRD, therapy will stop. [REDACTED]

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Inclusion Criteria

1. Patients must have histologically confirmed HCL or HCL variant with a need for therapy based on at least one of the following criteria:
 - a. neutrophils $< 1.0 \times 10^9/L$
 - b. platelets $< 100 \times 10^9/L$
 - c. hemoglobin $< 10 \text{ g/dL}$
 - d. symptomatic splenomegaly
2. Patients must be Pseudomonas-immunotoxin naïve
3. Patients must have received at least 2 prior systemic therapies, including 2 courses of courses of a PNA, or 1 course of either rituximab or BRAF inhibitor following a single prior course of PNA.
4. Men or women age ≥ 18 years. Because this disease does not generally occur in children, children are excluded from this study.
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 ([Appendix 2](#)).
6. Patients must have adequate organ function as defined below:
 - a. total bilirubin $\leq 1.5 \text{ mg/dL}$, unless consistent with Gilbert's (ratio between total and direct bilirubin > 5)
 - b. AST and ALT $\leq 3 \times$ upper limit of normal (ULN)
 - c. alkaline phosphatase $\leq 2.5 \text{ ULN}$
 - d. serum creatinine $\leq 1.5 \text{ mg/dL}$ or creatinine clearance $\geq 60 \text{ mL/min}$ as estimated by the Cockcroft-Gault equation ([Appendix 3](#))
7. Prothrombin time (PT)/international normalized ratio (INR) or partial thromboplastin time (PTT) $< 2.5 \text{ ULN}$, fibrinogen ≥ 0.5 lower limit of normal; if on warfarin, INR < 3.5 , if on any other anticoagulation, PT $< 2.5 \times$ baseline
8. Ability to understand and the willingness to sign a written informed consent document.
9. Life expectancy ≥ 6 months.
10. Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception prior to study entry and or the duration of study participation, and must agree to continue using such precautions for 4 months after completion of moxetumomab pasudotox administration; cessation of

contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

- a. Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are premenarchal or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
 - b. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Effective methods of contraception are described in [Table 3.1.1-1](#). Not all methods of contraception are highly effective. Female subjects must use a hormonal method in addition to a barrier method alone, to minimize the chance of pregnancy.
 - c. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
11. Nonsterilized males who are sexually active with a female partner of childbearing potential must use an effective method of contraception ([Table 3.1.1-1](#)) from Day 1 for 90 days after receipt of the final dose of investigational product. It is required that a female partner of a male subject also use an effective method of contraception throughout this period.

Table 3.1.1-1 Effective Methods of Contraception

Barrier Methods	Hormonal Methods
<ul style="list-style-type: none"> • Male condom plus spermicide ^{a, b} • Copper T intrauterine device • Levonorgestrel-releasing intrauterine system) (eg, Mirena[®]) ^c 	<ul style="list-style-type: none"> • Implants • Hormone shot or injection • Combined pill • Minipill ^b • Patch

^a Female partners of male subjects must use an effective method of birth control.

^b Not highly effective (< 1% pregnancy rate per year) when used as the only method of birth control.

^c This is also considered a hormonal method.

3.1.2 Exclusion Criteria

1. Patients who have had chemotherapy, immunotherapy or radiotherapy within 4 weeks prior to initiation of treatment.
2. Patients who are receiving any other investigational agents.
3. Patients 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 (AEs).
4. Patients with retinal or choroidal detachment identified during the screening ophthalmologic evaluation.

5. Pregnant or breastfeeding females. [REDACTED]
6. Positive for Hepatitis B core antibody or surface antigen unless the patient is on Lamivudine or Entecavir and Hepatitis B Viral deoxyribonucleic acid (DNA) load is < 2000 IU/mL.
7. Active second malignancy requiring treatment other than minor resection of indolent cancers like basal cell and squamous skin cancers.
8. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled hypertension, cardiac arrhythmia, malaria infection, or psychiatric illness/social situations that would limit compliance with study requirements.
9. Known human immunodeficiency virus (HIV)-positive patients unless taking appropriate anti-HIV medications with a CD4 count of > 200 [REDACTED]
10. History of allogeneic bone marrow transplant.
11. Patients with history of both thromboembolism and known congenital hypercoagulable conditions.
12. Uncontrolled pulmonary infection, pulmonary edema
13. Oxygen saturation at rest < 88% measured by pulse oximetry or PaO₂ ≤ 55 mm Hg
14. Serum albumin < 2 g/dL
15. Radioimmunotherapy within 2 years prior to enrollment in the study.
16. Absolute neutrophil count (ANC) < 1.0 x 10⁹/L, or platelet count < 50 x 10⁹/L, unless judged by the investigator to be due to underlying disease (ie, potentially reversible with anti-neoplastic therapy). A patient will not be excluded because of pancytopenia ≥ Grade 3, or erythropoietin dependence, if due to disease, based on the results of bone marrow studies.
17. Patients with < 50% of predicted forced expiratory volume (FEV1) or < 50% of predicted diffusing capacity for carbon monoxide, corrected for hemoglobin concentration and alveolar volume (DLCO). Note: Patients with no prior history of pulmonary illness are not required to have pulmonary function testing (PFT). Forced expiratory volume will be assessed after bronchodilator therapy.
18. Patients with history of thrombotic microangiopathy or thrombotic microangiopathy / HUS.
19. Patients with corrected QT interval (Frederica) elevation > 500 msec (manually over-read by medically qualified person) based on at least two separate 12-lead ECGs.
20. Patients on high dose estrogen (defined as > 0.625 mg/day of an estrogen compound).
21. Patients with clinical evidence of disseminated intravascular coagulation (Grade 3-4).

3.2 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. No clinically important sex/gender and/or race/ethnicity differences are expected from the intervention effect.

3.3 Protocol Evaluation

3.3.1 Performed Within 4 Weeks Prior to Treatment

- Informed consent
- Demographics
- Performance status (ECOG)
- Vital signs including temperature, blood pressure (BP), pulse rate, respiratory rate, and pulse oximetry
- Orthostatic BP
- Height
- Weight
- Baseline AEs and concurrent medications, then monitored continuously after enrollment
- History and physical examination, query for visual symptoms
- Complete blood count (CBC) with differential and peripheral blood smear
- Chem7 (sodium, potassium, chloride, bicarbonate, creatinine, glucose, blood urea nitrogen [BUN]), albumin, calcium, magnesium, phosphorus, AST (SGPT), ALT (SGOT), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, alkaline phosphatase, and uric acid
- Creatine kinase (CK)
- Triglycerides
- Cholesterol
- GGT
- Serum human chorionic gonadotropin (HCG) (in females of childbearing potential only)
- Urinalysis
- PT/PTT/Fibrinogen
- Serum ferritin
- 
- Computed tomography (CT) scan or magnetic resonance imaging (MRI) to evaluate organomegaly and/or lymph nodes (does not need to be repeated if performed within

8 weeks prior to treatment). Note: Subjects enrolled in Germany will utilize MRI for all radiographic assessments (CT not permissible).

- Bone marrow biopsy and aspirate (does not need to be repeated if performed within 8 weeks prior to treatment) for analysis by flow cytometry/sequencing.
- 12-lead electrocardiogram (ECG) (analyzed by central vendor, ERT)
 - The ERT-ECG machine, training on the proper usage of the ERT-ECG machine, and methods of submission of reports will be provided by ERT. Submission of ECG reports will be transmitted via fax or via FedEx to MedImmune in accordance with the instructions provided in the ERT training session and outlined in the ERT user manual.
- Thyroid stimulating hormone (TSH)
- Free thyroxine (fT4)
- C reactive protein (CRP)
- Haptoglobin
- Serum amylase
- Serum lipase
- [REDACTED]
- [REDACTED]
- Immunoglobulin G (IgG), IgA and IgM
- For patients with prior history of pulmonary illness; FEV1 and DLCO \geq 50% of predicted are required for enrollment
- Ophthalmologic Exam (slit lamp and fundus)
- Serum and urine protein electrophoresis
- Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb)
- Hepatitis B Viral DNA load (if HBsAg is positive)
- Hepatitis C antibody
- Human leukocyte antigen (HLA) typing (central lab analysis)
- Complement C3, C4, CH50

3.3.2 Pre-Cycle before Subsequent Cycles (Day -3 to Day 1)

- Physical exam, query for visual symptoms
- Performance status (ECOG)
- Weight (can be obtained on Day -4 to Day 1) - do not change dose during a cycle; dose should be adjusted for weight change \geq 10% from screening in subsequent cycles.

- AEs and concurrent medications
- [REDACTED]
- [REDACTED]
- Uric acid, creatine kinase (CK or creatinine phosphokinase), GGT, PT, Haptoglobin
- 12-lead ECG analyzed by central vendor, ERT.

3.3.3 During Cycle

- Day 1 (Prior to dosing)
 - Patients should be asked about visual symptoms and reminded to report any visual symptoms during the cycle. New visual symptoms of Grade 2 or greater should be evaluated with a full ophthalmologic assessment.
 - [REDACTED]
- Days 1, 3, and 5
 - AEs and concurrent medications
 - CBC with differential and peripheral blood smear
 - Chem7 (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine)
 - mineral panel (calcium, magnesium, phosphorus, albumin)
 - hepatic panel (AST-SGPT, ALT-SGOT, total bilirubin, direct bilirubin, alkaline phosphatase)
 - LDH
 - Urinalysis (Day 1 only)
 - Vital signs including pulse oximetry
 - Physical exam, query for visual symptoms
 - Orthostatic BP
 - Moxetumomab pasudotox dosing
- Days 1 and 5
 - 12-lead ECG (analyzed by central vendor, ERT), 30-60 minutes post end of infusion (Cycle 1 only)
 - PK (EDTA)
 - Day 1 pre (Odd cycles and Cycle 2)
 - Day 1 immediately post (Odd cycles and Cycle 2)
 - Day 1, 3 hours post (Cycles 1 and 2)
 - Day 5 pre, immediately post, 1 hour, 3 hours, 6 hours post (Cycle 1 only)
- Day 8 (±1 day): CBC with differential and peripheral blood smear , Chem7, mineral panel, hepatic panel, LDH, vital signs, orthostatic BP, weight, AEs, concurrent medications [REDACTED]

- Recommended on Days 15 and 21 (each ± 2 days): CBC with differential and peripheral blood smear, Chem 7 (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine), mineral panel (calcium, magnesium, phosphorus, albumin), hepatic panel (AST-SGPT, ALT-SGOT, total bilirubin, direct bilirubin, alkaline phosphatase), LDH, AEs, concurrent medications and vital signs
- [REDACTED] IgA, IgG, IgM, C3, C4, and CH50 should be repeated upon both diagnosis and resolution of HUS and $>$ Grade 2 CLS. Measurement of tumor burden is also recommended, but not required, in the event of HUS

Interim Disease Assessment (Optional)

- During treatment and prior to completion of 6 cycles of therapy, if blood counts are consistent with CR for at least 4 weeks, an interim disease assessment may be performed at the discretion of the investigator. All assessments listed in Section 3.3.4.1 are required if an optional interim disease assessment is performed. Imaging (CT or MRI) and ophthalmologic examination may be deferred for up to 7 days until after the bone marrow aspirate and biopsy if CR without MRD is confirmed. For a response less than CR without MRD, therapy should resume and imaging and ophthalmologic examination may be deferred (if not performed concurrently with the bone marrow examination) until the end of treatment assessment.

3.3.4 Tests in Follow-up After Treatment Ends:

3.3.4.1 All patients 28-42 days after the first day of dosing of prior cycle (end of treatment assessment)

- History and physical exam, concurrent medications, AEs, performance status (ECOG)
- Pulse Oximetry with vital signs and weight
- Ophthalmologic exam (slit lamp and fundus)
- 12-lead ECG (analyzed by central vendor, ERT)
- Imaging with CT or MRI for lymphadenopathy and organomegaly
- Bone marrow biopsy and aspirate with flow cytometry/sequencing
- CBC with differential (no peripheral blood smear)
- Chem 7 (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine)
- mineral panel (calcium, magnesium, phosphorus, albumin)
- Hepatic panel (AST-SGPT, ALT-SGOT, total bilirubin, direct bilirubin, alkaline phosphatase)
- Uric acid, total protein, triglycerides, cholesterol, GGT
- PT, PTT, LDH, fibrinogen, quantitative immunoglobulins, CK, CRP, serum ferritin

- TSH, fT4, serum amylase, serum lipase, haptoglobin, and urinalysis
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Patients with SD, PR or CR are then followed until relapse from baseline

3.3.4.2 Follow-up for those in Complete Response

- CBC with differential (no peripheral blood smear) performed monthly until 181 days after documentation of CR/end of treatment assessment, then every 3 months for 2 years, and then every 6 months thereafter

3.3.4.3 For those not in Complete Response

- CBC with differential (no peripheral blood smear) performed every 3 months for 2 years after end of treatment, then every 6 months thereafter

3.3.4.4 For all patients in follow-up

The Day 181 post-end of treatment assessment may not be performed prior to Day 181. This assessment may be performed between Day 181 and Day 195 post-end of treatment.

Refer to [Table 10-2](#):

- History and physical exam, concurrent medications, pulse oximetry with vital signs and weight, performance status
- [REDACTED]
- [REDACTED]
- For subjects with CR or PR, disease assessment by CT or MRI at Day 181 and 18-month time points after the end of treatment.
- Bone marrow biopsy and aspirate with flow cytometry/sequencing is required [REDACTED]
- Peripheral blood for disease B-cell clone detection [REDACTED]
- Chem 7/Acute Care Panel (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine)
- Mineral panel (calcium, magnesium, phosphorus, albumin)
- Hepatic panel (AST-SGPT, ALT-SGOT, total bilirubin, direct bilirubin, alkaline phosphatase)

- Uric acid, total protein, triglycerides, cholesterol, GGT, PT, PTT, LDH, quantitative immunoglobulins, CK, CRP, serum ferritin, TSH, fT4, serum amylase, serum lipase
- Haptoglobin (end of treatment and Day 181 post-end of treatment only)
- Urinalysis (end of treatment and Day 181 post-end of treatment only)

4 REGISTRATION PROCEDURES

Study participation begins (ie, a subject is “enrolled”) once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice response system), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria), including the reason(s) for screening failure. Subjects who fail to meet the inclusion/exclusion criteria and are rescreened will receive a new SID number.

5 TREATMENT PLAN

5.1 Agent Administration

Treatment may be administered on either an inpatient or outpatient basis. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Seventy-seven evaluable patients will be enrolled to receive moxetumomab pasudotox. Unevaluable patients may be replaced as discussed in Section 13.5.

5.1.1 Moxetumomab pasudotox

Moxetumomab pasudotox (40 µg/kg) will be administered by IV infusion over 30 (± 10) minutes on Days 1, 3 and 5 of each 28-day cycle until documentation of CR or for up to 6 cycles, progressive disease (PD), initiation of alternate therapy or unacceptable toxicity. The cycle interval can be decreased by up to 2 days. For a dosing delay, refer to Section 6. Subjects will receive up to 6 cycles of therapy.

In an attempt to prevent renal insufficiency, patients will receive fluid and aspirin prophylaxis. Patients will receive low-dose aspirin orally (81 mg daily or local standard dose)

on Days 1-8 of those cycles with platelet counts $\geq 100 \times 10^9/L$. Aspirin will be held on days where the platelet count is below $75 \times 10^9/L$. Patients will receive 1 L of 5% dextrose 0.45% NaCl, (recommended over 2-4 hours) prior to the beginning and after the end of each moxetumomab pasudotox infusion. Patients under 50 kg may receive 0.5 L instead of 1 L of fluid before the beginning and after the end of moxetumomab pasudotox infusion. On Days 0-8 of the cycle, patients are expected to drink at least 3 liters of fluid/day.

To mitigate risk for allergic reaction and fever, patients will be premedicated with 10- 25 mg hydroxyzine (dose to be determined by the investigator), 650 mg of acetaminophen, and 150 mg ranitidine orally 30-90 minutes prior to every moxetumomab pasudotox infusion. After the end of infusion, patients are recommended to receive acetaminophen 650 mg orally every 6 hours x 4 doses and hydroxyzine 10-25 mg orally every 8 hours for 2 doses. Substitutions of diphenhydramine for hydroxyzine and famotidine or cimetidine for ranitidine are permitted. In subjects experiencing infusion-related reactions, including, but not limited to pyrexia, nausea, or dyspnea, premedication with dexamethasone 4 mg intravenous (IV) or oral may be administered at the investigator's discretion as secondary prophylaxis.

Moxetumomab pasudotox will be infused in 50 mL of 0.9% NaCl containing IV Bag Protectant over 30 (± 10) minutes. Vital signs will be obtained every 15 (± 5) minutes during the infusion, then every hour (± 30 minutes) for an additional 4 hours during Cycle 1. During subsequent cycles, vital signs will be obtained every 15 (± 5) minutes during the infusion, then every hour (± 30 minutes) for an additional 2 hours. Vital signs will also be obtained on Day 8 ± 1 day for the first 3 dosing cycles. Patients will be monitored for orthostatic hypotension on Days 1, 3 and 5 of each cycle prior to moxetumomab pasudotox. Medications and equipment will be available at the patient's unit for treatment of an allergic reaction (including epinephrine, oxygen, corticosteroids, diphenhydramine). These procedures will be followed for all cycles of moxetumomab pasudotox.

Additional recommended safety monitoring includes weekly serum creatinine/albumin monitoring on Days 8, 15 and 21 (± 1 day) of Cycle 1 with additional attention to fluid status and weight. Investigator should consider establishing a maximum fluid intake of 6000 mL/day during the first cycle of drug administration with consideration of diuresis with a 5-10% increase in weight above baseline. The investigator may elect to have subjects measure their weight daily with further evaluation indicated if weight gain ($> 5\%$) is noted.

Subjects with hyperuricemia of > 10 mg/dL (> 0.59 mmol/L) prior to administration of moxetumomab pasudotox will receive allopurinol 300 mg once daily for tumor lysis

syndrome (TLS) prophylaxis. Treatment of TLS will be based on institutional guidelines. Adequate *Pneumocystis carinii* pneumonia (PCP) prophylaxis will be provided for patients receiving corticosteroids ≥ 10 mg of prednisone daily or equivalent, CD4 lymphocyte count $< 0.2 \times 10^9/L$, or at the discretion of the investigator. Viral prophylaxis is also required for subjects receiving chronic corticosteroids or with lymphopenia.

Patients should not receive non-steroidal anti-inflammatory medications (NSAIDs), other than aspirin for prophylaxis of renal insufficiency, during the course of the study through 7 days after the last dose of moxetumomab pasudotox.

An event of \geq Grade 2 hypercalcemia with calcium level corrected for serum albumin will require a delay in dosing until resolution to $<$ Grade 2.

If visual symptoms \geq Grade 2 are reported, an ophthalmologic examination including slit-lamp and fundoscopic evaluation is required.

If a $\geq 10\%$ increase in body weight due to fluid overload occurs, it is recommended that imaging of the chest is obtained for any evidence of pulmonary edema so appropriate treatment may be instituted promptly.

5.1.2 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

Product defects may be related to component, product, or packaging and labeling issues. The list below includes, but is not limited to, descriptions of product complaints that should be reported.

- **Component Issue:** Defect in container or dosing mechanism of the investigational product. The component defect may be damaged, missing, or broken. Component examples include vials, stoppers, caps, spray barrels, spray nozzles, or plungers.
- **Product Issue:** Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description.
- **Packaging/Labeling Issue:** Defect in the packaging or labeling of the product. The packaging or labeling defects may be damaged or unreadable, or the label may be missing.

When reporting a product complaint, site staff must be prepared to provide the following information:

1. Customer information: reporter name, address, contact number, and date of complaint.
2. Product information: product name, packaging kit number or lot number, expiry date, and clinical protocol number.
3. Complaint information: complaint issue category and description.

MedImmune contact information for reporting product complaints:

[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Concomitant Medications

Subjects may receive medications as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician.

All concomitant medications given to the subject from the time the subject signs the informed consent form through 181 days after end of treatment of moxetumomab pasudotox will be recorded on the source document. Beyond 181 days after the end of treatment of moxetumomab pasudotox until end of study, only administrations of blood component transfusions and hematopoietic growth factors will be recorded.

Subjects should continue to take their usual chronic maintenance medications (such as antihypertensives, thyroid replacement therapy, vitamin or mineral supplements) during the course of the study other than those contraindicated by the inclusion/exclusion criteria.

Instructions for specific medications are listed below:

1. Prophylactic use of hematopoietic growth factors, such as filgrastim, sargramostim, or pegfilgrastim, is permitted when IV antibiotics are given for fever ($> 38.0^{\circ}\text{C}$) and neutropenia ($< 0.5 \times 10^9/\text{L}$). Use at the discretion of the study principal investigator (PI) for Grade 4 neutropenia without fever is permitted but discouraged.
2. Concurrent chemotherapy, radiotherapy, immunotherapy, biologic, and hormonal therapy for treatment of cancer during the study are not permitted.
3. Use of steroids is not routinely recommended to prevent CLS or fever from moxetumomab pasudotox; however, secondary prophylaxis for infusion-related reactions with dexamethasone 4 mg IV or oral may be administered at the investigator's discretion.
4. Use of NSAIDs is not permitted from the first dose of the cycle through 7 days after the last dose of the cycle.

5.2.2 Supportive Care

5.2.2.1 Infections/Fever and Neutropenia

Fever [REDACTED] may be treated symptomatically.

5.2.2.2 Blood Product Support

Symptomatic anemia should be treated with appropriate red blood cell (RBC) support. Transfusion is generally recommended if the hemoglobin falls below 8g/dL, but lower levels are acceptable particularly for younger patients. Platelets are generally given when the platelet count is $< 10 \times 10^9/\text{L}$ or when there is bleeding.

5.2.2.3 Cytokine Support

Prophylactic filgrastim (G-CSF) or sargramostim (GM-CSF) is not indicated for chemotherapy in HCL but may be used in special situations, for example, when patients have serious neutropenic infections.

5.2.2.4 Capillary Leak Syndrome

Any subject with any Grade 2 weight gain, albumin, hypotension, edema, hypoxia, or pulmonary AEs will be evaluated by thorough clinical examination including vital signs and pulse oximetry, assessment of albumin, CBC, electrolytes, BUN, and creatinine. A chest x-ray will be obtained if clinically indicated. These subjects will be prospectively monitored for the potential worsening of the above symptoms. Subjects who develop CLS will be managed according to the respective institutional standards. It is important to recognize that weight gain during CLS is often associated with intravascular volume depletion rather than overload. Thus, use of diuretics should be avoided unless patients are experiencing AEs related to weight gain, particularly when associated with dyspnea. Albumin infusions may be used to permit diuresis with or without diuretics by transiently raising oncotic pressure, but

the need for albumin infusions is generally limited to situations where the serum albumin is below 2.5 g/dL.

The potential for developing CLS will be evaluated prior to each dose within a cycle by monitoring the subject's weight, orthostatic BP, and pulse. If any subject experiences an increase in weight of 5.5 lb (2.5 kg) or 5% (whichever is greater) of the Day 1 weight of that cycle, or orthostatic BP and pulse changes which are deemed clinically significant, the subject will be thoroughly evaluated for incipient CLS prior to administration of the next dose. Evaluation will include careful physical examination and evaluation of laboratory parameters, including serum albumin, which may indicate CLS.

5.2.2.5 Hemolytic Uremic Syndrome

Any subject with suspected Grade 1-4 HUS will be evaluated as for CLS and in addition will be followed with serial haptoglobin, LDH, CBCs, and urinalyses to detect urine free hemoglobin. Subjects with an unexplained drop in hemoglobin ≥ 1.5 g/dL during any treatment cycle should be evaluated for possible HUS. Peripheral blood will be assessed for schistocytes. Patients need not be managed with plasmapheresis, and rather may be managed with fluid repletion and/or diuretics at the discretion of the institution PI, with consultation of the sponsor. If HUS of any grade develops, treatment should be suspended until resolution of all laboratory abnormalities, and should only be resumed if the maximum grade was ≤ 2 , and after consultation and agreement with the sponsor. [REDACTED]

[REDACTED] Diuresis early on may worsen the creatinine by causing dehydration, and should only be used to treat symptoms of fluid overload. Patients may have creatinine elevations and/or microscopic hematuria without evidence of HUS, but such patients may be managed similarly with attention to adequate hydration. Patients should be observed carefully for evidence of severe HUS, including mental status abnormalities, renal failure, and bleeding from severe thrombocytopenia.

5.2.2.6 Ocular Events

In the event of visual symptoms of Grade 2 or greater, an ophthalmologic evaluation is required. Subjects must be queried for and encouraged to report any ocular symptoms on dosing days prior to the administration of moxetumomab. [REDACTED]

[REDACTED] Due to the potential association of HUS with retinal damage, subjects with visual symptoms and new finding(s) on ophthalmologic examination should be

hospitalized with daily monitoring of renal function with serum creatinine and close observation.

If the subject displays any retinal abnormalities, dosing with the investigational agent must be discontinued. In the event that an ocular event or symptom occurs without any evidence of retinal abnormalities, dosing must be interrupted and may not resume until there is full resolution of ocular symptoms.

5.3 Duration of Therapy

Treatment may continue until one of the following criteria applies:

- Completion of 6 cycles of therapy.
- Disease progression
- Documented CR without assessable MRD
- Treatment delay of > 2 weeks beyond scheduled start of subsequent cycle
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AEs as defined in Section 6
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Severe or life-threatening anaphylaxis or hypersensitivity reaction
- Withdrawal of consent from further treatment with investigational product or lost to follow-up
- Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation
- Pregnancy
- Any of the following liver function abnormalities:
 - ALT or AST > 5 x ULN for more than 2 weeks
 - ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN or INR > 1.5); see Section 7.6.2 for additional details regarding reporting of subjects with ALT or AST > 3 x ULN and total bilirubin > 2 x ULN with unknown etiology (ie, Hy's law cases)
 - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
 - Corrected QT interval (Fridericia) > 500 msec confirmed (persistent for at least 5 minutes; based on manual over-read by medically qualified person) and determined post dose either during continuous 12-lead ECG monitoring or on a repeat 12-lead ECG

Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments (Table 10-2) including follow-up of any AEs unless consent is withdrawn specifically from further study participation, the subject is lost to follow-up, the subject starts alternative treatment, or the subject is enrolled in another clinical study.

5.4 Duration of Follow Up

Patients will be followed according to the follow-up timepoints in Table 10-2. Patients who are in CR will be followed until clinical relapse (defined as loss of HR, development of disease related symptoms, or organomegaly), subsequent therapy, death, or withdrawal of consent. Patients in CR should not receive any anti-cancer therapies for remission maintenance. Patients removed from study for unacceptable AEs will be followed until resolution or stabilization of the AE. The sponsor may, in the future, request that subjects be transitioned to a long-term follow-up study to allow for closure of the study database and final reporting of the primary outcome, while allowing for additional follow-up under a separate study to facilitate assessment of secondary endpoints.

5.5 Off Study Criteria

- Unexpected illness or other comorbid condition, by PI discretion after consultation with the sponsor
- Manufacturer no longer able to supply study agent
- Participant requests to be withdrawn from study
- Patient has completed study intervention and follow-up period
- Death
- Subject non-compliance that, in the opinion of the investigator or sponsor, warrant withdrawal (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmation of disease progression or relapse
- Lost to follow-up

The reason for study removal and the date the patient was removed must be documented in the electronic case report form (eCRF).

5.5.1 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through the Day 181 post-end of treatment visit, regardless of the number of doses of investigational product that was received. Subjects are encouraged to continue study follow-up detailed in [Table 10-2](#) so that duration of response to moxetumomab pasudotox can be determined.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up if prior to completion of the Day 181 post-end of treatment visit.

The end of the study (“study completion”) is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study. This date will be 3 years after the final subject is entered into the study.

6 DOSING DELAYS/DOSE MODIFICATIONS

- There will be no dose reductions for moxetumomab pasudotox.
- Dosing may be delayed up to 2 weeks for toxicity or logistical reasons. Patients should not begin a subsequent treatment cycle of moxetumomab if there is active, ongoing infection requiring treatment. Patients with excessive delay (delay > 2 weeks) are permanently discontinued from treatment and should be followed but not retreated.
- Moxetumomab pasudotox infusion should be interrupted for Grade 2 or Grade 3 infusion related reactions (eg, rapid tumor lysis) and should be permanently discontinued for Grade 4 (life-threatening) anaphylaxis or hypersensitivity reaction
- Patients with \geq Grade 3 CLS or \geq Grade 3 HUS should be permanently discontinued from treatment.
- If the ANC is $< 1.0 \times 10^9/L$, dosing should be held during Grade 1 or higher fever ($\geq 38.0^\circ C$).
- Dosing should be delayed until Grade 3 or Grade 4 AEs attributed to the study drug decrease to at least Grade 2 or below EXCEPT for the following (ie, dosing delay not required if any of the following are present):
 - Grade 3 hematologic toxicity.
 - Grade 4 hematologic toxicity resolving within < 4 weeks (lymphopenia, leukopenia and lymphocyte subsets will not be considered as grounds for a dosing delay).
 - Hematologic toxicity managed with transfusion and/or other support.
 - Grade 3 transaminase elevations.
 - Grade 3 electrolyte and mineral levels, hyperlipidemia, lipase, proteinuria and fever not associated with $ANC < 1.0 \times 10^9/L$.

- Hypocalcemia is graded after correction for the albumin, which increases the measured calcium level by 0.2 mmol/L or 0.8 mg/dL for each 1 g/dL of albumin less than 4 g/dL.
- An event of \geq Grade 2 hypercalcemia with calcium level corrected for serum albumin will require a delay in dosing until resolution to $<$ Grade 2.
- Worsening of the coagulation profile of patients on anticoagulation.
- Grade 4 hyperlipidemia if pre-existing at Grade 2-4 levels or resolved to $<$ Grade 4 by $<$ 2 months.
- Grade 3 hypoalbuminemia unless related to CLS.
- After dosing delays and re-challenge:
 - Patients who redevelop \geq Grade 3 non-hematologic toxicities, which are not covered by the exclusions in this section, with at least possible attribution to the study drug, will result in the patient discontinuing treatment but not off-study.

7 ASSESSMENT OF SAFETY

7.1 Definition of Adverse Events

The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

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

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine RBC increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

AEs may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom,

disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or serious adverse event (SAE).

7.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

7.3 Definition of Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Hepatic function abnormality meeting the definition of Hy's law is considered an AESI. See Section 7.6.2 for the definition and reporting of AESIs of hepatic function abnormality.

7.3.1 Capillary Leak Syndrome

CLS is a rare and life-threatening condition that can be characterized by capillary hyperpermeability resulting in a shift of intravascular fluid and protein to the interstitial space resulting in transient shock and generalized or segmental edema accompanied by hypotension, elevated hematocrit, and hypoalbuminemia. The systemic CLS may be difficult to recognize and diagnose on initial presentation. A characteristic triad of hypotension, hemoconcentration (elevated hematocrit, leukocytosis, and thrombocytosis), and hypoalbuminemia in the absence of secondary causes of shock is typical. Although CLS has no pathognomonic marker, it should be considered in any patient with acute, severe hypotension, without obvious cardiac dysfunction - particularly if it is unresponsive to or worsens despite aggressive IV fluid resuscitation or vasopressor support and is accompanied by an elevated hematocrit. Treatment of the acute phase is generally supportive, focusing on adequate but not overzealous fluid resuscitation ([Druey and Greipp, 2010](#)). The references are provided as guidance only. Management of the subjects is ultimately at the PI's or designee's discretion.

The sponsor recommends that any subject with any Grade 2 weight change, decrease in albumin (> 1 mg/dL), hypotension, peripheral edema, hypoxia or pulmonary AEs be thoroughly evaluated for other signs and symptoms consistent with CLS. Monitoring for the development of CLS, as well as instructions for supportive care in the event of CLS are outlined in Section 5.2.2.4.

CLS should be suspected if any of the following are observed:

1. A requirement for fluids in excess of 20 mL/kg/hour to treat hypotension.
2. Grade 3 hypotension in temporal association with CLS.
3. Symptomatic pulmonary edema requiring supplemental oxygen or > 10% (absolute) decrease in oxygen saturation in the absence of another clinical explanation.

[REDACTED]

Any changes in body weight must be reported by the subject or caregiver to the staff at the site so the subject can be monitored closely for any other signs/symptoms suggestive of CLS or HUS. PIs should consider inpatient hospitalization for subjects who show signs or have symptoms of CLS.

If subjects develop any grade of CLS during study treatment, [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] a disease assessment including bone marrow examination is encouraged, but not mandatory.

Instructions to the site on how to record (in the eCRF) and report these events (to MedImmune Patient Safety) are provided in Section 7.4.3 and Section 7.6.4, respectively.

7.3.2 Thrombotic Microangiopathy/Hemolytic Uremic Syndrome

Thrombotic microangiopathy/HUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and progressive renal failure. Patients also may develop various combinations of pulmonary edema, systemic arterial hypertension, neurologic dysfunction, and cardiac abnormalities ([Corrigan and Boineau, 2001](#); [Banerjee et al, 2009](#)).

If HUS is suspected, the PI or designee will monitor the subject to confirm or rule out a diagnosis of HUS. Subjects with Grade 2 or higher HUS will be admitted for inpatient management.

HUS will be graded using the following expanded guidelines:

Grade 1: Evidence of RBC destruction, without clinical consequences:

- The appearance of schistocytosis (≥ 5 /high power field [HPF]) in a subject with no schistocytosis at baseline, or an increase in the frequency of schistocytes (≥ 5 /HPF) over baseline.

Grade 2: Laboratory findings without clinical consequences:

- Microangiopathic anemia (schistocytosis as defined for Grade 1, and decreased Hgb by 1 g/dL), and
- Mild renal insufficiency (increased creatinine, Grade 1).

Grade 3: Laboratory findings with clinical consequences (eg, renal insufficiency, petechiae):

- Microangiopathic anemia (schistocytosis as defined for Grade 1, and decreased Hgb by 1 g/dL), and/either:
- Grade 4 Thrombocytopenia if platelets were normal at baseline; or

- Moderate renal insufficiency (increased creatinine, Grade 2 if normal at baseline or 1 grade worse than baseline).

Grade 4: Laboratory findings with life-threatening or disabling consequences (eg, CNS hemorrhage/bleeding, or thrombosis/embolism, or renal failure) laboratory findings:

- Microangiopathic anemia (schistocytosis as defined for Grade 1, and decreased Hgb by 1 g/dL), and/either:
- Thrombocytopenia (Grade 4, if platelets were normal at baseline), or
- Moderate renal insufficiency (increased creatinine, Grade 3 if normal at baseline or 2 grades worse than baseline).

Subjects meeting all of the above criteria for Grade 2-4 HUS except for the requirement ≥ 5 schistocytes/HPF will be defined as having an “HUS-like event”. Subjects experiencing an HUS-like event should be managed and reported using the same guidelines as for subjects meeting all criteria for HUS.

Any subject with Grade 1-4 HUS or Grade 2-4 HUS-like event will be evaluated with serial haptoglobin, LDH, CBCs, peripheral smear, and urinalyses. Peripheral blood smears will be used to assess for schistocytes. Subjects need not be managed with plasmapheresis, and rather may be managed with fluid repletion and/or diuretics and other supportive measures at the discretion of the PI or designee. Diuresis early on may worsen the creatinine by causing dehydration, and should only be used to treat symptoms of fluid overload. Subjects should be observed carefully for evidence of severe HUS, including mental status abnormalities, renal failure, and bleeding from severe thrombocytopenia. For additional management, PIs or designee may refer to the following publications: [Ariceta et al, 2009](#) and [Michael et al, 2009](#).

If subjects develop any grade of HUS during study treatment, [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] a disease assessment including bone marrow examination is encouraged, but not mandatory.

[REDACTED]
[REDACTED]
[REDACTED]

Instructions to the site on how to record (in the eCRF) and report this event (to MedImmune Patient Safety) are provided in Section 7.4.3 and Section 7.6.4, respectively. Each reported

event of thrombotic microangiopathy/HUS of Grade 3 or greater will be followed by the PIs or designees and evaluated by the sponsor. [REDACTED]

7.3.3 Ocular Events

Ocular events of special interest to the sponsor are defined as any clinically significant change in vision, retinal abnormalities, or choroidal disturbance that occurs during the course of the study. Subjects will be queried for ocular symptoms at screening, prior to initiation of a new treatment cycle, prior to administration of each moxetumomab dose, and at the end of treatment.

In the event of visual symptoms \geq Grade 2, ophthalmologic evaluation is required. If a subject has an ocular event with new abnormality by ophthalmologic examination during study treatment, PK and immunogenicity samples, and serum complement factors and serum Ig levels will be collected within 24 hours of diagnosis, during the event as clinically indicated (eg, in order to capture peak intensity of event as well as at least one time point during period of improvement), and after resolution of the event.

Due to the potential association of HUS with retinal damage, subjects should be hospitalized with daily monitoring of renal function with serum creatinine and close observation. If the subject displays any retinal abnormalities, dosing with the investigational agent must be permanently discontinued.

In the event of an ocular event or symptoms occur without any evidence of retinal abnormalities, dosing must be interrupted and may not resume until there is full resolution of ocular symptoms.

In the event of an ocular event where the etiology is unknown, timely follow-up investigations and inquiries must be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event. Ocular events will be followed to resolution until the end of subject participation in the study. Prompt notification of the sponsor is required as with other AESIs.

[REDACTED]

Instructions to the site on how to record (in the eCRF) and report these events (to MedImmune Patient Safety) are provided in Section 7.4.3 and Section 7.6.4, respectively.

7.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to MedImmune Patient Safety. See Section 7.2 for the definition of SAEs and Appendix 4 for guidelines for assessment of severity and relationship. If an AE evolves into a condition that meets the regulatory definition of “serious,” it will be reported on the SAE Report Form.

Infusion of biological products is commonly associated with infusion related reactions. Anaphylaxis and infusion related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion related reactions are commonly observed during or shortly after the first time exposure to therapeutic monoclonal antibodies delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and or mucosal reactions. The Investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to moxetumomab pasudotox, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the Investigator’s convenience and in order to facilitate consistency in judgments a copy of the National Institute of Allergy and Infectious Diseases (NIAID) and Food and Allergy Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Appendix 5.

7.4.1 Time Period for Collection of Adverse Events

All AEs and SAEs will be recorded from the time of informed consent. AEs will be collected within 4 weeks prior to treatment enrollment, throughout the treatment period, and 4-6 weeks after the last dose (end of treatment).

7.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

7.4.3 Recording of Adverse Events of Special Interest

7.4.3.1 Hepatic Function Abnormality

Events of hepatic function abnormality (as defined in Section 7.6.2) should be recorded in the eCRF according to the definitions of AE and SAE (Section 7.1 and Section 7.2, respectively):

- If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE per Section 7.4.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE per Section 7.4.

7.4.3.2 Capillary Leak Syndrome

Events of CLS (as defined in Section 7.3.1) should be recorded in the eCRF according to the definitions of AE and SAE (Section 7.1 and Section 7.2, respectively).

7.4.3.3 Thrombotic Microangiopathy/Hemolytic Uremic Syndrome

Events of thrombotic microangiopathy/HUS (as defined in Section 7.3.2) and HUS-like events should be recorded in the eCRF according to the definitions of AE and SAE (Section 7.1 and Section 7.2, respectively).

7.4.3.4 Ocular Events

Ocular events (as defined in Section 7.3.3) should be recorded in the eCRF according to the definitions of AE and SAE (Section 7.1 and Section 7.2, respectively).

7.5 Reporting of Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and fax it to MedImmune Patient Safety or designee.

MedImmune contact information:



The sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements. The sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

7.6 Other Events Requiring Immediate Reporting

7.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety or designee using the Safety Fax Notification Form (Section 7.5 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE eCRF (Section 7.4). Overdose does not automatically make an AE serious, but if the

consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (Section 7.4 and Section 7.5). MedImmune does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

7.6.2 Hepatic Function Abnormality

AEs of hepatic function abnormality of special interest to the sponsor are defined as any increase in ALT or AST to greater than $3 \times \text{ULN}$ **and concurrent** increase in bilirubin to greater than $2 \times \text{ULN}$ (ie, Hy's law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE.

[REDACTED]

The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

- If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, or is considered attributable to investigational product, permanent discontinuation of dosing for the study subject should be considered.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor.

7.6.3 Pregnancy

Pregnancy in a female subject who has received investigational product is required to be reported **within 24 hours of knowledge of the event** to MedImmune Patient Safety or designee using the Safety Fax Notification Form (see Section 7.5 for contact information).

Subjects who become pregnant during the study period must not receive additional doses of investigational product and will be withdrawn from the study. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to MedImmune Patient Safety or designee after outcome.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported **within 24 hours of knowledge of the event** to MedImmune Patient Safety or designee using the Safety Fax Notification Form (see Section 7.5 for contact information). The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

7.6.4 Other Adverse Events of Special Interest

If any AESIs defined in Section 7.3 require immediate reporting to Patient Safety, including the following: Events of CLS, HUS and ocular events (as defined in Section 7.3) are required to be reported **within 24 hours of knowledge of the event** to MedImmune Patient Safety using the SAE Report Form, even if the event is considered to be non-serious (see Section 7.5 for contact information).

7.7 Safety Management During the Study

The MedImmune medical monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes review of SAEs and timely review of AEs and “other events” reported during the study. MedImmune Patient Safety is responsible for the receipt, immediate review, investigation, and follow-up of SAEs and other immediately reportable events (eg, overdose and pregnancies) reported from the clinical study sites.

A DMC will be convened to review the study data after the first 15 subjects have been treated at a dose level of 40 µg/kg. The DMC will continue to evaluate safety at a frequency of at least every 6 months during the study to identify any safety signals (Section 13.7).

8 PHARMACEUTICAL INFORMATION

Other Names: CAT-8015, HA22

Classification: Recombinant anti-CD22 MAb Conjugated Immunotoxin

Molecular Weight: 63.5 kDa

Mode of Action: Moxetumomab pasudotox specifically binds to CD22 on the cell surface of B cells. Following binding, the complex is endocytosed and then processed to release the exotoxin. The exotoxin domain is translocated to the cytosol, where it catalyzes the adenosine diphosphate ribosylation of elongation factor 2, causing inhibition of protein translation and subsequent cell death.

Description: Moxetumomab pasudotox is a recombinant conjugated immunotoxin composed of a disulfide-stabilized anti-CD22 Ig Fv genetically fused to a truncated form of *Pseudomonas* exotoxin, PE38.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Route of Administration: IV infusion

[REDACTED]

[REDACTED]

[REDACTED]

8.1 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

8.2 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be translated into local languages, as required.

8.3 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

8.4 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Pharmacokinetic Studies

9.1.1 Moxetumomab Pasudotox PKs

A laboratory manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.2 Laboratory Correlative Studies

A laboratory manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

9.2.1 Evaluation of Immunogenicity

[REDACTED]

[REDACTED]

9.2.2 Bone Marrow Aspirate Minimal Residual Disease Analysis

[REDACTED]

[REDACTED]

[REDACTED]

9.2.3 Peripheral Blood Flow Cytometry

[REDACTED]

9.2.4 Lymphocyte Enumeration

[REDACTED]

9.2.5 Peripheral Blood Disease B-cell Clone Detection

[REDACTED]

9.3 Sample Storage, Tracking, and Disposition

All research samples will be used for the assays specified in this protocol. The assays will be performed using the entire sample designated for the particular study.

The PI would be notified upon discovery of sample loss or unplanned destruction associated with unforeseen problems such as, but not limited to, natural disasters, laboratory or equipment malfunctions and human error. The PI (or designee) would in turn notify the IRB.

All patient samples that are shipped to [REDACTED] and stored must have patient identifying information removed to maintain patient anonymity. These samples will be used only for purposes described in the protocol and informed consent form and remaining samples will be destroyed at the end of the study. Assay results will be kept in a secure database prior to disclosure in the final study report and any public disclosure (manuscripts, presentations, etc).

Table 10-1 Study Calendar for Cycle 1 and Subsequent Cycles

Evaluation/Intervention	Screening ^a	Pre-cycle ^b	Day 1	Day 3	Day 5	Day 8 (±1D)	Day 15 (±2D) ^c	Day 21 (±2D) ^c
Vital signs	X		X	X	X	X	X	X
Orthostatic BP	X		X	X	X	X		
Weight ^h	X	X				X		
Performance status	X	X						
█			█		█			
█			█					
Moxetumomab pasudotox dosing			X	X	X			

1 cycle = 28 days

Alk Phos = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; BM = bone marrow; BP = blood pressure; BUN = blood urea nitrogen; CK = creatinine kinase; CRP = C reactive protein; D = day; ECG = electrocardiogram; GGT = gamma-glutamyl transferase; HBcAb = Hepatitis B core antigen; HBsAG = hepatitis B surface antigen ; HLA = human leukocyte antigen; HPF = high power field; LDH = lactate dehydrogenase; PFTs = pulmonary function tests; fT4 = free thyroxine; TSH = thyroid stimulating hormone; β-HCG = beta human chorionic gonadotropin.

^a Please see Section 3.3 for tests needed for eligibility. Baseline bone marrow and imaging evaluations do not need to be repeated if tests have been performed within 8 weeks prior to treatment. Subsequent blood counts too high for eligibility will not disqualify the patient providing the patient does not have blood counts at the time of treatment which would be required for CR.

^b Pre-cycle tests may be done Day -3 to Day 1, and may be combined with either Baseline (for Cycle 1) or Day 1 or both.

^c Tests may be done on **one** of the indicated days. Assessments on Day 15 and Day 21 are optional.

^d Cycle 1 only. To be completed 30- 60 minutes after completion of moxetumomab pasudotox infusion.

^e Schistocyte count (reported as schistocytes/HPF based upon review of the peripheral blood film) will be collected at screening, prior to each cycle, on Cycle 1 Day 8, and within 24 hours of diagnosis of HUS or an HUS-like event, during the event as clinically indicated (eg, in order to capture peak intensity of event as well as at least one time point during period of improvement), and after resolution of the event.

█

^g Subjects enrolled in Germany will utilize MRI for all radiographic assessments (CT not permissible).

^h Investigators may choose to monitor weight daily during treatment, but mid-cycle dose adjustments are not allowed.

█

Table 10-1 Study Calendar for Cycle 1 and Subsequent Cycles

Evaluation/Intervention	Screening ^a	Pre-cycle ^b	Day 1	Day 3	Day 5	Day 8 (±1D)	Day 15 (±2D) ^c	Day 21 (±2D) ^c
█	█	█	█	█	█	█	█	█
█	█	█	█	█	█	█	█	█
█	█	█	█	█	█	█	█	█

Table 10-2 Study Calendar for End of Treatment and Follow-up

Evaluation/Intervention	EOT ^a	From end of treatment assessment					Yearly Thereafter (± 1M)
		Every month for 6 months (if in CR) (± 1W)	Every 3 months for 24 months (± 2W)	181D (+ 2W)	12 months (± 1M)	18 months (± 1M)	
History and Physical exam	X			X	X	X	X
Vital signs including pulse oximetry and weight	X			X	X	X	X
Performance Status	X			X	X	X	X
Concurrent medications	X			X	X ^b	X ^b	X ^b
Adverse events	X						
Ophthalmologic exam	X						
12-lead ECG (analyzed by central vendor ERT)	X						
Imaging with CT or MRI of abdomen ^c	X			X		X	
BM biopsy and aspirate (flow cytometry/sequencing)	X			X ^d			
Clinical response assessment			X		X	X	X
CBC with differential (no peripheral blood smear)	X	X ^e	X ^e	X	X	X	X
Chem 7 (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine)	X			X	X	X	X
Mineral panel (calcium, magnesium, phosphorous, albumin)	X			X	X	X	X
Hepatic panel (AST, ALT, total bilirubin, direct bilirubin, AlkPhos)	X			X	X	X	X
Uric acid, LDH, total protein, triglycerides, cholesterol, GGT, PT, PTT, fibrinogen, quantitative immunoglobulins, CK, CRP, serum ferritin	X			X			
TSH, fT4, serum amylase, serum lipase, haptoglobin, urinalysis	X			X			
████████████████████	█						

Table 10-2 Study Calendar for End of Treatment and Follow-up

Evaluation/Intervention	EOT ^a	From end of treatment assessment					Yearly Thereafter (± 1M)
		Every month for 6 months (if in CR) (± 1W)	Every 3 months for 24 months (± 2W)	181D (+ 2W)	12 months (± 1M)	18 months (± 1M)	
[REDACTED]	■			■	■	■	■
[REDACTED]	■			■			

AlkPhos = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; BM = bone marrow; BUN = blood urea nitrogen; CBC= complete blood count; CK = creatinine kinase; CR = complete response; CRP = C reactive protein; CT = computed tomography; D = day; ECG = electrocardiogram; EOT = end of treatment; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; M = month; MRI = magnetic resonance imaging; PT = prothrombin time; PTT = partial thromboplastin time; TSH = thyroid stimulating hormone; W = week.

- ^a End of treatment is 28-42 days after the first dose of the last cycle. At the discretion of the investigator, a full disease assessment may be performed prior to completion of 6 cycles of therapy if the patient maintains blood counts needed for CR for at least 4 weeks. This interim assessment will include all assessments required at EOT.
- ^b Only to collect blood component transfusions and hematopoietic growth factors uses.
- ^c CT or MRI abdomen at 6 and 18 month time points after EOT. Subjects enrolled in Germany will utilize MRI for all radiographic assessments (CT not permissible).
- ^d This assessment is required 6 months after EOT only for patients in CR or PR.
- ^e Patients in CR will have a CBC with differential (no peripheral blood smear) monthly from the EOT assessment until the 181D assessment, then every 3 months for 24 months, then every 6 months thereafter. For patients not in CR, repeat CBC with differential (no peripheral blood smear) every 3 months for 24 months after the end of treatment, and every 6 months thereafter.

■ [REDACTED]

11 MEASUREMENT OF EFFECT

For the purposes of this study, patients will receive up to 6 cycles of therapy as described in Section 5.3. Bone marrow examination and radiographic disease assessment will be performed at screening, the end of treatment, and 6 months post-end of treatment. If during treatment and prior to completion of 6 cycles of therapy, blood counts are consistent with CR for at least 4 weeks, an interim disease assessment may be performed at the discretion of the investigator. If a CR without MRD is documented, treatment will be discontinued. For any other response, treatment should be continued to complete 6 cycles of therapy, with the full disease assessment repeated at EOT (Table 10-2).

11.1 Response Criteria

Following the end of treatment, 6 month post-end of treatment, and interim (during treatment; if applicable) disease assessment, the Principal or Associate Investigator will record the tumor response. Responses include: CR with or without MRD, PR, stable disease (SD), PD, and relapse. The Principal or Associate Investigator will also record the clinical response prior to each treatment cycle, and at each follow-up visit after the 6 month post-end of treatment assessment. PD may only be used during therapy. Once a subject has ended therapy, worsening of disease no longer meeting criteria for best response will be designated as disease relapse. Response criteria will be based on previous HCL studies ([Cheson et al, 1998](#); [Grever et al, 1995](#); [Hoffman et al, 1997](#); [Catovsky et al, 1987](#)). Although the requirements varied slightly among these trials, certain requirements are well accepted and considered standard. Isolated laboratory values not consistent with a response may be ignored in the assessment of a response, at the discretion of the investigator, if preceded and followed by the values for the same laboratory that are consistent with the identified response, or if they occur within the first 12 days of the cycle. The CBC used as a baseline for determining improvement is generally the last one prior to drug, unless that CBC is not representative of others immediately preceding it and is thought to contain lab errors. Response is verified independently through a central disease response assessment vendor to be determined.

Complete Response with or without Minimal Residual Disease

CR ± MRD requires all of the following to be present:

- No evidence of leukemic cells in the peripheral blood and/or by routine H/E staining of bone marrow. Minimal Residual Disease: CR with HCL evident in blood or marrow by flow cytometry or in bone marrow biopsy by immunohistochemistry (**NOTE:** A second confirmatory bone marrow examination is not required).

- Resolution of any hepatomegaly, splenomegaly, and abnormal (≥ 2 cm minimum length) lymphadenopathy by CT or MRI. Although a normal spleen size is not defined, the maximum diameter of the spleen should be either < 17 cm or have decreased by $>25\%$ from its baseline.
- Normal CBC as exhibited by: Neutrophils $\geq 1.5 \times 10^9/L$, Platelets $\geq 100 \times 10^9/L$, and Hemoglobin ≥ 11.0 g/dL without transfusions or growth factors for at least 4 weeks.

Definition of Hematologic Remission

HR is defined as the blood counts required for CR. The primary endpoint requires that CRs maintain HR for >180 days after first achieving CR. Once a CR is achieved, the HR duration is not interrupted by transient decreases in normal blood counts.

Complete Response Duration

The duration of complete remission is calculated from the time of achievement of all criteria of CR to the time of relapse from CR. Relapse from CR will be defined as any CR criteria (blood counts, imaging or bone marrow) no longer consistent with CR. However, to meet the primary endpoint, patients will need to achieve CR and then maintain a HR for >180 days.

Partial Response

PR requires all of the following for a period of at least 4 weeks (**NOTE:** PR does not require bone marrow examination):

The patient must have the following (if abnormal prior to treatment):

- $\geq 50\%$ decrease or normalization ($<5.0 \times 10^9/L$) in peripheral blood lymphocyte count from the pretreatment baseline value,
- $\geq 50\%$ reduction in lymphadenopathy by CT or MRI, based on sum of products of perpendicular diameters, or resolution to size consistent with CR,
- $\geq 50\%$ reduction in abnormal hepatosplenomegaly by CT or MRI, or resolution to size consistent with CR,
- Neutrophils $\geq 1.5 \times 10^9/L$ or 50% improvement over baseline without growth factors for at least 4 weeks,
- Platelets $\geq 100 \times 10^9/L$ or 50% improvement over baseline, and
- Hemoglobin ≥ 11.0 g/dL or 50% improvement over baseline without transfusions or growth factors for at least 4 weeks. For patients who are transfusion-dependent at baseline, a hemoglobin of ≥ 9.0 g/dL without transfusions or growth factors for at least 4 weeks.

- The beginning of PR will be considered the beginning of the 4-week duration of required blood counts meeting PR criteria.

Progressive Disease

PD is defined by at least one of the following compared to pretreatment:

- $\geq 25\%$ increase in the sum of the products of the greatest perpendicular dimensions of at least two lymph nodes by CT or MRI on two consecutive examinations at least 2 weeks apart (at least 1 node must be ≥ 2 cm in minimum length) or appearance of new palpable lymph nodes
- $\geq 50\%$ increase in the absolute number of circulating lymphocytes, on two consecutive examinations showing abnormal lymphocytosis at least 2 weeks apart
- $\geq 25\%$ decrease in hemoglobin (must be < 11 g/dL), platelets (must be $< 100 \times 10^9/L$), or ANC (must be $< 1.5 \times 10^9/L$) unless these are judged to be effects of treatment.

Stable Disease

SD will be characterized by not meeting the criteria for CR, PR, or PD as outlined above.

Relapse

- Relapse from CR: Loss of criteria needed for CR, excluding transient decrease in lab values below criteria for CR.
- Relapse from PR: Loss of criteria needed for PR, excluding transient decrease in lab values below criteria for PR.
- Relapse from SD: Patients who meet above criteria for PD when compared to measurements after end of therapy.

11.2 Data Collection

Data will be collected prospectively and entered into [REDACTED] according to the data management plan. The PI is responsible for the collection, maintenance and quality control of study data.

Quality assurance complete records must be maintained on each patient treated on the protocol. These records should include primary documentation (eg, laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc) which confirm that:

- The patient met all eligibility criteria

- Signed informed consent was obtained prior to treatment
- Treatment was given according to protocol (dated notes about doses given, complications, and clinical outcomes)
- Toxicity was assessed according to protocol (laboratory report slips, etc)
- Response was assessed according to protocol (X-ray, scan, lab reports, date noted on clinical assessment, as appropriate)

All data will be kept secure. Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique SID number.

12 STUDY AND DATA MANAGEMENT

12.1 IRB/IEC Approvals

The PI will provide the sponsor with a copy of the participating institution's approved continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the IRB/IEC.

12.2 Study Agreements

The PI at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between the sponsor and the PI must be in place before any study-related procedures can take place, or subjects are enrolled.

12.3 Archiving of Study Documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

12.4 Training of Study Site Personnel

A sponsor representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

12.5 Monitoring of the Study

During the study, a sponsor representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The sponsor representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

12.5.1 Protocol Deviation

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A protocol deviation may be categorized as major or minor depending on its effect on the risk/benefit; subject's rights, safety, or welfare; and/or on the integrity of the data.

A major protocol deviation generally increases risk or decreases benefit; affects the subject's rights, safety, or welfare; or affects the integrity of the data. Examples include failure to obtain informed consent, obtaining informed consent after initiation of study procedures, failure to report SAE to the IRB or sponsor, and failure to document drug administration. A minor protocol deviation does not increase risk or decrease benefit; does not have a

significant effect on the subject's rights, safety, or welfare; and/or does not have a significant effect on the integrity of the data. Examples include receiving prior radioimmunotherapy between 6 months to 2 years prior to enrollment in study and missing optional visits.

The investigator(s) should document any deviation from the protocol regardless of the reason for the deviation. Only when the protocol was not followed in order to avoid an immediate hazard to the subjects or for other medically compelling reason, the investigator should prepare and submit the records explaining the reasons thereof to MedImmune and the head of study site and retain a copy of the records.

13 STATISTICAL CONSIDERATIONS

13.1 General Considerations

Data will be provided in data listings sorted by subject number and in tabular summaries. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals (CIs) will be two-sided, unless otherwise stated. Details of endpoint analyses will be described in the statistical analysis plan.

13.2 Analysis Populations

The intent-to-treat (ITT) subject population will include all subjects who have been entered into the study and treated by moxetumomab pasudotox. The ITT population is the primary population for the efficacy analyses and the summary of baseline characteristics.

The efficacy evaluable subject population will include all subjects who have received at least 1 dose of moxetumomab pasudotox and have a baseline and at least one post baseline disease assessment including bone marrow examination and cross sectional imaging. The evaluable subject population will be identified prior to database lock and will be the secondary population for efficacy analysis.

The safety subject population will include all subjects who receive at least 1 dose of moxetumomab pasudotox.

13.3 Primary Endpoint

The primary objective of this study of moxetumomab pasudotox in relapsed HCL is to determine the rate of durable CR, defined as the proportion of subjects who meet blood, bone marrow, and imaging criteria for CR, followed by a > 180 day duration of HR, with HR

being defined as the blood counts needed for CR. The durable CR rate and its 95% CI will be constructed using the exact probability method (Clopper-Pearson exact interval) in the Intent-to-Treat population. [REDACTED]

[REDACTED] Seventy-seven subjects will provide 90% power to detect a difference between 28% and 13% durable CR rates using 2-sided significance level of 0.05. As a supportive analysis, the durable CR rate and its 95% CI will be estimated based on the evaluable population. [REDACTED]

The central independent review of disease response and disease progression will be the basis for primary analyses. Blinded independent review of response to treatment will be performed by a central vendor. An imaging manual will be distributed to provide guidance to both imaging and study personnel regarding review of scanning parameters and associated activities required for study image collection. Bone marrow slides will be used for response assessment. Images, pathology slides from bone marrow biopsies/aspirates, reports of CBC, and associated documentation must be acquired as instructed in this manual and submitted to the central vendor.

13.4 Secondary Endpoints

The secondary objectives of this study are to evaluate the safety of moxetumomab pasudotox in this subject population, other antitumor activities, PK, and immunogenicity.

13.4.1 Other Antitumor Activities

Other assessments of antitumor activity include rate of CR, objective response (OR), time to response (TTR), duration of CR and OR, and PFS.

13.4.1.1 CR Rate, Duration of CR (Disease-Free Survival), and Duration of Hematologic Remission

The CR rate is defined as the proportion of subjects that have achieved CR. The 95% CI of the CR rate will be constructed using the exact probability method (Clopper-Pearson exact interval). Duration of CR (also called disease-free survival) will be measured from the first documentation of CR (by imaging, bone marrow biopsy and blood counts) to the time of relapse as defined in Section 11.1. Duration of HR will be measured from the first documentation of CR (by imaging, bone marrow biopsy and blood counts) to the time of loss of HR. Duration of CR will be censored on the date of the last disease assessment or clinical

response assessment for subjects who have no documented relapse prior to data cutoff, dropout, or the initiation of alternative anticancer therapy. Duration of HR will be censored on the date of the last evaluable hematologic assessment for subjects who have no documented loss of HR prior to data cutoff, dropout, or the initiation of alternative anticancer therapy. The proportion of subjects with a CR and HR at certain time points (eg, 6 month, 1 year, or 2 year) and the median duration of CR and HR may be estimated, if feasible, for the subgroup of subjects with CR using the Kaplan-Meier method. It should be noted that CR duration, which may be shorter than HR duration, is a secondary endpoint and will be summarized separately.

13.4.1.2 Objective Response Rate

Objective response rate is defined as the proportion of subjects with CR or PR. The 95% CIs of ORR will be estimated using the exact probability method.

13.4.1.3 Time to Response

Time to response will be measured from the start of moxetumomab pasudotox administration to the first documentation of response (CR or PR). Descriptive statistics of time to response (median, minimum, and maximum) will only be summarized for subjects who have achieved objective response.

13.4.1.4 Duration of Objective Response

Duration of objective response will be measured from the first documentation of objective response to the event of relapse as defined in Section 11.1. Duration of objective response will be censored on the date of last disease assessment for subjects who have no documented relapse prior to data cutoff, dropout, or the initiation of alternative anticancer therapy. Duration of objective response will be summarized descriptively by using minimum and maximum of duration of objective response observed at a certain follow-up period. The proportion of subjects with response at certain time points (eg, 6 month, 1 year, or 2 year) and the median duration of response may be estimated, if feasible, for the subgroup of subjects with objective response using the Kaplan-Meier method.

13.4.1.5 Progression-Free Survival

PFS is measured from the start of moxetumomab pasudotox administration to relapse, PD, or death from any cause. Relapse is considered post-end of treatment when patients no longer meet criteria required for their best response (Section 11.1). PFS will be censored on the last hematologic assessment for subjects without relapse, PD, or death. PFS will be evaluated using the Kaplan-Meier method.

13.4.1.6 Time to Treatment Failure

TTF will be measured from the start of moxetumomab pasudotox administration until relapse, PD, initiation of alternate cancer therapy, or death due to disease or disease-related complication. ([Else et al, 2009](#)). TTF will be censored as in PFS but will also be censored for death not accompanied by relapse, and will also be evaluated using the Kaplan-Meier method.

13.4.2 Safety Assessment

Safety endpoints include assessment of AEs, SAEs, changes in clinical laboratory evaluations and vital signs. The occurrence of AEs, abnormal laboratory values, and SAEs reported from the first administration of moxetumomab pasudotox through 30 days after last dose of moxetumomab pasudotox will be summarized for all subjects who received any moxetumomab pasudotox. AEs and SAEs will be graded according to the NCI CTCAE V4.0 and described by system organ class and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and relationship to moxetumomab pasudotox. Frequency rates will be calculated for each system organ class and MedDRA preferred term.

13.4.3 Pharmacokinetic Assessment

Individual moxetumomab pasudotox serum concentrations will be tabulated by treatment cycles along with descriptive statistics. Noncompartmental PK data analysis will be performed for Cycle 1 and 2 concentration data using scheduled or actual PK sample collection times.

If data allows, descriptive statistics of noncompartmental PK parameters will be provided.

[REDACTED]

13.4.4 Immunogenic Potential of Moxetumomab Pasudotox

Immunogenicity results will be listed for each subject. The number and percentage of subjects who develop detectable ADA and NAb will be summarized. Titers and specificity will be reported for NAb-positive subjects. The impact of ADA on PK, safety and efficacy will be evaluated if data allow. Summaries of ADAs and NABs will be provided at the completion of the study and will not be performed on a real-time basis.

13.5 Sample Size and Power Calculations

The sample size estimation in this study is based on the assumption that the historical durable CR rate in this population is $\leq 13\%$ (null hypothesis). [REDACTED], a total of 77 subjects will provide 90% power to detect a difference between 28% and 13% durable CR rates at a 2-sided significance level of 0.05. [REDACTED]

13.6 Early stopping Rule Due to Lack of Efficacy

[REDACTED]

13.7 Data Monitoring Committee

An external DMC composed of individuals with no involvement in the study will be employed. The committee will review safety data, including AEs, SAEs, treatment-related mortality, and laboratory data. The planned DMC analysis will occur after the first 15 subjects are treated and followed for at least one treatment cycle and every 6 months thereafter until the end of the study. [REDACTED]

[REDACTED] The committee will report its findings to an internal MedImmune safety review committee. In addition, the DMC may be asked by the medical monitor or a MedImmune safety review committee to independently review data on an ad hoc basis. At each review, the DMC will make a recommendation to continue the study with or without modification, or to halt enrollment for safety concerns. This recommendation will be relayed to a MedImmune safety review committee and appropriate action will be taken. Where applicable, regulatory authorities and IRBs/IECs will be notified of any actions taken with the study.

14 HUMAN SUBJECTS PROTECTIONS

14.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

14.2 Rationale for Subject Selection

Subjects with histologically confirmed HCL will be eligible for participation in this study. Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status.

14.3 Evaluation of Benefits and Risks/Discomforts

14.3.1 Benefits

The potential benefits to patients on this study, based on the results of a completed Phase 1 study in subjects with multiply relapsed HCL, include a high ORR and CR rate that is durable (Section 2.2). This may lead to improved disease-free survival and overall survival compared to available salvage therapies.

14.3.2 Risks

The primary risks of participation in this study include the possible occurrence of any of a range of side effects from moxetumomab pasudotox which are described in Section 2.2 and in the consent document. Frequent monitoring for adverse effects and exclusion of subjects at risk for these adverse effects will help to minimize the risks associated with administration.

14.3.2.1 Important Potential Risks

[REDACTED]

Potential Risks Common to Any Immunoglobulin

Potentially severe or fatal infusion-related reactions and acute IgE-mediated allergic reactions may occur following the administration of any Ig.

Administration of polyclonal Ig preparations and mAbs has been associated with infusion-related reactions that occur during or shortly after dosing such as fever, chills, myalgia, nausea, vomiting, pruritus, rash, headache, flushing, sweating, tachycardia, dyspnea, bronchospasm, hypotension, dizziness or lightheadedness, and hemodynamic instability. These reactions are more common with higher doses, higher rates of infusion, and in subjects with a history of allergies.

IgE-mediated allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, and unresponsiveness. Acute severe allergic reactions (anaphylaxis) usually occur soon after exposure, usually within 10 minutes. Subjects may experience paresthesia, hypotension, laryngeal edema, mental status changes, facial or pharyngeal angioedema, airway obstruction, bronchospasm, urticaria and pruritus, serum sickness, arthritis, allergic nephritis, glomerulonephritis, temporal arteritis, and death.

Potential Risks Associated with Immune Reactivity

[REDACTED]

Potential Risks Associated with Administration

Moxetumomab pasudotox is administered IV. Possible risks associated with IV administration of moxetumomab pasudotox are infection, redness, swelling, pain, and induration at the administration site.

14.3.2.2 Identified Risks

[REDACTED]

14.4 Risks/Benefits Analysis

For patients with HCL without effective therapy, median survival is about 4 years.

Moxetumomab pasudotox has shown activity [REDACTED] in patients with multiply relapsed HCL in an early phase clinical trial. [REDACTED]

[REDACTED]

[REDACTED] For these reasons, the risk/benefit ratio of this protocol is favorable; [REDACTED]

[REDACTED]

14.5 Consent Process and Documentation

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts, and the potential benefits will be carefully explained to the patient or the patient's advocate. This process will include a general description of the disease process, as well as a description of the patient's expected clinical course. Alternative therapies will be carefully explained, and outlined in the consent document. The patient will be asked to read the consent at his/her convenience and will be encouraged to ask questions. Enrollment on this study will only occur if the patient meets all eligibility criteria, is judged by the Investigator to potentially benefit from the therapy, is able and willing to provide full consent, and has signed the consent document. The PI or an associate investigator on the trial will obtain consent.

14.6 Ethics and Regulatory Review

An IRB/IEC should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to

the subjects. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to the sponsor before enrollment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

The sponsor should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrollment of subjects, the final study protocol, including the final version of the Informed Consent Form, should be approved by or notified to the national regulatory authority, according to local regulations.

The sponsor or sponsor's designee will provide regulatory authorities and PIs with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

Each PI is responsible for providing IRB/IECs with reports of SUSARs with the investigational product. The sponsor will provide this information to the PI so that he/she can meet these reporting requirements.

14.7 Changes to the Protocol and Informed Consent Form

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to IRB/IEC see Section [14.6](#).

If a protocol amendment requires a change to a site's Informed Consent Form, MedImmune and the site's IRB/IEC are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

14.8 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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16 CHANGES TO THE PROTOCOL

Protocol Amendment 9, 29Mar2017

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 9. Major changes to the protocol are summarized below.

1. Section 5.2.1 (Concomitant Medications): Text referring to the time period through which concomitant medications should be collected was changed from 30 days after the last dose of moxetumomab pasudotox to 181 days after the end of treatment of moxetumomab pasudotox. [REDACTED]
[REDACTED] In addition, text was added to indicate that beyond 181 days after end of treatment until the end of study, only administrations of blood component transfusions and hematopoietic growth factors will be recorded [REDACTED]
[REDACTED]
2. Table 10-2 (Study Calendar for End of Treatment and Follow-up): Table modified to reflect collection of blood component transfusions and hematopoietic growth factors uses on 12 months, 18 months, and yearly thereafter. Footnote added to indicate that collections on those dates include only blood component transfusions and hematopoietic growth factors uses.

Protocol Amendment 8, 06Jan2017

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 8. Major changes to the protocol are summarized below.

1. Cover page – The medical monitor [REDACTED] was changed to [REDACTED]
2. PRECIS (Background) – [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
3. Section 11.1 (Response Criteria – Complete Response with or without Minimal Residual Disease) – The text referring to requirements for CR ± MRD that need to be present was changed from “No evidence of leukemic cells by routine H/E stains of

the peripheral blood and bone marrow” to “No evidence of leukemic cells in the peripheral blood and/or by routine H/E staining of bone marrow.” [REDACTED]

[REDACTED] In addition, the replacement of “and” with “and/or” was done to align with both ESMO and NCCN guideline regarding the definition of CR. See reference: Grever MR. How I treat hairy cell leukemia. *Blood*. 2010;115(1):21-28.

4. Section 12.5 (Clinical Monitoring) – A new subsection 12.5.1 (Protocol Deviation) was added. [REDACTED]

5. Section 13.3 (Primary Endpoint) – [REDACTED]

6. Section 13.3 (Primary Endpoint) – A sentence was added after the sentence “...review of scanning parameters and associated activities required for study image collection.” The new text is “**Bone marrow slides will be used for response assessment.**” [REDACTED]

7. Section 13.3 (Primary Endpoint) – The text “from bone marrow biopsies/aspirates, reports of CBC” was added to the sentence “Images, pathology slides from bone marrow...” The revised sentence is “Images, pathology slides **from bone marrow biopsies/aspirates, reports of CBC**, and associated documentation must be acquired as instructed in this manual and submitted to the central vendor.” [REDACTED]

8. Section 13.4.1.1 (CR Rate, Duration of CR (Disease-Free Survival), and Duration of Hematologic Remission) – The text “as defined in Section 11.1” was added at the end of to the sentence “Duration of CR (also called disease-free survival) will be

measured ...” The revised sentence is “Duration of CR (also called disease-free survival) will be measured from the first documentation of CR (by imaging, bone marrow biopsy and blood counts) to the time of relapse **as defined in Section 11.1.**”

[REDACTED]

9. Section 13.4.1.1 (CR Rate, Duration of CR [Disease-Free Survival], and Duration of Hematologic Remission) – The sentence “Duration of CR and HR will be censored...” was revised to “Duration of CR will be censored on the date of the last disease assessment or clinical response assessment for subjects who have no documented relapse prior to data cutoff, dropout, or the initiation of alternative anticancer therapy.” A new sentence explaining how the duration of HR will be censored was added as follows: “Duration of HR will be censored on the date of the last evaluable hematologic assessment for subjects who have no documented loss of HR prior to data cutoff, dropout, or the initiation of alternative anticancer therapy.”
- [REDACTED]
- [REDACTED]

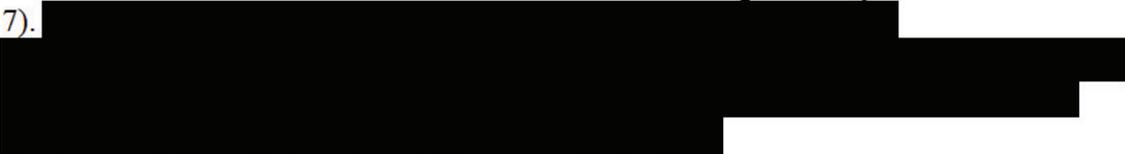
10. Section 13.4.1.4 (Duration of Objective Response) – The text “as defined in Section 11.1” was added at the end of the sentence “Duration of objective response will be measured...” The revised text is “Duration of objective response will be measured from the first documentation of objective response to the event of relapse as defined in Section 11.1.”
- [REDACTED]

11. Section 13.4.1.5 (Progression-Free Survival) – The text “PFS is measured from the start of moxetumomab pasudotox administration to relapse, PD, initiation of alternative anticancer therapy, or death from any cause (Saven et al, 1998; Else et al, 2009)” was changed to “PFS is measured from the start of moxetumomab pasudotox administration to relapse, PD, or death from any cause.”
- [REDACTED]
- [REDACTED]

12. Section 13.4.1.5 (Progression-Free Survival) – The text “PFS will be censored on the last hematologic assessment for subjects without relapse, PD, alternate therapy, or death” was changed to “PFS will be censored on the last hematologic assessment for subjects without relapse, PD, or death.”
- [REDACTED]
- [REDACTED]

Protocol Amendment 7, 23Apr2015

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 7. Major changes to the protocol are summarized below.

1. Section 3.1.1 (Inclusion Criteria) – Inclusion criteria 10 and 11, and Table 3.1.1-1 relating to methods of contraception were revised to clarify that not all methods of contraception are highly effective and to specify that female subjects must use a hormonal method in addition to a barrier method alone, to minimize the chance of pregnancy (inclusion criterion 10). For inclusion criterion 11, the following statement was added: “It is required that a female partner of a male subject also uses an effective method of contraception throughout this period.” Additionally, the length of time that nonsterilized males are required to use an effective method of contraception was increased from Day 1 for 60 days after receipt of the final dose of investigational product to Day 1 for 90 days after receipt of the final dose of investigational product. Table 3.1.1-1 was revised as follows: 1) the table title was re-titled from “Highly Effective Methods of Contraception” to “Effective Methods of Contraception”; 2) a footnote was added to the contraceptive method of male condom plus spermicide to specify that female partners of male subjects must use an effective method of birth control; and 3) a footnote was added to clarify that male condom plus spermicide or the minipill are not considered highly effective when used as the only method of birth control.
2. Section 3.1.2 (Exclusion Criteria) – The following language in exclusion criterion 1 was changed from “... prior to entering the study” to “... prior to initiation of treatment” for consistency with other sections in the protocol. Prior splenectomy and lymph nodes > 4 cm have been removed from the list of exclusion criteria (previously exclusion criterion 7).

3. Section 3.3.2 (Pre-Cycle before Subsequent Cycles [Day -3 to Day 1]) and Section 3.3.3 (During Cycle) – AEs and concurrent medications were added to these sections for clarity and for consistency with Table 10-1 (Study Calendar for Cycle 1 and Subsequent Cycles).
4. Section 3.3.3 (During Cycle) – Haptoglobin was removed from the Day 8 (±1 day) assessments for consistency with Table 10-1 (Study Calendar for Cycle 1 and Subsequent Cycles).
5. Section 5.1.1 (Moxetumomab pasudotox) – The collection timepoints for vital signs were added for clarity.
6. Section 5.4 (Duration of Follow Up) – Language was added to remind investigators not to treat patients in CR with any anti-cancer therapies, as this will result in the patient being discontinued from the study.
7. Section 7.3.1 (Capillary Leak Syndrome) – For clarification, the following wording was changed from: “Capillary leak syndrome Grade 3 will be defined as any of the following” to “Capillary leak syndrome should be suspected if any of the following are observed”.

8. Section 9 (Biomarker, Correlative, And Special Studies) – A global change was made to this section for providing additional language stating that a laboratory manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information specific to this study.

[REDACTED]

9. Section 9.2.3 (Peripheral Blood Flow Cytometry) –

[REDACTED]

10. Section 9.2.4 (Lymphocyte Enumeration)

[REDACTED]

11. Section 10 (Study Calendar, Table 10-1 [Study Calendar for Cycle 1 and Subsequent Cycles]) – The word “total” was added to bilirubin in row 9 for consistency with how it is stated in the protocol evaluation section (Section 3.3).

Administrative Change 1, 11Mar2015

The purpose of this administrative change is to allow for minimal residual disease (MRD) analysis of bone marrow aspirate and peripheral blood by flow cytometry to be performed by either a local or site-contracted laboratory or by the central laboratory [REDACTED]

[REDACTED] The following changes were made:

- Section 9.2.2 (Bone Marrow Aspirate MRD Analysis) – Revised to allow MRD analysis of bone marrow aspirate to be evaluated either at a local or site-contracted laboratory or at the central laboratory [REDACTED]
- Section 9.2.2.2 (Sample processing) and Section 9.2.2.3 (Site Performing the Study) – Revised to allow for samples to be processed and analyzed by either a local or site-contracted laboratory or by [REDACTED]
- Section 9.2.3 (Peripheral Blood Flow Cytometry) - Revised to allow for the use of either a local or site-contracted laboratory or [REDACTED] to perform the evaluation of HCL phenotypes through peripheral blood flow cytometry.
- Section 9.2.3.2 (Sample processing) and Section 9.2.3.3 (Site Performing the Study) - Revised to allow for samples to be processed and analyzed by either a local or site-contracted laboratory or by [REDACTED]

Protocol Amendment 6, 22Jan2015

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 6. Major changes to the protocol are summarized below.

The primary reason for this amendment is to update the risk/benefit section [REDACTED] [REDACTED]. Additional changes to this amendment include: more closely aligning the immunogenicity collection timepoints with the PK collection timepoints; [REDACTED] [REDACTED] to provide clarifying language in reference to when screening evaluations are to be performed; to describe the methods to be used [REDACTED] [REDACTED] to add [REDACTED] as the central laboratory; to provide a note for Germany sites that MRI will be performed for all radiographic assessments, as CT is not permissible; and to correct discrepancies created during the last protocol amendment.

1. Section 2.2 (IND Agent - Moxetumomab pasudotox) – [REDACTED] [REDACTED]
2. Section 2.3 (Rationale) [REDACTED] [REDACTED]
3. Section 3.3.1 (Performed Within 4 Weeks Prior to Treatment Enrollment) – The word “Enrollment” was removed from the heading title for clarity; [REDACTED] [REDACTED] deleted pulse oximetry as a separate bulleted item, [REDACTED] query for visual symptoms, alkaline phosphatase and uric acid were added for consistency with Section 10 (Study Calendar); the wording “for analysis by flow cytometry/sequencing” was added as a description for the collection of the bone marrow biopsy and aspirate; [REDACTED] [REDACTED] The following note was added for Germany sites: “Subjects enrolled in Germany will utilize MRI for all radiographic assessments (CT not permissible).”
4. Section 3.3.2 (Pre-Cycle before Subsequent Cycles [Day -3 to Day 1]) – [REDACTED] [REDACTED] Query for visual symptoms was added for consistency with Section 10 (Study Calendar).
5. Section 3.3.3 (During Cycle) – [REDACTED] [REDACTED] [REDACTED] For clarity, the wording :”30-60 minutes post end of infusion“ was removed from the Days 1 and 5

- bulleted item and moved to the 12 Lead ECG sub-bulleted item, and clarified that this collection timepoint was for Cycle 1 only. Physical exam, pulse oximetry and query for visual symptoms were added for consistency with Section 10 (Study Calendar).
6. Section 3.3.4.1 (All patients 29-43 days after the first day of dosing of prior cycle [end of treatment assessment]) – The title was changed to: All patients 28-42 days after the first day of dosing of prior cycle [end of treatment assessment]) in order to allow for restaging to occur the same day of the week that treatment was initiated.
 7. Section 3.3.4.1 (All patients 28-42 days after the first day of dosing of prior cycle [end of treatment assessment]) and Section 3.3.4.4 (For all patients in follow-up) – The word “sequencing” was added to the bulleted item for bone marrow biopsy and aspirate with flow cytometry to clarify that MRD will be assessed by sequencing. [REDACTED]
 8. Section 3.3.4.4 (For all patients in follow-up) – [REDACTED]
 9. Section 5.2.2.5 (Hemolytic Uremic Syndrome [HUS]) – [REDACTED]
 10. Section 7.3.2 (Thrombotic Microangiopathy/Hemolytic Uremic Syndrome) – Added language to clarify the definition of a HUS-like event.
 11. Section 7.4.3.3 (Thrombotic Microangiopathy/Hemolytic Uremic Syndrome – Added the wording “and HUS-like events.”
 12. Section 7.6.4 (Other Adverse Events of Special Interest) – [REDACTED]
 13. Section 9.1.1.1 (Collection of Specimens) – [REDACTED]
 14. Section 9.1.1.3 (Shipping of Specimens) – Shipping and contact information for shipping samples to MedImmune was removed, as samples will be processed by [REDACTED] and all shipping information will be provided in the laboratory manual.
 15. Section 9.2.1 (Evaluation of Immunogenicity) – Immunogenicity evaluation timepoints were corrected to be consistent with the changes made to the Protocol Evaluation

Sections 3.3.1, 3.3.2, 3.3.3, and 3.3.4.4 as noted above. [REDACTED]

16. 9.2.1.1 (Collection of Specimen[s]) – Collection timepoints for immunogenicity were revised to be consistent with changes as described for Section 9.2.1.
17. Section 9.2.1.3 (Shipping of Specimen[s]) – Contact information for MedImmune was removed and [REDACTED] was added as samples will be shipped to [REDACTED] and all shipping information will be provided in the laboratory manual.
18. Section 9.2.1.4 (Site Performing the Study) – Language was added to specify that samples will be processed by [REDACTED]
19. Section 9.2.2 (Bone Marrow Aspirate MRD Analysis) – Clarifying language was added to this section to indicate that [REDACTED]
20. Section 9.2.2.1 (Collection of Specimen[s]) – Clarified that samples to be collected at 181 days after end of treatment are only for subjects in PR or CR.
21. Section 9.2.2.2 (Sample Processing) and Section 9.2.2.3 (Site Performing the Study) – Central clinical laboratory was replaced with [REDACTED]
22. Section 9.2.3.1 (Collection of Specimen[s]) – Provided clarifying language for the Cycle 3 and Cycle 5 collection timepoints for peripheral blood flow cytometry.
23. Section 9.2.4 (Lymphocyte Enumeration) [REDACTED]
24. Section 9.2.4.1 (Collection of Specimen[s]) – [REDACTED]
25. Section 9.2.4.2 (Sample Processing) and Section 9.2.4.3 (Site Performing the Study) – Central clinical laboratory was replaced with [REDACTED]
26. Section 9.2.5 (Peripheral Blood Disease B-cell Clone Detection) – New section and subsequent subsections 9.2.5.1 (Collection of Specimen[s]); 9.2.5.2 (Sample Processing); and 9.2.5.3 (Site Performing the Study) were added [REDACTED]
27. Section 10 (Study Calendar) – Tables 10-1 (Study Calendar for Cycle 1 and Subsequent Cycles) and 10-2 (Study Calendar for End of Treatment and Follow-up) were updated to reflect the changes made to Section 3 (Protocol Evaluation) and Section 9 (Biomarker, Correlative, and Special Studies). Table 10-1 was also updated to include collection of schistocyte counts (at select timepoints) as part of the CBC differential assessment.
28. Section 14.3.2.1 (Important Potential Risks) – [REDACTED]

29. Section 14.3.2.2 (Identified Risks) – [REDACTED]
30. Section 15 (References) – Deleted 3 references, as they were not cited in the protocol.

Protocol Amendment 5, 02Oct2014

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 5. Major changes to the protocol are summarized below.

The primary reason for this amendment is to add key safety enhancements and to include a DMC.

1. Précis: Updated to be consistent with the changes made to the body of the protocol.
2. Section 2.2 (IND Agent - Moxetumomab pasudotox): [REDACTED]
3. Section 2.3 (Rationale): The last paragraph, [REDACTED]
4. Section 5.2.1 (Concomitant Medications): Additional language was added to item #3 to allow for secondary prophylaxis with dexamethasone 4 mg intravenous or oral for infusion-related reactions to be administered at the investigator's discretion.
5. Section 5.2.2.6 (Ocular Events): Language was added to clarify reporting of ocular symptoms on dosing days should be done prior to the administration of moxetumomab pasudotox.
6. Section 6 (DOSING DELAYS/DOSE MODIFICATIONS): The following sentence was added to the second bulleted item: "Patients should not begin a subsequent treatment cycle of moxetumomab if there is active, ongoing infection requiring treatment." This statement was added to be in line with exclusion criterion 9, which excludes subjects who have an ongoing or active infection and are not eligible for therapy.
7. Section 7.3.2 (Thrombotic Microangiopathy/Hemolytic Uremic Syndrome): Additional safety reporting instructions were provided to describe the added safety reviews that will occur in the event that a Grade 3 or greater HUS is reported.
8. Section 7.3.3 (Ocular Events): clarifying language was added to indicate that ocular symptoms will be queried prior to each dose.

9. Section 7.7 (Safety Management During the Study): This is a new section that has been added to describe the responsibility of the MedImmune medical monitor, MedImmune Patient Safety, and the DMC concerning the review of safety data.
10. Section 9.1.1.1 (Collection of Specimens): [REDACTED]
11. Section 9.2.2 (Bone Marrow Aspirate MRD Analysis), Section 9.2.2.1 (Collection of Specimen(s); 9.2.2.2 (Sample Processing); and 9.2.2.3 (Site Performing the Study): New sections added to describe how bone aspirate for MRD will be analyzed, the collection timepoints during the study, and where it will be processed and analyzed.
12. Section 9.2.3.1 (Collection of Specimen[s]): The sample collection time at 6 months was changed to 181 days to align with the Study Calendar.
13. Section 10.0 (Study Calendar): [REDACTED] Added an X for all dosing days to clarify that visual symptoms will be queried prior to each dose. [REDACTED]
14. Section 13.7 (Data Monitoring Committee): This new section has been added to include the addition of a DMC and to describe their responsibilities.

Protocol Amendment 4, 12Aug2014

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. Changes to the protocol are summarized below and are divided into 3 sections that include: 1) a list of the sections that were changed to be compliant with the MedImmune Protocol Template 16.2; 2) changes specific to the study design and study assessments in order to be in line with a pivotal Phase 3 trial; and 3) global changes made throughout the document for consistency and/or clarity. Minor changes such as the addition of abbreviations, minor edits for clarity, corrections in spelling, grammar, and formatting are not shown below.

The primary reason for this amendment is [REDACTED]

[REDACTED]

Sections Updated to Align with MedImmune Protocol Template 16.2

1. Title page [REDACTED]
2. Section 3.1.1 (Inclusion Criteria): Inclusion Criterion #6 was removed (with the exception of the last sentence) and replaced with inclusion criterion #11 to include MedImmune protocol template language for females of child bearing potential. The last sentence of inclusion criterion #6 was added to the end of inclusion criterion #11, which reads as: "Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately." An additional criterion #12 was added to include information for nonsterilized males.
3. Section 3.3 (Accrual Targets): [REDACTED]
4. Section 4 (Registration Procedures): Entire section replaced with MedImmune Protocol Template language.
5. Section 5.1 (Agent Administration): First sentence modified from "Treatment may be administered on an inpatient or outpatient basis depending on the needs of the patient and the institution at which they are seen" to "Treatment will be administered on either an inpatient or outpatient basis.
6. Section 5.1.2 (Reporting Product Complaints): New section per MedImmune Protocol Template.
7. Section 5.2.2.6 (Ocular Events): New section. [REDACTED]
8. Section 5.5.1 (Off Study Procedures): Title was changed to Study Timetable and End of Study and content was replaced with MedImmune Protocol Template language.
9. Section 7.0 (Adverse Events: List and Reporting Requirements): This section was removed and replaced with the Assessment of Safety section per MedImmune Protocol Template.
10. Section 8.0 (Pharmaceutical Information): Revised to follow MedImmune specific information and instruction for administration of this product. Additional subsections were added, including Additional Study Medications, Labeling, Treatment Compliance, and Accountability per the MedImmune Protocol Template.
11. Section 9.3 (Sample Storage, Tracking and Disposition): [REDACTED]
12. Section 11.2 (Data Collection): [REDACTED]
13. Sections 11.3 (Data Reporting), 11.4 [REDACTED] Multicenter Guidelines), and 11.5 (Collaborative Agreements Language) [REDACTED] replaced with Section 12 (Study Data Management) per the MedImmune Protocol Template.

14. Section 14.0 – formerly Section 13.0 (Human Subjects Protections): This section was revised to be in line with MedImmune Protocol Template language, [REDACTED]
15. Three Appendices were added to include the signature pages (Appendix 1); Additional Safety Guidance (Appendix 4); and National Institute of Allergy and Infectious Diseases (NIAID) and Food and Allergy Anaphylaxis Network (FAAN) Guidance for Anaphylaxis Diagnosis (Appendix 5).

Changes to the Study Design and Study Assessments

1. Section 2.3 (Rationale): Text was added to provide additional information on BRAF inhibitors and to include information from another moxetumomab pasudotox trial [REDACTED] regarding the number of cycles to be given during this trial.
2. Section 3.1.1 (Inclusion criterion # 3): Re-worded for clarity and was changed from “Patients must have had at least 2 prior purine analogs, or at least 1 course of purine analog and 1 of either rituximab or BRAF inhibitor” to “Patients must have received at least 2 prior systemic therapies, including 2 courses of a purine nucleoside analog (PNA), or one course of either rituximab or BRAF inhibitor following a single prior course of PNA.”
3. Section 3.1.1 (Inclusion criterion # 7.d): The Cockcroft-Gault equation, provided as part of this criterion, was removed from this section and placed in Appendix 3 titled, Cockcroft-Gault Equation. It was moved to an Appendix, as this is an equation and is not an exclusion criterion.
4. Section 3.1.2 (Exclusion criterion # 4): Changed from “Patients with clinically significant ophthalmologic findings during screening” to “Patients with retinal or choroidal detachment identified during the screening ophthalmologic evaluation.” This change was made in order to clarify the meaning of, “clinically significant ophthalmologic findings.”
5. Section 3.1.2 (Exclusion criterion # 9): Uncontrolled hypertension was added to the list of conditions that are exclusionary for this study.
6. Section 3.1.2 (Exclusion criterion # 20): Changed from “Patients with QTc elevation > grade 1” to “Patients with corrected QT interval (Frederica) elevation > Grade 2.” [REDACTED]
7. Section 3.3 (Protocol Evaluation): The following global changes were made to this section: Changed the assessment of triiodothyronine (T3) to free thyroxine T4 (fT4), as this is the prohormone of T3 and is both the major form of thyroid hormone in the blood and more widely utilized for routine diagnostic testing; T&B cells was changed to lymphocyte enumeration for clarity and differentiation from peripheral blood flow cytometry for HCL phenotype cells.
8. Section 3.3.2 -formerly Section 3.4.2 (Performed Within 8 weeks Prior to Treatment Enrollment): Was deleted and combined with Section 3.3.1- formerly Section 3.4.1 (Performed Within 4 Weeks Prior to Treatment Enrollment) for clarification, as most assessments are to be performed within 4 weeks prior to treatment enrollment. Language was added to the assessments for bone marrow biopsy and aspirate and CT or MRI

imaging to state that if these assessments are performed within 8 weeks prior to therapy, they do not need to be repeated. The assessment of spleen ultrasound for spleen size was removed, as CT and MRI generally provide more accurate bi-dimensional measurements for response assessments. Further, our organization experience is that the quality of ultrasound studies submitted for central review can vary widely, yielding more difficult central radiographic interpretation. HIV was removed as a screening test, because HIV is not exclusionary for patients on HAART therapy and because CD4 counts will be monitored during the course of the study.

9. Section 3.3.2 -formerly Section 3.4.3 (Pre-Cycle before retreatment [day -3 to day 1]): The title for this section was changed to Pre-Cycle before Subsequent Cycles ((Day -3 to Day 1), for clarity. In addition, assessment for weight was clarified to indicate that dose, rather than total dose not be changed during a cycle; and the following language was added: dose should be adjusted for weight change $\geq 10\%$ from screening in subsequent cycles.” [REDACTED]

[REDACTED]. The following assessments were removed:

- If baseline measurable lymphadenopathy or baseline spleen diameter $>17\text{cm}$, image with U/S, CT or MRI abdomen. Otherwise precycle imaging may be with spleen U/S. Precycle imaging needed only until consistent with CR). [REDACTED]

- Bone Marrow Biopsy and Aspirate with Flow Cytometry (Do after at least 4 weeks of counts consistent with CR, repeat every 1-2 cycles until negative). [REDACTED]

10. Section 3.3.3- formerly Section 3.4.4 (During Cycle): Clarifying language stating that new visual symptoms of Grade 2 or greater should be evaluated with a full ophthalmologic assessment was added to the assessment for visual [REDACTED] a statement was added for recommending measurement of tumor burden in the event of HUS; and for Days 1, 3, and 5 assessments, urinalysis was clarified as only being collected on Day 1 [REDACTED]. A subsection was added for an optional interim disease assessment to be performed at the discretion of the investigator during treatment and prior to completion of 6 cycles of therapy, if blood counts are consistent with CR for at least 4 weeks.

11. Section 3.3.4.1 - formerly Section 3.4.5.1 (All patients 4-6 weeks after last dose [end of treatment]): The title was changed to “All patients 29-43 days after the first day of dosing of prior cycle (end of treatment assessment)” for clarity. Ophthalmologic exam was added, as it is considered one of the end of treatment assessments; the following was changed from “Peripheral Blood Flow Cytometry (if not yet negative)” to “Peripheral Blood Flow Cytometry”; the wording “Imaging with CT or MRI of abdomen (or spleen ultrasound if no lymph nodes on prior imaging)”, was changed to “Imaging with CT or MRI for lymphadenopathy and organomegaly”; the following wording: “if needed to confirm CR for the 1st time in those with counts consistent with CR for 4 weeks”, was removed from the bone marrow biopsy and aspirate with flow cytometry assessment; and the bulleted item stating that for patients with SD, PR or CR are then followed until PD from baseline was changed to “Patients with SD, PR or CR are then followed until relapse from baseline.”
12. Section 3.3.4.2 - formerly Section 3.4.5.2 (For those in CR): Title was changed to “Follow-up for those in CR” and clarifying language was added.
13. Section 3.3.4.4 - formerly Section 3.4.5.4 (6, 12, 18 and 30 months from the time best response begins (or, for those with best response of SD, from the end of treatment), then every 2 years): Re-titled to “For all patients in follow-up.” The following sentences were added: “The Day 181 post-end of treatment assessment may not be performed prior to Day 181. This assessment may be performed between Day 181 and Day 195 post-end of treatment.” For clarity, 6 months was changed to Day 181 throughout this section, and reference was made to Table 10-2 for specific follow-up timepoints. Under the revised schedule of assessments, there is no distinction between the 30 month post and “yearly thereafter” assessments, as such the 30 month post end of treatment assessment was removed because these data will be captured in the first subsequent annual follow-up visit.
14. Section 5.1.1 (Moxetumomab pasudotox): Additional text was added to specify that subjects will receive up to 6 cycles of therapy. [REDACTED] Additional text was added for detection, prophylactic treatment, and management of CLS, TLS, or ocular events.
15. Section 5.2.1 (Concomitant Medications): Clarifying language was added to instruction #1 to indicate that use at the discretion of the study PI for Grade 4 neutropenia without fever is permitted but discouraged.
16. Section 5.2.2.3 (Cytokine Support): The last portion of the sentence in this section was deleted, as it was not necessary for the instructions for management of neutropenic infections.
17. Section 5.2.2.5 (Hemolytic Uremic Syndrome [HUS]): The following language: “If HUS of any grade develops, treatment should be suspended until resolution of all laboratory abnormalities, and should only be resumed if the maximum grade was ≤ 2 , and after consultation and agreement with the sponsor” was added [REDACTED]
18. Section 5.2.2.6 (Ocular Events): New section. [REDACTED]

19. Section 5.3 (Duration of Therapy): Added a criterion specifying that 6 cycles of therapy are allowed for this study; treatment delay was specified as > 2 weeks; [REDACTED]
20. Section 5.4 (Duration of Follow Up): Additional language was added for clarity.
21. Section 5.5 (Off Study Criteria) [REDACTED] the fifth bullet “Severe or life-threatening anaphylaxis or hypersensitivity reaction was moved to Section 5.4 (Duration of therapy); and an additional bulleted items were included, [REDACTED]
22. Section 6.0 (Dosing Delays/Dose Modifications): Revised to be consistent with changes made to Section 5.3 (Duration of Therapy); to specify that moxetumomab pasudotox infusion should be interrupted for Grade 2 or Grade 3 infusion related reactions and should be permanently discontinued for Grade 4 (life-threatening) anaphylaxis or hypersensitivity reaction; to clarify that patients with \geq Grade 3 CLS or \geq Grade 3 HUS should be permanently discontinued from treatment; and clarified fever as not being associated with $ANC < 1.0 \times 10^9/L$ for one of the sub-bullets.
23. Section 9.2 (Laboratory Correlative Studies): the following instructions were added to this section: “A laboratory manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.
24. Section 9.2.2.2 (Sample processing) and Section 9.2.2.3 (Site Performing the Study): Wording was changed from “local” to “central” clinical laboratory [REDACTED]
25. Section 10.0 (Study Calendar): For clarity, the table in this section was divided into 2 tables with the first table including assessment timepoints for Cycle 1 and subsequent cycles and the second table including the assessment timepoints for end of treatment and follow-up. Additional changes were made to this section in order to be consistent with the changes made to the Protocol Evaluation Section 3.3, [REDACTED]
26. Section 11.0 (Measurement of Effect) and Section 11.1 (Response Criteria): Revised to reflect changes made in the Protocol Evaluation Section 3.3.
27. Section 13.1 – formerly Section 12.2 (Analysis Populations): Specified the inclusion of bone marrow examination and cross sectional imaging as post baseline disease assessments.
28. Section 13.3 – formerly Section 12.3 (Primary Endpoint): The following sentence was removed: “Relapsed HCL refers to patients who have received at least 2 prior purine analog treatment regimens unless refractory to the 1st course, with ‘refractory’ defined as response lasting < 1 year.” [REDACTED]
[REDACTED] Because this is a multi-site study with an efficacy endpoint as primary, central independent response review has been added.
29. Section 13.4.1.1- formerly Section 12.4.1.1(CR Rate and Duration of CR [Disease-Free Survival]): Title was changed to CR Rate, Duration of CR (Disease-Free Survival), and Duration of HR to include the measurement of HR and measurement for the duration of HR was described. The following sentence was changed from “Duration of CR will be

censored on the date of the last disease assessment for subjects” to “Duration of CR and HR will be censored on the date of the last disease assessment or clinical response assessment for subjects” The final sentence of this section stated that CR and HR duration may be different; therefore additional text is provided to clarify how HR will be assessed.

30. Section 13.4.1.5- formerly Section 12.4.1.5 (Time to Treatment Failure (TTF) or Progression-Free Survival (PFS): Title changed to “Progression-Free Survival (PFS).” Text was added to include initiation of alternative anticancer therapy as a stopping point for the measurement of PFS and clarifying language was added to define PFS separately from TTF.
31. Section 13.4.1.6- formerly Section 12.4.1.6 (Relapse-Free Survival [RFS]): Title was changed to “Time to Treatment Failure (TTF)” [REDACTED] Wording was modified to be specific for TFS rather than RFS.
32. Section 13.5- formerly Section 12.5 (Sample Size and Power Calculations): [REDACTED]
33. Appendix 3 (Cockcroft-Gault Equation) was added for determining creatinine clearance.

Global Changes for Consistency and/or Clarity

1. Sections and subsections were re-formatted [REDACTED]
2. Changed units for neutrophil and platelet counts to SI units, as this is the preferred standard of measure.
3. [REDACTED]
4. Lymphocyte phenotyping T& B, subsequently referred to as T & B throughout, was replaced with lymphocyte enumeration for clarity.
5. The wording “CBC+Diff with Slide” was changed throughout to “CBC with differential and peripheral blood smear.”

Protocol Amendment 3 [REDACTED]

[REDACTED] **09Jun2014**

SUMMARY OF CHANGES

1. Title page: The version date has been updated to June 9, 2014; [REDACTED]

- [REDACTED]
2. Précis and Section Inclusion Criteria 3.1.1: The eligibility criteria have been modified to clarify that subjects with hairy cell leukemia variant are eligible for enrollment. In addition, the eligibility criterion regarding prior systemic therapies has been revised to state that patients who have had at least 2 prior purine analogs, or at least 1 course of purine analog and 1 of either rituximab or BRAF inhibitor are eligible for enrollment.
[REDACTED]
 3. Section 2.3, Rationale: The following has been added as the last sentence of the “Standard 1st and 2nd-line treatment for HCL” heading: “However, it is becoming more common now for patients to try non-chemotherapy options even after a long response to purine analog, given the known long-term and likely permanent toxicities of the latter, particularly when used in 2nd line.
In addition, the following has been added under the heading, “Primary endpoint for moxetumomab pasudotox”: “The minimum prior treatment required for this protocol, namely 2 purine analogs or 1 purine analog plus one course of rituximab, is appropriate because repeat courses of purine analog are now used less frequently due to their cumulative toxicity and decreasing benefit. Moreover, the largest prospective trial of rituximab alone for HCL, which showed a 13% CR rate, included patients with only 1 prior purine and no other therapy.”
 4. Section 3.1.2.21: The exclusion criterion regarding high dose estrogen has been updated to include the excluded dose, >0.625 mg/day.
 5. Section 3.1.2.22: It has been clarified in this section that this exclusion criterion refers to disseminated intravascular coagulation grades 3 and 4.
 6. Section 3.4.4, During cycle: The timing of procedures for Cycle 1 days 1 and 5 has been revised from 30 minutes after the end of infusion to 30-60 minutes after end of infusion. Additionally, the immunogenicity evaluation has been removed from the list of day 8 assessments.
 7. Section 3.4.5.4: The immunogenicity evaluation has been removed from the list of assessments scheduled to occur 6, 12, 18 and 30 months from the time best response begins.
 8. Section 5.1.1, Moxetumomab pasudotox: The second and third paragraphs in this section have been revised to more clearly indicate the guidelines for fluid and antihistamine administration. Additionally, this section has been updated to allow a window of +30 minutes to provide flexibility in the administration of all protocol medications. A + 10 minute window has been added for the collection of vital signs during the moxetumomab pasudotox infusion and a window of +30 minutes has been added for the hourly vital sign assessment.
 9. Section 5.2.1: Subsection 4) has been updated to include the following underlined content: Use of non-steroidal anti-inflammatory medications (NSAIDs) is not permitted from the first dose of the cycle through 7 days after the last dose of the cycle.

10. Section 5.2.2.5, Hemolytic Uremic Syndrome (HUS): [REDACTED]
11. Section 7, Adverse Events: List and Reporting Requirements: Throughout this section, references to the [REDACTED]. Additionally, the website for adverse event reporting guidelines has been updated in Section 7.1.1.
12. Section 7.2.1, Adverse Event: The adverse event definition has been updated to include the following underlined content: Pre-existing (baseline) laboratory abnormality will be considered the last one obtained prior to the first dose of drug, unless the PI considers an abnormality of higher grade occurring within 100 days prior to the first dose to be a truer baseline.
13. Section 9.1.1.1, Collection of Specimens: This section has been updated to include clarification that “post infusion” means after the end of infusion.
14. Section 9.2.1.1 Collection of Specimen(s): [REDACTED]
15. Section 10, Study Calendar: The study calendar has been updated to:
 - a. Remove the reference to adverse event and concurrent medication assessments.
 - b. Clarify that the CBC with differential (slide) will be repeated at least 6 months after confirmation of CR, then every 3 months for 2 years, and then every 6 months; a differential but no slide is needed with each of these off-treatment assessments. This was done by removing footnote 16 and consolidating the information into footnote 8.
 - c. Placed immunogenicity evaluation on its own line to differentiate the time points for assessment
 - d. Removed 12 month timepoint from footnotes 4 and 13.
 - e. Update footnote 13 to indicate that off-treatment assessments will occur 4-6 weeks after the last dose of Moxetumomab pasudotox.
16. Section 11.1, Response Criteria: This section has been updated to clarify that in addition to the principal investigator, an associate investigator may record tumor response.
17. Section 15.3, Appendix C: Registration Cover Memo: The [REDACTED]

Protocol Amendment 2 [REDACTED] 20Feb2014

SUMMARY OF CHANGES

This amendment was submitted [REDACTED]. In addition, the Investigator included additional participating institutions, updated timing of study procedures and responded to recommendations [REDACTED].

Changes made to the protocol [REDACTED] are provided below:

1. Section 3.4.4: It was clarified in this section that EKG and PKs will be performed on Cycle 1 days 1 and 5 within 30 minutes after the end of Moxetumomab pasudotox infusion.
2. Section 3.4.5.4: The heading in this section currently states: 6, 12, 18 and 30 months from the time best response begins (or, for those with best response of SD, from the end of treatment), then every 2 years.
3. Section 12.4.1.5 has been updated to state:

Time to Treatment Failure (TTF) or Progression-Free Survival (PFS)

TTF, like PFS, is measured from the start of moxetumomab pasudotox administration to relapse or death from any cause. Relapse is considered when patients no longer meet criteria required for their best response. TTF/PFS will be censored on the last day of disease assessment for subjects without relapse or death, including subjects who drop out or obtain alternative therapy. TTF/PFS will be evaluated using the Kaplan-Meier method. Additionally, Section 12.4.1.6, Relapse-Free Survival (RFS) has been updated to state: RFS will be measured from the start of moxetumomab pasudotox administration until relapse as defined by TTF/PFS. RFS will be censored as in TTF/PFS but will also be censored for death not accompanied by relapse, and will also be evaluated using the Kaplan-Meier method.

[REDACTED]

Additional protocol changes:

1. Title page: The version date has been updated to February 20, 2014; [REDACTED]

- [REDACTED]
2. Précis: The secondary objective has been updated to include time to treatment failure (TTF).
 3. Section 1.2: The secondary objectives have been modified to replace relapse-free survival (RFS) with time to treatment failure (TTF) [REDACTED]
 4. Section 3.1.2.9: This section has been updated to include malaria infection as an excluded intercurrent illness.
 5. Section 3.1.2.12: The exclusion criterion previously listed in this section has been removed and replaced by: Patients with history of both thromboembolism and known congenital hypercoagulable conditions.
 6. Section 3.1.2.21: [REDACTED] the exclusion criterion previously listed in this section has been removed and replaced with: “Patients on high dose estrogen”.
 7. Section 3.1.2.22: [REDACTED] the following exclusion criterion has been added to this section: “Patients with clinical evidence of disseminated intravascular coagulation”.
 8. Section 3.4, Protocol Evaluation and Section 10, Study Calendar: Section 3.4 has been modified to reflect a change in the timing of various study procedures and laboratory tests. Section 10 illustrates the timing for the various protocol procedures. Specifically:
 - a. Section 3.4.1: Hepatitis B surface antigen, HBV viral load, HIV test, Hep C antibody, qualitative immunoglobulins, and serum protein electrophoresis are no longer required within 4 weeks prior to treatment enrollment; IgG, IgA and IgM have been added to the testing required with 4 weeks prior to enrollment
 - b. Section 3.4.2: Hepatitis B surface antigen and core antibody, HBV viral load, HIV test, Hep C antibody, HLA typing [REDACTED] and Complement C3, C4, and CH50 are now required within 8 weeks prior to treatment enrollment
 - c. Section 3.4.3: Guidance was provided with regard to imaging for disease assessment and EKG has been added to pre-cycle study procedures
 - d. Section 3.4.4: Added that patients will be asked about visual symptoms and reminded to report visual symptoms experienced during the cycle
 - e. Section 3.4.5.2: Redundant timing of CBC was removed from this section
 - f. Section 3.4.5.4: Guidance was provided with regard to imaging for disease assessment and EKG was removed from this section
 9. Section 5.1.1: The third paragraph in this section has been revised to include the following underlined content: “Substitutions of diphenhydramine for hydroxyzine and famotidine or cimetidine for ranitidine may be done if needed with approval from the PI.” In addition, the following has been added as the final paragraph in this section [REDACTED] [REDACTED] “An event of \geq Grade 2 hypercalcemia with calcium level corrected for serum albumin will require a delay in dosing until resolution to $<$ Grade 2. If visual symptoms are reported, it is recommended

that an ophthalmologic examination be performed for evidence of fluid accumulation/retinal detachment in the eye. If a $\geq 5\%$ increase in body weight due to fluid overload occurs and visual symptoms are reported, then it is recommended that an ophthalmologic examination be performed for evidence of fluid accumulation/retinal detachment in the eye. If a $\geq 10\%$ increase in body weight due to fluid overload occurs, it is recommended that imaging of the chest is obtained for any evidence of pulmonary edema so appropriate treatment may be instituted promptly.”

10. Section 5.3: The following content has been removed for the final paragraph of this section [REDACTED] “Moxetumomab pasudotox may be stopped/ discontinued if patient does NOT show measure of improvement by 50% by bone marrow flow cytometry OR peripheral blood flow cytometry, every other cycle.”
11. Section 6: [REDACTED] this section has been modified to state that patients who experience grade 4 CLS and grade 3 HUS will be taken off treatment instead of off study. [REDACTED] it was specified that an event of ≥ 2 hypercalcemia with calcium level corrected for serum albumin will require a delay in dosing until resolution to $<$ Grade 2.
12. Section 8.1: [REDACTED]
13. Section 9.1.1.1: [REDACTED]
14. Section 9.2.1: The first sentence in this section has been revised to include the following underlined content (deleted content appears in strike-through text): [REDACTED]
[REDACTED] Additionally in Section 9.2.1 [REDACTED] the final sentence in this section has been revised to include the following underlined content: “Titer and the specificity of ADA will be determined for subjects with positive neutralizing anti-drug antibodies (NAb) and may be determined in subjects with negative NAb.”
15. Section 11.1.1: Length of abnormal lymphadenopathy has been updated to ≥ 2 cm.
16. Section 11.1.2: The final bulleted statement has been revised [REDACTED] to include the following underlined content, deleted content appears in strike-through text: “The beginning of PR will be considered the beginning of the 4-week duration of required normal blood counts meeting PR criteria.”
17. Section 11.1.5: [REDACTED] relapse from CR, relapse from PR and relapse from SD have been defined in this section.
18. Section 12.2: [REDACTED] the first sentence in this section has been revised to clarify that subjects will be included in the intent-to-treat population if they have been treated with moxetumomab pasudotox.
19. Section 12.4.1.1: [REDACTED] it has been clarified that CR duration will be summarized separately as it is a secondary endpoint.
20. Section 15.3: The registration cover memo has been updated to include additional sites, [REDACTED]

Protocol Amendment 1 [REDACTED] **26Mar2013**

SUMMARY OF CHANGES

This amendment was submitted [REDACTED]. Changes made to the protocol [REDACTED] are provided below:

1. Section 6 has been updated (Page 24, 6th Bullet) to include stopping rules for when patients redevelop ~ Grade 3 non-hematologic toxicities after holding and re-challenge. The revised language is located below:
 - a. After dosing delays and re~challenge: Patients who redevelop \geq : Grade 3 non-hematologic toxicities, which are not covered by the exclusions in this section, with at least possible attribution to the study drug, will result in the patient coming off treatment but not offstudy.
2. The following exclusion criterion has been added to Section 3.1.2.4 (Page 17) [REDACTED]
[REDACTED] "Patients with clinically significant ophthalmologic findings during screening"
3. The protocol was revised to include Ophthalmologic Exam to be performed during baseline and during follow-up. The following sections of protocol were revised:
 - a. Page 18, Section 3.4, Screening Evaluation, 2nd Bullet
 - b. Page 41, Section 10, Study Calendar

Appendix 1 Signatures

Sponsor Signature(s)

A Pivotal Multicenter Trial of Moxetumomab Pasudotox in Relapsed/Refractory Hairy Cell
Leukemia

I agree to the terms of this protocol.

Signature and date: _____

[REDACTED]

[REDACTED]

[REDACTED]

One MedImmune Way, Gaithersburg MD, 20878, USA

[REDACTED]

Signature of Principal Investigator

A Pivotal Multicenter Trial of Moxetumomab Pasudotox in Relapsed/Refractory Hairy Cell Leukemia

I, the undersigned, have reviewed this protocol and all amendments, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

Telephone number: _____

Site/Center Number (if available) _____

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from MedImmune or AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

Appendix 2 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 3 Cockcroft-Gault Equation

A commonly used surrogate marker for actual creatinine clearance is the Cockcroft-Gault formula, which employs creatinine measurements and a patient's weight to predict the clearance (Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.*, 16(1):31-41 (1976)).

The formula, as originally published, is:

$$x = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{creatinine}}$$

This formula expects weight (actually mass) to be measured in kilograms and creatinine to be measured in mg/dL, as is standard in the USA. The resulting value is multiplied by a constant of 0.85 if the patient is female. This formula is useful because the calculations are relatively simple and can often be performed without the aid of a calculator.

Appendix 4 Additional Safety Guidance

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V4.0 as provided in below. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered “not related” to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered “related” to use of the investigational product if the “not related” criteria are not met.

“Related” implies that the event is considered to be “associated with the use of the drug” meaning that there is “a reasonable possibility” that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject’s medical record.

Not protocol related: The event is related to an etiology other than the procedure/
intervention that was described in the protocol (the alternative etiology
must be documented in the study subject's medical record).

Appendix 5 National Institute of Allergy and Infectious Diseases (NIAID) and Food and Allergy Anaphylaxis Network (FAAN) Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006;117:391-7.

NAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to >95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
2. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
3. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
4. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
5. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
6. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
7. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
8. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
9. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline