STATISTICAL ANALYSIS PLAN

Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Multiple Dose Regimens of MT-3724 for the Treatment of Subjects with Relapsed non-Hodgkin's B-Cell Lymphoma and B-Cell Chronic Lymphocytic Leukemia, and Extended Treatment Access Study for Subjects who Have Completed the Main Study

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APPROVAL SIGNATURE PAGE

Protocol Title:	Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Multiple Dose Regimens of MT-3724 for the Treatment of Subjects with Relapsed non-Hodgkin's B-Cell Lymphoma, and Extended Treatment Access Study for Subjects who Have Completed the Main Study
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Date:_____

Sponsor Approval:
By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

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Signature:_____

Date:_____

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration versus time curve
AUC_{0-4}	Area under the concentration versus time curve from time 0 to the end of the dosing interval 4 hours later, calculated using linear trapezoid rule
β-HCG	Beta human chorionic gonadotropin
BLQ	Below the limit of quantification
BSA	Body surface area
BUN	Blood urea nitrogen
C	Celsius
C_{max}	Maximum serum concentration
C_{min}	Trough serum concentration, taken 24 hours after dose and prior to subsequent dose
CBC	Complete blood count
CI	Confidence interval
CK	Creatine kinase
CL	Clearance
cm	Centimeter
CNS	Central nervous system
CO_2	Carbon dioxide
CR	Complete remission
CRu	CR/unconfirmed
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
DLCO	Diffusion capacity of carbon dioxide
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EE	Efficacy-evaluable

Abbreviation	Definition
EEG	Electroencephalography
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
g	Gram
GGT	Gamma glutamyl transferase
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IWG	International Working Group
IV	Intravenous
kg	Kilogram
L	Liter
LDH	Lactic dehydrogenase
m^2	Square meter
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalence
mg	Milligram
mL	Milliliter
mm	Millimeter
mm^3	Cubic millimeter
Msec	Millisecond
MTD	Maximum tolerated dose
µL	Microliter
N	Number
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PASS	Power and Sample Size
PD	Progressive disease
PDn	Pharmacodynamic
%	Percent
PET	Positron emission tomography
PFS	Progression-free survival
PFT	Pulmonary function test
pH	Hydrogen ion concentration

Abbreviation	Definition
PK	Pharmacokinetic
PR	Partial remission
PT	Preferred term
PTT	Partial thromboplastin time
QT	Interval between Q and T waves
QTc	Corrected interval between Q and T waves
RBC	Red blood cell (count)
RECIST	Response evaluation criteria in solid tumors
Rel Day	Relative study day
RTF	Rich text format
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Stable disease
SDR	Stable disease rate
SI	International System of Units
SOC	System organ class
SPD	Sum of the Product of Diameters
$T_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum serum concentration
TTP	Time to progression
ULN	Upper limit of normal
US	United States
VC	Vital capacity
V_{dss}	Volume of distribution at steady state
WBC	White blood cell (count)
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOLS

1.1. Introduction

1.1.1. Introduction

According to American Cancer Society statistics non-Hodgkin's Lymphoma (NHL) is the most prevalent hematopoietic neoplasm, representing approximately 4% of all cancer diagnoses in men and women and ranking seventh in frequency among all cancers. Since the early 1970s, the incidence rates of NHL have nearly doubled. Lymphoma includes a heterogeneous group of malignancies originating from lymphoid tissues (mainly of lymph nodes) with different biology and prognoses divided into 2 large groups of neoplasms: (1) non-Hodgkin's lymphoma and (2) Hodgkin's disease. Various neoplastic tumor cell lines correspond to each of the cellular components of antigen-stimulated lymphoid follicles. Almost 85% of NHLs are of B-cell origin.

NHL includes many clinicopathologic subtypes, each with a distinct epidemiology; etiology morphology, immunophenotype, genetic features, clinical characteristics and response to therapy. For many of the B-cell NHL subtypes, the pattern of growth and cell size may be important determinants of tumor aggressiveness.

MT-3724 is a single polypeptide chain consisting of 512 amino acids and a recombinant homodimeric fusion protein. Each monomer consists of a single chain variable fragment (scFv) with affinity for human CD20 cell surface protein fused to the enzymatically active Shiga-like toxin-I A1 subunit (SLT-I A1). MT-3724 has not yet been given to human subjects.

The main study, a Phase I, multiple ascending dose study will seek to enroll subjects with progressive B-cell NHL with measurable disease (lesion > 1.5 cm) who have received standard treatment with at least one anti-CD20 antibody containing front-line regimen that resulted in initial response, followed by relapse/recurrence and who are not eligible for any further approved biologic therapy, chemotherapy and/or autologous stem transplantation and/or refuse alternative approved therapies and/or are unlikely to achieve clinical benefit from any therapy of higher priority by Investigator assessment. The extended access, compassionate use study is available only to those subjects who have successfully completed the MT-3724 NHL main study and require continued treatment for their NHL.

1.2. Study Objectives

This statistical analysis plan (SAP) contains detailed information on definitions of analysis populations, derived variables, and statistical methods for the analysis of safety and efficacy data from the Phase I/ Ib clinical studies: MT-3724_NHL_001_US and MT-3724_NHL_001_EXT_US. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial. This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

The SAP is based upon the following study documents:

- Study protocols v7.0 dated 08 February 2018 for MT-3724_NHL_001_US and v2.0 dated 16 April 2016 for MT-3724_NHL_001_EXT_US.
- Electronic Case Report Form (eCRF), v10.0 dated 16 May 2018.

Although Part 1 of this study allows for the enrollment of subjects with NHL or Chronic Lymphocytic Leukemia (CLL), at the time of writing this SAP there are no plans to enroll subjects with CLL, as Part 1 of this study is complete. No subject with CLL were enrolled in Part 1.

1.2.1. Main Study

1.2.1.1. Primary Objectives

In Part 1, subjects with NHL or CLL were enrolled, and the primary objectives were:

- To define the maximum tolerated dose (MTD) of a single course of MT-3724 given on Days 1, 3, 5, 8, 10 and 12 at which there are negligible side effects (adverse events) and/or at which maximum pharmacokinetic (PK)/pharmacodynamic (PDn) parameter changes are observed.
    - The MTD was determined to be 75 mcg/kg/dose. However, due to safety concerns, an adjusted MTD (50 mcg/kg/dose) is used for Part 2.
- To determine PK and PDn profiles of a single course of MT-3724 in escalating dose cohorts.

In Part 2, up to 40 additional subjects with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) will be treated with the adjusted MTD (50 mcg/kg/dose) of MT-3724 in the MTD expansion cohort. The primary objectives will be to:

- Identify the frequency and nature of clinical and laboratory adverse events (AEs), both reported and observed, as a measure of safety and tolerability over repeated cycles of MT-3724 at the adjusted MTD.
- Define the PK and PD profiles of MT-3724 at the adjusted MTD in this sub-population.

1.2.1.2. Secondary Objectives

For Part 1, the secondary objectives are as follows:

- To identify the frequency and nature of clinical and laboratory adverse events, both reported and observed, as a measure of safety and tolerability over repeated courses of MT-3724.
- To assess the PK and PDn over repeated courses of MT-3724 from Day 1 though 112.
- To assess the efficacy of MT-3724 in subjects with DLBCL.

1.2.1.3. Exploratory Objectives

The exploratory objectives for Parts 1 & 2 are as follows:

1.2.2. Extension Study

1.2.2.1. Primary Objectives

The primary objectives of this study are as follows:

- To provide extended access to MT-3724 on a compassionate use basis for subjects who require continued treatment for their NHL or CLL and have (1) tolerated MT-3724 throughout the MT-3724_NHL_001_US Phase I/Ib study (Core and Repeat Dosing), (2) maintained stable disease or better and (3) have no other acceptable and better treatment options available to them in the Investigator's judgment.
- To identify the frequency and nature of clinical and laboratory adverse events, both reported and observed, as a measure of safety and tolerability over repeated cycles of MT-3724 beyond those administered in the MT-3724_NHL_001_US Phase I/Ib study.

1.2.2.2. Exploratory Objectives

The exploratory objectives of this study are the following:

1.3. Study Design

1.3.1. Synopsis of Study Design

1.3.1.1. Main Study

This is an open-label, phase 1/1b, dose-escalation study of MT-3724. There are two parts to this study, which include Part 1: Evaluating doses of MT-3724 in subjects with relapsed, refractory B-cell NHL or CLL to determine the MTD; and Part 2 (implemented in version 6.0 of the study protocol): The MTD cohort was expanded to evaluate safety, tolerability, and potential efficacy at the MTD. Implemented in version 7.0 of the study protocol, up to 40 additional subjects with DLBCL will be treated with MT-3724 at the adjusted MTD (50 mcg/kg/dose).

Part 1: The first 12-day course of treatment will be followed by at least 16 days of observation to provide a 28-day safety assessment following initiation of dosing. Each additional treatment cycle will be at least 21 days in length. In Part I, the first treatment cycle is 28 days (Core Study). All subsequent cycles (Cycles 2 – 5, Repeat Dosing Study) will be 21-day cycles. Subjects may receive up to 5 total cycles in the absence of clear disease progression or toxicity. If a subject achieves complete remission (CR), post Cycle 2, then 2 additional cycles will be attempted, after which dosing may be suspended.

Part 2: Each treatment cycle will be at least 21 days in length. Subjects may receive up to 5 total cycles in the absence of clear disease progression or toxicity

Parts 1 and 2: Retreatment under a separate extension protocol will be considered for subjects who exhibit PR or SD after completing 5 cycles (or 2 cycles after a complete remission) in consultation with the Sponsor.

Schematics of Parts 1 & 2 of the main study is presented in Figures 1 and 2.

Figure 1: Part 1 Study Schematic

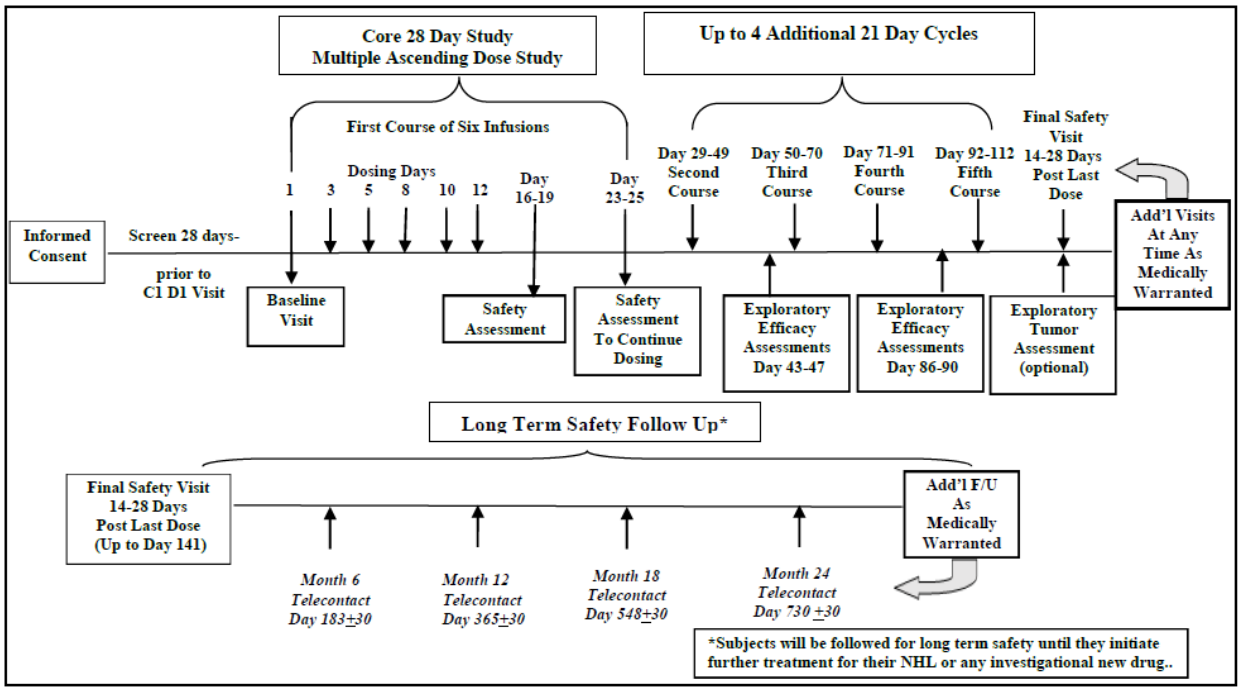
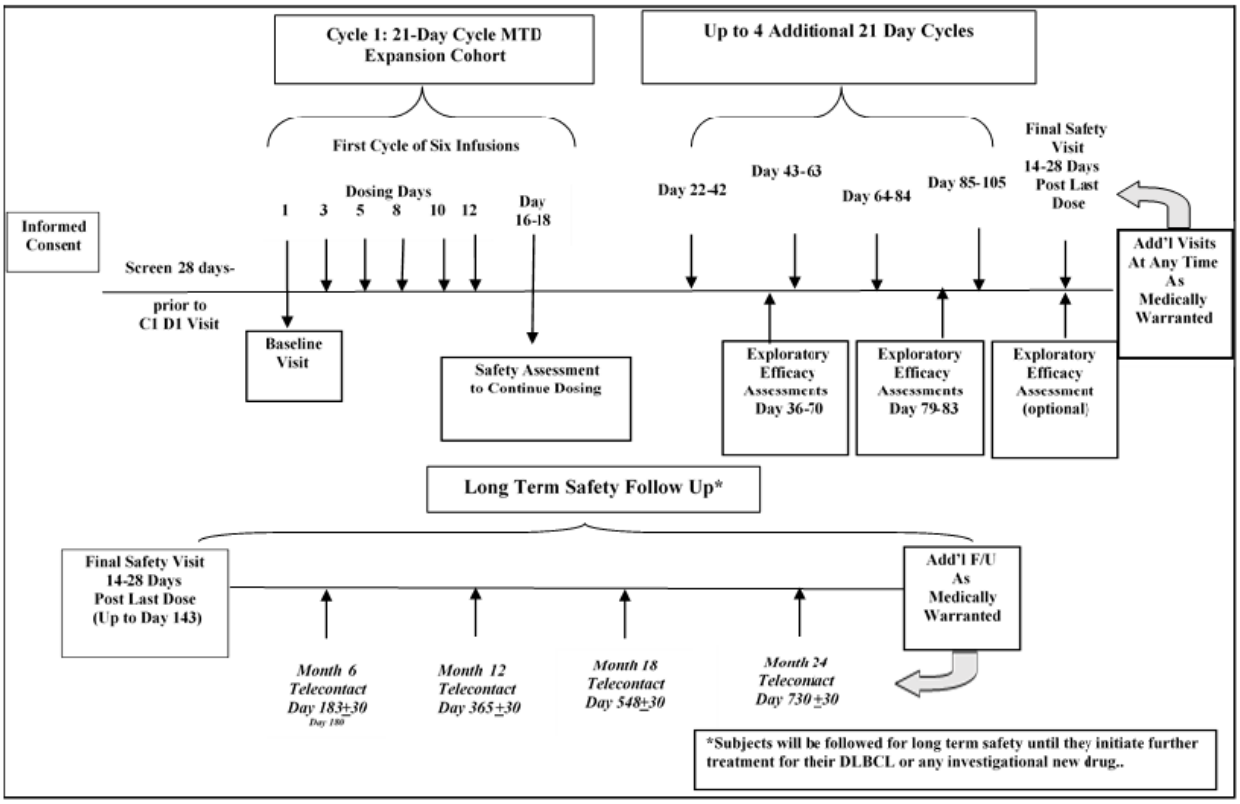


Figure 2: Part 2 (MTD Expansion) Study Schematic



Core Study (Cycle 1, Days 1 to 28)

Subjects will receive a single course of study drug via a 2 to 4 hour intravenous (IV) infusion of MT-3724 on Days 1, 3, 5, 8, 10 and 12. The first dosing cohort will receive 5 micrograms per kilogram (mcg/kg) per dose of MT-3724. Each cohort is planned to have from 3 to 6 subjects, but additional subjects may be added to one or more dosing cohorts to further explore safety and/or efficacy signals. Following the first dose in the Core Study, there will be a minimum 28-day observation period for each subject to document safety and tolerability prior to initiating any additional treatment cycles in the Repeat Dosing Study (see below). Subjects experiencing a dose limiting toxicity (DLT) in the Core Study (Days 1-28) must be withdrawn from the study and receive no further doses of MT-3724. Subjects will have successfully completed the Core Study if they receive at least 4 of the 6 infusions in their first cycle and they are followed for 28 days after their first dose. If a subject in the Core Study completes less than 4 of the 6 infusions in the first 12 days and the missed infusions were not due to an MT-3724-related DLT or AE that contraindicates further dosing then the Investigator in consultation with the Sponsor may attempt to achieve a minimum 4 infusions by administering the missed doses in the third week (Days 15 - 19) of the Core Study. In such instances, subjects must still be observed for 28 days following the first dose in the Core Study prior to initiating any further study drug dosing.

Following Data Monitoring Committee (DMC) safety review and approval to escalate, the subsequent cohorts are planned to be dosed at 10, 20, 50, 100, 150, and 200 mcg/kg/dose.

- **Dose Escalation:** Additional dose cohorts may be added above the 200 mcg/kg/dose cohort if (1) less than two DLTs are observed at the completion of that cohort's first cycle and (2) maximum PK/PD parameter changes have not yet been observed. The incremental increases of cohorts beyond 200 mcg/kg/dose/day will be determined by the PK/PD observations and all safety data.
- **Dose-De-escalation:** Additional cohorts at dose levels below an identified toxic dose level will be added to more accurately identify the MTD. At the identification of the first dose cohort that has > 33% DLTs, the maximal administered dose, an interim cohort will be added at a dose that is approximately 25 mcg/kg/dose lower than the maximal administered dose. If that lower dose has > 33% DLTs then the next highest cohort by a further 25 mcg/kg/dose reduction will be studied. For example, if there are > 33% DLTs at the 150 mcg/kg/dose, it will become the maximal administered dose and a 125 mcg/kg/dose cohort will be added. If the 125 mcg/kg/dose cohort has > 33% DLTs then the next lowest dose cohort (100 mcg/kg/dose in this example) will be expanded to 6 subjects if not previously done. Cohorts will be explored at ~25 mcg/kg/dose reductions until the MTD has been identified by documenting < 33% DLTs in a cohort expanded to the required 6 subjects. If the MTD cohort identified in the Core Study is expanded beyond 6 subjects for further PK, PD and/or efficacy exploration then from their first cycle, the subjects added to this expansion cohort will be dosed according to the Repeat Dosing 21-day cycle.

Part 1 Repeat Dosing (Cycles 2-5)

Following successful completion of the 28-day Core Study of Part 1, subjects may continue to receive up to 4 more cycles of treatment as long as they have experienced no AE attributable to MT-3724, which would contraindicate further dosing and provided their disease has not progressed.

If a subject has tolerated repeat cycles of MT-3724 without evidence of a toxicity that would prohibit further dosing or evidence of disease progression, but their dose is subsequently determined to be above the MTD, he/she may continue to receive additional cycles at the highest studied dose in Part 1 that has been confirmed to be below the MTD or at the dose confirmed to be the MTD.

Part 2

Up to 40 subjects will be enrolled in Part 2. Subjects may be enrolled and treated simultaneously through competitive enrollment at multiple study centers in North America and Europe.

All subjects will receive a single course of study drug via a 2 (±15 minutes) IV infusion of MT-3724 on Days 1, 3, 5, 8, 10 and 12. Each dose of MT-3724 will be at the adjusted MTD (50 mcg/kg/dose). Three subjects were started in Part 2 at 75 mcg/kg/day but later had possibly related TEAEs that required dose reduction or a treatment discontinuation Following the first dose in each cycle, there will be a minimum 21-day observation period for each subject prior to initiating the next treatment cycle. Subjects experiencing a serious adverse event (SAE) attributable t MT-3724 may be withdrawn from the study or depending upon the nature of the

event, the Investigator, in consultation with the DMC, may, once the event has resolved, resume dosing at a dose reduced by 25-33%. Subjects will have successfully completed a cycle if they receive at least 4 of the 6 infusions in that cycle, and they are followed for 21 days after their first dose in that cycle. If a subject completes less than 4 of the 6 infusions in the first 12 days of a cycle and the missed infusions were not due to an event that would contraindicate further dosing, then the Investigator in consultation with the Sponsor may attempt to achieve a minimum of 4 infusions by administering the missed doses in the third week (Days 15 - 19) of that cycle. In such instances, subjects must still be observed for a minimum of 21 days following the first dose in Cycle 1 prior to initiating any further study drug dosing.
No dose escalation will be permitted above the adjusted MTD (50 mcg/kg/dose) identified by the DMC. However, at the Investigator's discretion, the dose for any subject in the Part 2 expansion cohort may be reduced by 25-33% for one or more doses in any cycle (see below) based upon a subject's response at the adjusted MTD (50 mcg/kg/dose).

Subjects must receive a minimum of 4 of the 6 infusions in a cycle in order to successfully complete that cycle and continue in the study. For subjects in Parts 1 and 2 who complete **at least** 4 of the 6 infusions in any cycle, and the missed infusions were not due to an MT-3724-related event that contraindicates further dosing (see above for criteria for continued dosing), then up to 5 total cycles may be administered on the same schedule (Days 1, 3, 5, 8, 10 and 12) and at the same dose (as long as that dose is not subsequently identified to be a toxic dose).

If the adjusted MTD (50 mcg/kg) is determined to be causing adverse effects for a subject, at the Investigator's discretion, that subject may continue to receive additional cycles at a dose that is 25-33% lower than the adjusted MTD.

For both Parts 1 & 2, subjects in any cohort who complete **less than** 4 of the 6 infusions in any cycle and the missed infusions were not due to an MT-3724-related AE that would contraindicate further dosing, the Investigator (in consultation with the Sponsor) may attempt to achieve a minimum of 4 infusions by administering the missed dose(s) in the third week (Days 15-19) of the cycle. In such instances, subjects must still be observed for at least 21 days after their first dose in one cycle prior to initiating their next cycle in Part 1, repeat dosing cycles, or Part 2, all cycles.

Long Term Safety Follow-up

Following the Final Safety Assessment, subjects will be contacted by telephone every 6 months from the date of their first dose for up to 2 years or until they initiate further treatment for their B-cell NHL, CLL, or other malignancies or take any other investigational new drug for any reason. Subjects will be asked about their current medical status and if they have experienced any new AE attributable to their MT-3724 treatment. If the subject continues to participate in the MT 3724 extension study, no AEs will be captured with respect to long-term safety within this parent study, as they will be captured in the extension study.

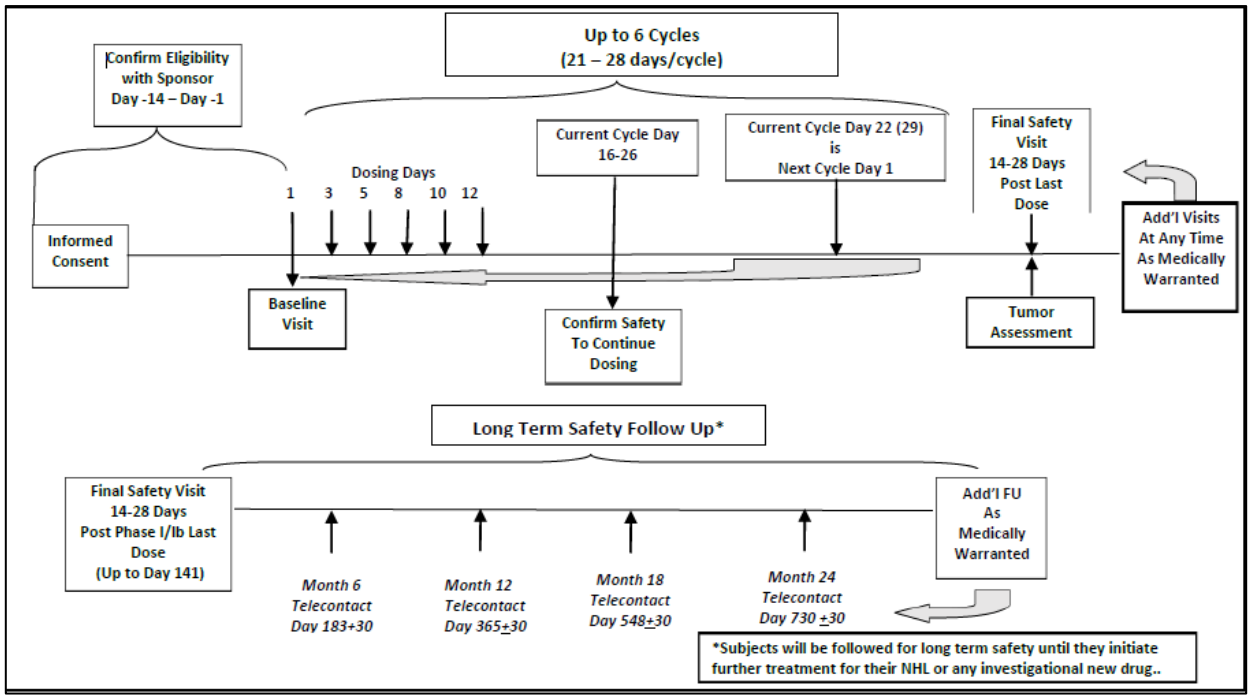
1.3.1.2. Extension Study

This is an active treatment, extended access study open solely to those subjects who have successfully completed the Core and Repeat Dosing portions of the MT-3724_NHL_001_US

clinical study and who, in the Investigator's judgment (i) have not had progressive disease while on MT-3724 treatment (i.e., have shown a complete or partial response or stable disease), (ii) have experienced no clinical or laboratory toxicities that would contraindicate further MT-3724 dosing, and (iii) have no acceptable and better alternative treatment available to them. Each treatment cycle will consist of 6 doses of MT-3724 to be administered over 12 days followed by at least 9 days of observation; longer intervals between dosing cycles will be allowed at the Investigator's discretion (e.g., 6 doses of MT-3724 over 12 days followed by 16 days observation). Subjects in this extension study may continue to receive up to 6 additional cycles in the absence of clear disease progression or toxicity. If a subject achieves complete remission (CR), two additional cycles will be attempted, after which dosing may be suspended prior to completion of the maximum 6 cycles.

A schematic of the extension study is presented in Figure 3, and schedule of assessments are provided in Table 3.

Figure 3: Extended Access Schematic



Dosing Cycles

As in the MT-3724_NHL_001_US Repeat Dosing Study each subject will continue to receive six (6) MT-3724 intravenous (IV) infusions over approximately 12 days (Days 1, 3, 5, 8, 10 and 12) followed by at least 9 days observation (Days 13 – 21) observation for a maximum of 6 cycles. At the Investigator's discretion the observation period between treatment periods may be extended to 16 days for one or more cycles following discussion with the Sponsor. Each subject may continue to receive the same dose (mcg/kg) which they had been receiving in the Repeat Dosing Study OR, in consultation with the Sponsor, a subject may be reassigned to receive the maximum tolerated dose (MTD) identified in the MT-3724_NHL_001_US Core Study. If a

subject enrolls in this study prior to the identification of the MTD in the Core Study, the subject must continue at their originally assigned dose (mcg/kg) until the MTD is identified. If a subject has tolerated repeat cycles of MT-3724 without evidence of (i) a toxicity that would prohibit further dosing or (ii) disease progression, but their dose is subsequently determined to be above the MTD, they may continue to receive additional cycles at the highest studied dose that has been confirmed to be below the MTD or at the dose confirmed to be the MTD. Following the successful completion of a treatment cycle in this extended access study, subjects are eligible to receive the next cycle (to a maximum of 6 cycles) as long as (i) they have experienced no AE attributable to MT-3724 which contraindicates further dosing AND (ii) their disease has not progressed. For subjects in any dosing cohort who complete less than 4 of the 6 infusions in a cycle, and the missed infusions were not due to an MT-3724 related AE that would contraindicate further dosing then the Investigator may attempt to achieve a minimum of 4 infusions by administering the missed doses in the third week of that dosing cycle. In such an instance, for that cycle only, at the Investigator's discretion and in consultation with the Medical Monitor, a subject may be observed for less than 9 days prior to initiating their next cycle.

Long Term Safety Follow-up (Extension)

Following the assessment performed 14 - 28 days after the last MT-3724 dose in this study, subjects will be contacted by telephone every 6 months from the date of their first dose in the MT-3724_NHL_001_US Core Study for up to 2 years OR until they initiate further treatment for their B-cell Non-Hodgkin's Lymphoma (NHL) or B-cell Chronic Lymphocytic Leukemia (CLL) OR until they take any other investigational new drug for any reason. During these telephone contacts subjects will be asked about their current medical status and if they have experienced any new AE attributable to their MT-3724 treatment.

1.3.2. Randomization Methodology

Not applicable as this is an open label study.

1.3.3. Stopping Rules

The list of study stopping rules that follows is based on key safety parameters. This list will be used to determine whether:

Part 1:

- dosing may proceed to a subsequent dosing cohort (per protocol or alternate dose based upon DMC recommendation),
- the cohort must be stopped and no additional subjects dosed at that dose level,
- dosing must be suspended for an individual subject pending DMC review, or
- the subject must be withdrawn because an AE is determined to be a DLT or it is determined to be in the subject's best interest to receive no further doses of MT-3724.

Part 2:

- Dosing must be suspended for an individual subject pending DMC review, or

- The Investigator and Medical Monitor and/or the DMC approve dosing be resumed for an individual subject at a dose 25-33% less than the MTD, or
- The subject must be withdrawn, because it is determined to be in the subject's best interest to receive no further doses of MT-3724.

Additional DMC and/or Investigator meetings may be triggered by occurrence of specific stopping rules (see the list that follows) or may be called at the request of an Investigator or of the DMC. Based on the event and the study stopping rules, it may or may not be reasonably safe to proceed with dose administration of the next subject in a cohort and/or to continue the study per the current protocol. A subject will be withdrawn from further MT-3724 treatment if any of the stopping rules outlined in Section 6.13 (main study) or Section 6.12 (extension study) of the protocol are met.

1.3.4. Study Procedures

The schedules of assessments for the main study are provided in Table 1 (Core Study) and Table 2 (Repeat Dosing). The schedule of assessments for the extension study is presented in Table 3.

Table 1: Schedule of Assessments – Main Study Cycle 1 – Parts 1 and 2

Assessment	Qualification Screen	MT-3724 Infusion Schedule						Safety Assessment	Safety Assessment Part 1 ONLY	Final Safety Assessment
	Visit 1 Day -28 to Day -1	**Visit 2 Day 1 Dose 1**	**Visit 3 Day 3 Dose 2**	**Visit 4 Day 5 Dose 3**	**Visit 5 Day 8 Dose 4**	**Visit 6 Day 10 Dose 5**	**Visit 7 Day 12 Dose 6**	**Visit 8 Day 16-19** (If early withdrawal, must still be performed)	**Visit 9 Day 23-25** (If early withdrawal, must still be performed)	(If withdrawing replaces Day 28 safety assessment prior to Cycle 2) **Day 28-35**
Informed Consent	X									
Inclusion/Exclusion	X									
Medical History Review and Physical Exam including ECOG[1]	X	X								X
Baseline Disease Assessments	X									
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory CBC w/differential	X	X		X (post infusion)				X	X	X
Serum Chemistry	X	X						X	X	X
B2 microglobulin	X									X
Serum Rituximab	X									
For CLL subjects ONLY: soluble CD23 and thymidine kinase 1	X									X
For CLL subjects ONLY: anti-globulin test	X									

Assessment	Qualification Screen	MT-3724 Infusion Schedule						Safety Assessment	Safety Assessment Part 1 ONLY	Final Safety Assessment
	Visit 1 Day -28 to Day -1	**Visit 2 Day 1 Dose 1**	**Visit 3 Day 3 Dose 2**	**Visit 4 Day 5 Dose 3**	**Visit 5 Day 8 Dose 4**	**Visit 6 Day 10 Dose 5**	**Visit 7 Day 12 Dose 6**	**Visit 8 Day 16-19** (If early withdrawal, must still be performed)	**Visit 9 Day 23-25** (If early withdrawal, must still be performed)	(If withdrawing replaces Day 28 safety assessment prior to Cycle 2) **Day 28-35**
PT, aPTT, INR	X									
Urinalysis	X									X
Estimated Cr Clearance[3]	X								X	X
Pregnancy Test (urine)[4]	X	X (-72 hrs)								
Complement (CH50 and C3)	X									
Quantitative Serum Immunoglobulins	X									X
Viral Serology: HepBAb HepBsAg HepCAb and/or HIV if clinically indicated	X									
Flow Cytometry , Lymphocyte subsets[5]	X				X (pre-infusion)				X	X (including MRD analysis for CLL)
Serum Cytokines[6]	X	X		X					X	X
MT-3724 Administration[7]		**MT-3724**	**MT-3724**	**MT-3724**	**MT-3724**	**MT-3724**	**MT-3724**			
MT-3724 Serum Levels (PK)[8]		X (pre- and post-infusion)		X (post-infusion)	X (pre-infusion)		X (post-infusion)		X	X
ADA/Immunogenicity[9]	X	Additional specimens tob e drawn as clinically indicated.							X	X
12-Lead ECG[10]	X	X								
Malignancy Histology	X									

Assessment	Qualification Screen	MT-3724 Infusion Schedule						Safety Assessment	Safety Assessment Part 1 ONLY	Final Safety Assessment
	Visit 1 **Day -28** **to Day -1**	**Visit 2** **Day 1** **Dose 1**	**Visit 3** **Day 3** **Dose 2**	**Visit 4** **Day 5** **Dose 3**	**Visit 5** **Day 8** **Dose 4**	**Visit 6** **Day 10** **Dose 5**	**Visit 7** **Day 12** **Dose 6**	**Visit 8** **Day 16-19** (If early withdrawal, must still be performed)	**Visit 9** **Day 23-25** (If early withdrawal, must still be performed)	(If withdrawing replaces Day 28 safety assessment prior to Cycle 2) **Day 28-35**
Radiological Response Assessment[11]	X									X (optional)

Table 2: Schedule of Assessments – Main Study Cycles 2-5 – Parts 1 and 2

Assessment	MT-3724 Infusion Schedule Repeated for Each Course						Safety Assessment	Exploratory Efficacy Assessment	Final Safety Assessment
	Visit 1 Day 1 Dose 1	**Visit 2 Day 3 Dose 2**	**Visit 3 Day 5 Dose 3**	**Visit 4 Day 8 Dose 4**	**Visit 5 Day 10 Dose 5**	**Visit 6 Day 12 Dose 6**	**Telephone Contact Day 16-18**	**Days 15-21of each even-numbered cycle**	**(replaces interim safety assessment after last infusion) Day 14-28**
Medical History Review and Physical Exam including ECOG[1]	X								X
Vital Signs[2]	X	X	X	X	X	X			X
Concomitant Medications	X	X	X	X	X	X	X		X
Adverse Events	X	X	X	X	X	X	X		X
Clinical Laboratory CBC w/differential	X								X
Serum Chemistry	X								X
B2 microglobulin									X
Urinalysis									X
Estimated Cr Clearance[3]									X
Pregnancy Test (urine)[4]	X								
Quantitative Serum Immunoglobulins									X
NHL Flow Cytometry, Lymphocyte Subsets[5]	X (Day 1 of Cycle 4, pre-infusion)								X
Serum Cytokines[6]	Specimens to be drawn as clinically indicated.								X
MT-3724 Administration[7]	**MT-3724**	**MT-3724**	**MT-3724**	**MT-3724**	**MT-3724**	**MT-3724**			
ADA/Immunogenicity[9]	X	Additional specimens to be drawn as clinically indicated.							X
MT-3724 serum levels (PK)[8]	X	A concurrent MT-3724 serum level (PK) sample should be drawn whenever an Immunogenicity (ADA) sample is drawn for clinical indication(s).							X

Assessment	MT-3724 Infusion Schedule Repeated for Each Course						Safety Assessment	Exploratory Efficacy Assessment	Final Safety Assessment
	Visit 1 Day 1 Dose 1	Visit 2 Day 3 Dose 2	Visit 3 Day 5 Dose 3	Visit 4 Day 8 Dose 4	Visit 5 Day 10 Dose 5	Visit 6 Day 12 Dose 6	Telephone Contact Day 16-18	Days 15-21of each even-numbered cycle	(replaces interim safety assessment after last infusion) Day 14-28
12-Lead ECG[10]	(at investigator's discretion)								
Radiological Response Assessment[11]								X	X (optional)

[1] Height and weight are collected at the Screen visit. Weight is collected again at final safety visit 14-28 days after last infusion. The MT-3724 dose is calculated using Screening visit weight.

[2] **For the first two infusions in Cycle 1 (Doses 1 & 2)**, vital signs (temperature, blood pressure, pulse, and respiration rate) will be collected at pre-dose prior to initiation of dosing on each dosing day, at 20, 40 and 60 min (± 5 min), at 90 min (± 10 min), at 2 hours (± 15 min) and no less than hourly (± 15 min) until the infusion is completed. **For all other infusions**, vital signs should be collected prior to the initiation of the infusion and at the conclusion of the infusion (±15 min). **Beyond these times and at all other infusions**, subjects should be monitored as clinically indicated. The frequency of interim monitoring during and following all infusions beyond the second infusion should be determined by the Investigator based on the subject's clinical condition. In addition, in all subjects, orthostatic vital signs will be performed as needed after all doses prior to the subject standing or ambulating for any reason during the observation period.

[3] Calculate estimated creatinine clearance by Cockcroft Gault formula.

[4] All female subjects of child bearing potential must have a urine pregnancy test performed **prior to the first dose of each new cycle** of MT-3724 beginning with the first cycle and continuing through the last cycle. Pregnancy test should be done within 72 hours prior to the first dose of each new cycle.

[5] Lymphocyte subset samples must be processed and shipped to the Central Laboratory according to Site Reference Manual and Laboratory Manual instructions. The baseline flow cytometry sample should be drawn at the Screening Visit whenever possible. If not obtained at the Screening Visit, the baseline flow cytometry sample may be drawn on Dose Day 1 prior to initiation of dosing. The sample drawn on Cycle 1 Day 8 (Visit 5, Dose 4) during the first cycle of MT-3724 should be drawn PRIOR to the initiation of Dose 4 infusion. Additionally, **Part 1 only: FOR SUBJECTS WITH CLL, flow assessment for minimal residual disease (MRD) will be obtained at Baseline and the Final Safety Assessment** respectively.

[6] During the first cycle, serum cytokine samples will be obtained at the Screening Visit (Days -28 to -1) or on Dose Day 1 prior to initiation of dosing and then at 2 hours post infusion on Visit 2 (Day 1, Dose 1) and Visit 4 (Day 5, Dose 3) and again at the Visit 9 (Days 23-25). Serum cytokine samples must always be obtained at the **Final Safety Assessment Visit** regardless of how many doses have been administered (any cycle). Additional samples may be drawn at the Investigator's discretion as clinically indicated. Serum will be assayed for TNFα, IFN-γ, IL1β, IL-6, IL-8, IL-10 and IL-12. For suspected CRS, SIRS, or TLS, unscheduled tests for LDH, D-dimer and PT should be sent to the site's local laboratory. If the reaction is considered to be a possible hypersensitivity reaction then a serum histamine level should also be sent.

[7] MT-3724 will be administered according to Site Reference Manual directions over a period 2 hours ±15 minutes. During the first cycle, all subjects should remain in the clinic for a minimum of 4 hours after completion of the first dose of MT-3724 and for a minimum of 2 hours after completion of the second and third doses. For these and all subsequent infusions, subjects will not be discharged to home until any signs or symptoms consistent with an adverse reaction to study drug or study procedures have completely cleared.

[8] **During Cycle 1**, serum PK samples will be taken at the following times:

- **Day 1 (First Infusion, Dose 1):** Samples: Baseline sample within 4 hours prior to initiation of infusion (concurrent baseline ADA/immunogenicity sample and cytokine samples may be obtained simultaneously), within 10 minutes prior to the end of primary infusion, and then starting **at the completion of the infusion**, post-infusion samples at 5 minutes (+ 1 min); 0.5, 1, 2, 3 and 4 hours (±5 minutes).
- **Day 5 (Third Infusion, Dose 3):** Samples at 10 minutes prior to the end of primary infusion, and then at 5 minutes (+ 1 min) and 2 hours (± 5 minutes) **after completion of infusion.**
- **Day 8 (Fourth Infusion, Dose 4):** Single sample **pre infusion.**
- **Day 12 (Sixth Infusion, Dose 6):** Samples within 10 minutes prior the the end of primary infusion, and at 5 minutes (+ 1 min) and 2 hours (± 5 minutes) **after completion of infusion**.
- **Day 23-25 (Visit 9):** Sample should be drawn concurrent with ADA/Immunogenicity sample and other safety lab tests at this visit.

During the Repeat Dosing Study, at the first visit starting each cycle, an ADA/immunogenicity sample should be drawn prior to the initiation of MT-3724 infusion and a PK sample should be drawn at 5 minutes (+1 minute) following the end of that infusion. Whenever an unscheduled ADA/immunogenicity sample is drawn for clinical indication(s), a serum PK sample should be drawn concurrently.
During Cycles 2 - 5, at the first visit starting each cycle, an ADA/Immunogenicity sample should be drawn prior to the initiation of MT-3724 infusion and a PK sample should be drawn at 5 minutes (+1 minute) following the end of that infusion. Whenever an unscheduled ADA/Immunogenicity sample is drawn for clinical indication(s), a serum PK sample should be drawn concurrently.
Final Safety Assessment: A single MT-3724 serum PK sample will be obtained concurrent with the immunogenicity (ADA) sample no matter how many doses have been administered (all cycles). Additional samples may be requested if indicated.

[9] Serum samples for ADA/Immunogenicity will be collected during the **Core Study** during Screening (Day -28 to -1) or on Dose Day 1 prior to initiation of dosing and at the Visit 9 Safety Assessment 11 to 14 days following the sixth dose of the first course (Day 23-25). Additional ADA/immunogenicity samples will be obtained pre-dose on Day 1 of each Repeat Dosing Study cycle and at **the Final Safety Assessment** 14-28 days following infusion of the final dose in the **Core Study** or **Repeat Dosing Study**. For subjects who withdraw early, a serum ADA/Immunogenicity sample will be collected at the Final Safety Assessment 14-28 days following their last infusion. **Additional samples may be requested if clinically indicated.** Additional ADA/immunogenicity samples obtained for any "clinical indication" should have a PK sample obtained at the same time.

[10] Standard 12-lead ECG printouts will be obtained at screening, during Cycle 1 (Table 5) on Day 1 (Visit 2, Dose 1) within 3 hours prior to initiation of dosing and then at 1 hour (± 15 min) and 2 hours (± 15 min) post start of infusion. For Cycles 2-5, standard 12-lead ECG printouts will be captured at any time it is clinically indicated.

[11] See Study Protocol Appendix 3. CT scans will be performed for disease assessment. Where clinically indicated, PET scan will also be performed per investigator discretion.

Table 3: Schedule of Assessments – Extension Study

Assessment	Qualification Screen	MT-3724 Infusion Schedule (21-28 day cycles, up to 6 cycles)						Safety Observation	Final Safety Assessment
	Visit 1 Day -14 to Day -1	Visit 2 Day 1 Dose 1	Visit 3 Day 3 Dose 2	Visit 4 Day 5 Dose 3	Visit 5 Day 8 Dose 4	Visit 6 Day 10 Dose 5	Visit 7 Day 12 Dose 6	Day 16-25	(If withdrawing replaces interim safety assessment after last infusion) Day 26-40
Informed Consent	X								
Inclusion/Exclusion	X								
Medical History Review and Physical Exam including ECOG[1]	X	X (directed history and PE as clinically indicated)							X
Disease Assessments[2]	X	X (only when clinically indicated)							X
Vital Signs[3]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Clinical Laboratory CBC w/differential	X	X (only when clinically indicated)							X
Serum Chemistry Na,K,Cl,CO_2, BUN, Cr, LDH, Bilirubin, AST (SGOT), ALT (SGPT), GGT, CPK, albumin, total protein, Ca, Mg, glucose, uric acid, phosphate, amylase, lipase, alkaline phosphatase	X	X (only when clinically indicated)							X
B2 microglobulin	X (only when clinically indicated)								
PT, aPTT, INR	X (only when clinically indicated)								
Urinalysis	X	X (only when clinically indicated)							X

Assessment	**Qualification Screen**	**MT-3724 Infusion Schedule (21-28 day cycles, up to 6 cycles)**						**Safety Observation**	**Final Safety Assessment**
	Visit 1 Day -14 to Day -1	**Visit 2 Day 1 Dose 1**	**Visit 3 Day 3 Dose 2**	**Visit 4 Day 5 Dose 3**	**Visit 5 Day 8 Dose 4**	**Visit 6 Day 10 Dose 5**	**Visit 7 Day 12 Dose 6**	**Day 16-25**	**(If withdrawing replaces interim safety assessment after last infusion) Day 26-40**
Estimated Cr Clearance[4]	X	X (only when clinically indicated)							X
Pregnancy Test (urine)[5]	X	X (-72 hrs 1st dose of each cycle)	X (only when clinically indicated)						X
Complement (CH50 and C3)	X (only when clinically indicated)								
Quantitative Serum Immunoglobulins	X (only when clinically indicated)								
Viral Serology: Hepatitis and/or HIV if clinically indicated	X (only when clinically indicated)								
Flow Cytometry, Lymphocyte subsets[5]	X (including MRD analysis for CLL)	X (only when clinically indicated)							X (including MRD analysis for CLL)
Serum Cytokines[6]		X (Cycle 1)	X (only when clinically indicated)						
MT-3724 Administration[7]		**MT-3724**	**MT-3724**	**MT-3724**	**MT-3724**	**MT-3724**	**MT-3724**		
MT-3724 Serum Levels (PK)[8]	X (Concurrent with ADA only when clinically indicated)								
ADA/Immunogenicity[9]	X	X (only if not drawn at Screening Visit)	X (additional specimens to be drawn as clinically indicated)						X

Assessment	**Qualification Screen**	**MT-3724 Infusion Schedule (21-28 day cycles, up to 6 cycles)**						**Safety Observation**	**Final Safety Assessment**
	Visit 1 Day -14 to Day -1	**Visit 2 Day 1 Dose 1**	**Visit 3 Day 3 Dose 2**	**Visit 4 Day 5 Dose 3**	**Visit 5 Day 8 Dose 4**	**Visit 6 Day 10 Dose 5**	**Visit 7 Day 12 Dose 6**	**Day 16-25**	**(If withdrawing replaces interim safety assessment after last infusion) Day 26-40**
12-Lead ECG[10]	X (only when clinically indicated)								
Cancer Histology	X (Confirm history)	X (repeat only when clinically indicated)							

Abbreviations: ADA: anti-drug antibodies; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Ca: calcium; CBC: complete blood count; Cl: chloride; CO_2: carbon dioxide; CPK: creatine phosphokinase; Cr: creatinine; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; GGT: gamma-glutamyl transferase; HepBAb: hepatitis B antibody; HepBAg: hepatitis B surface antigen; HepCAb: hepatitis C antibody; HIV: human immunodeficiency virus; IFN-γ: interferon gamma; IL-6: interleukin 6; K: potassium; LDH: lactate dehydrogenase; Mg: magnesium; MRD: minimal residual disease; NA: sodium; PET: positron emission tomography; PK: pharmacokinetic; TNFα tumor necrosis factor alpha

[1] Height and weight are collected at the Screening Visit. Weight is collected again at Final Safety Visit 14-28 days after last infusion. MT-3724 dose is re-calculated using Screening Visit weight if subject's weight has changed by ± 10% from MT-3724_NHL_001_US study, the dose OR subject's mcg/kg/dose must be changed due to MTD identification.

[2] See Protocol Appendix 3. CT scans will be performed for tumor assessment at screening and Final Safety Visit. Additional tumor assessment (s) will be performed per investigator. Where clinically indicated, PET scan may also be performed per Investigator discretion.

[3] For all infusions, all cycles, vital signs (temperature, blood pressure, pulse, and respiration rate) should be collected prior to the initiation of the infusion and at the conclusion of the infusion. Beyond these times subjects should be monitored as clinically indicated. The frequency of interim monitoring during and following all infusions should be determined by the Investigator based on the subject's clinical condition. In addition, in all subjects, orthostatic vital signs will be performed as needed after all doses prior to the subject standing or ambulating for any reason during the observation period

[4] Calculate estimated creatinine clearance by Cockcroft Gault formula.

[5] All female subjects of child bearing potential must have a urine pregnancy test performed **prior to the first dose of each new cycle** of MT-3724. Pregnancy test should be done within 72 hours prior to the first dose of each new cycle at their Final Safety Assessment and at any other time deemed clinically indicated.

[6] A sample for serum cytokines samples will be obtained **prior to first dose, first cycle for baseline**. Additional samples should be drawn as clinically indicated. Serum will be assayed at study's central laboratory for TNFα, IFN-γ, IL1β, IL-6, IL8, IL10 and IL12. For suspected CRS, SIRS, or TLS unscheduled tests for LDH, D-dimer and PT should be sent to the site's local laboratory. If an adverse event is considered to be a possible hypersensitivity reaction then a serum histamine level should also be sent.

[7] MT-3724 will be administered according to Site Reference Manual directions over a period not less than 2 hours and not more than 4 hours. Subjects will not be discharged to home until any signs or symptoms consistent with an adverse reaction to study drug or study procedures have completely cleared.

[8] A serum PK sample will be taken concurrently whenever an unscheduled ADA/Immunogenicity sample is drawn for clinical indication(s). Additional samples may be requested if indicated.

[9] Serum samples for ADA/Immunogenicity will be collected **prior to first dose, first cycle at Screening Visit or on Day of first dose**, **first cycle prior to initiation of dosing for baseline and again at the Final Safety Assessment 14-28 days following the last infusion**. **Additional samples may be requested if clinically indicated. (n.b., for any additional ADA/Immunogenicity samples obtained "when clinically indicated" a concurrent PK sample must be obtained.).**

[10] Standard 12-lead ECG printouts will be captured at any time it is clinically indicated.

1.3.5. Safety, Efficacy, and Pharmacokinetic Parameters

1.3.5.1. Safety Parameters

The safety and tolerability of MT-3724 will be evaluated by means of drug related DLT, AE reports, physical examinations, and clinically significant changes in the laboratory safety evaluations. Adverse events will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

The evaluation of the MTD and DLT will be performed on all subjects enrolled in Part 1 of the main Core Study who receive at least one infusion of MT-3724. MTD is defined as the highest dose level at which ≤33% (or 2/6) of subjects experience a DLT.

A DLT will be defined as a toxic effect that is presumed to be related to MT-3724 and considered unacceptable because of its severity and/or irreversibility and as such may limit further dose escalation. Dose-limiting toxicities will be defined based upon any toxic effects seen in the Core Study. Adverse events during Repeat Dosing will not be classified as DLTs. If a toxicity can be satisfactorily documented to be unrelated to MT-3724, then that specific toxicity will not be considered to impact the stopping or dose escalation rules.

A DLT will be determined as follows:

1. Grade 3 or greater AE: Any Grade 3 or greater adverse event that cannot clearly be determined to not be related to MT-3724 or disease progression will be considered to be a DLT.
2. Grade 3 or greater non-hematologic laboratory abnormality: Any Grade 3 or greater non-hematologic laboratory abnormality that fails to spontaneously recover to less than Grade 3 on retest prior to the next scheduled dose of MT-3724 or within 10 days (whichever is shorter) unless the event can be clearly determined to not be related to MT-3724 or tumor progression will be considered a DLT excepting the following:
    - Parameters for liver function test (AST, ALK, PT [INR], aPTT, Bilirubin, and Alk Phos) abnormalities to be considered a DLT are detailed in Section 1.3.3.
3. Grade 3 or greater hematologic laboratory abnormality: Because subject treated with anti-CD20 MAb develop Grade 3 or higher lymphopenia and because it is an expected pharmacodynamic effect of MT-3724, lymphopenia will not be considered a DLT.
    - Unless the event can be clearly determined to not be related to MT-3724 or disease progression changes in the following specific hematologic parameters will qualify as a DLT:
        i. Febrile neutropenia (absolute neutrophil count <1000/mcl and temperature ≥ 38.5°C)
        ii. Grade 4 neutropenia for > 10 days
        iii. Grade 3 thrombocytopenia with bleeding
        iv. Grade 4 thrombocytopenia
        v. Grade 4 anemia not due to underlying disease

For all other hematologic laboratory abnormalities, any grade 3 or greater hematologic toxicity that fails to spontaneously recover to less than grade 3 within 10 day (and prior to additional doses of MT-3724) unless the event can be clearly determined to not be related to MT-3724 or tumor progression will be considered a DLT.

4. A grade 2 (moderate) AE might invoke a stopping rule if:
    - It is not pre-existing
    - It is not due to disease progression
    - It is not manageable with standard outsubject therapies AND
    - It persists in the judgment of the Investigator(s) for an unreasonable people.
5. Any new Grade 1 (Mild) AE attributable to MT-3724 will **not** be considered a DLT.

1.3.5.2. Efficacy Parameters

As this is a dose finding study and is designed to assess the safety and tolerability of MT-3724, all efficacy analyses are exploratory in nature, based on documented tumor responses.

Tumor response following completion of even numbered (e.g., 2, 4, etc.) courses of MT-3724 and at final safety assessment following termination of MT-3724 will be assessed according to the Tumor Response Criteria for malignant lymphoma (Cheson et al 2007) defined by the International Working Group.

In addition, source document verified tumor lesion measurement data that was not reported in the EDC was collected and tallied by the Sponsor via an Excel Spreadsheet. The data in this Spreadsheet will be used for the analysis of percent change in tumor size.

Endpoints will include:

- Best Overall Response.
- Objective response rate (ORR) - Objective response will be determined as the proportion of subjects with either CR or PR using the tumor response criteria described below.
- Disease Control Rate (DCR) will be calculated as the proportion of subjects who achieve either CR, PR or stable disease status.
- Duration of tumor response (DOR) - Duration of response is defined as the time from the first occurrence of either complete or partial response to first documented evidence of disease recurrence or progression. Subjects without evidence of progression will be censored at time of last disease assessment.Only responders (CR or PR) will be included for this analysis.
- Progression-free survival (PFS) – Progression-free survival is calculated from the date of first infusion of MT-3724 to first documented evidence of disease recurrence or progression or death due to any cause. Subjects who are last known to be alive and without evidence of progression will be censored at time of last disease assessment.
- Duration of stable disease (i.e., duration of disease control) - Duration of at least stable disease is defined as the time from the date of first infusion of MT-3724 to first

documented radiologic evidence of disease recurrence or progression. Subjects without evidence of progression will be censored at time of last disease assessment.

- Overall survival (OS) – Overall survival is calculated from the date first dose of study treatment to the date of death. Subjects who are still alive prior to the data cutoff for final efficacy analysis, or who dropout prior to study end, will be censored at the day they were last known to be alive.
- Percent change from baseline in lesion size based on the Sum of the Product of Diameters (SPD).

1.3.5.3. Pharmacokinetic and Pharmacodynamic Parameters

During the study, PK serum samples will be analyzed for concentrations of free MT-3724 and if indicated may also be analyzed for any other anti-CD20 biologic agent which the subject may have received prior to enrolment. Analysis of PK/PDn parameters will be described in a separate PK/PDn analysis document.

1.3.5.4. Immunogenicity

Immunogenicity parameters will be described in a separate analysis document.

2. SUBJECT POPULATION

2.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Safety Set (SS): All subjects who received any amount of MT-3724.
- Pharmacokinetic Analysis Set (PAS): All subjects from the Safety Set with sufficient serum concentration data to determine the primary PK parameters.
- Full Analysis Set (FAS): All subjects from the Safety Set who have at least one tumor re-evaluation performed (scheduled or unscheduled).

The Safety Set is the primary population for the analysis of safety. The PAS is the primary population for all PK and PDn analyses. The FAS is the primary population for all exploratory efficacy analyses.

2.2. Protocol Violations

The Sponsor or designee will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with Veristat and the data monitoring group as applicable; this file will include a description of the protocol violation. This file will be finalized prior to hard database lock.

All protocol violations will be presented in a data listing.

2.3. Withdrawals and Subject Replacement

Subjects may be withdrawn at any time for reasons including the following:

- at their own request or at the request of their legally authorized representative,
- if, in the Investigator's or Sponsor's opinion, continuation in the study would be detrimental to the subject's well-being, and/or
- when Stopping Rules have been met.

2.3.1. Main Study

Part 1: If a subject terminates study participation prior to per protocol Core Study completion the Investigator or their representative should notify Molecular Templates and the CRA immediately. In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's medical records. If the reason is not known, the subject must be followed to establish whether the reason was an AE, and, if so, this must be recorded. If a subject withdraws for reasons other than a DLT and prior to completing the Core Study Molecular Templates and the CRA must be informed immediately so a timely decision can be made regarding replacement of the subject. If a subject withdraws because of disease progression prior to completion of the Core Study, Molecular Templates and the CRA must be informed immediately so a timely decision can be made regarding replacement of the subject. Subjects in any cohort will not be replaced if they are withdrawn because of a DLT in the Core Study or they are withdrawn because of an AE or disease progression in the Repeat Dosing Study.

Part 2: If a subject terminates study participation prior to per-protocol post-Cycle 2 tumor assessment for any reason other than progressive disease, the Investigator or their representative should notify Molecular Templates and the CRA immediately. In all early withdrawal cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records. If the reason is not known, the subject must be followed up to establish whether the reason was an AE, and, if so, this must be recorded. If a subject terminates study participation prior to per-protocol post-Cycle 2 tumor assessment for any reason other than progressive disease, the Investigator or theirrepresentative should notify Molecular Templates and the CRA immediately. The DMC must review the study data from any subject who withdraws from the study prior to completing at least eight of twelve infusions in Cycles 1 and 2 and completing the post-Cycle 2 tumor reassessment. If withdrawal is for any reason other than disease progression, the DMC must review all safety data available for that subject and determine if the subject should be replaced in the MTD expansion cohort.

2.3.2. Extension Study

If a subject terminates study participation prior to per protocol completion of 6 cycles the Investigator or their representative should notify Molecular Templates and the CRA immediately. In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's medical records. If the reason is not known, the subject must be followed to establish whether the reason was an adverse event, and, if so, this must be recorded. The Investigator will make every effort to contact subjects lost to follow-up. Subjects withdrawing from this open access extension study due to an MT-3724 related toxicity will not be eligible for further MT-3724 treatment.

If a subject is discontinued early from the study for any reason after receiving one or more doses of MT-3724, they will be requeted to undergo all the same safety assessments as outlined for the final assessment and exploratory efficacy examinations within 14 to 28 days of withdrawal that the subjects who complete the study are required to undergo.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

Part 1: An estimated 20 to 40 subjects will be enrolled in this standard 3+3 cohort expansion safety and tolerability dose escalation study. The dose escalation cohorts will proceed per protocol as follows:

- Cohort 1: 5mcg/kg/dose/day
- Cohort 2: 10mcg/kg/dose/day
- Cohort 3: 20mcg/kg/dose/day
- Cohort 4: 50mcg/kg/dose/day
- Cohort 5: 100mcg/kg/dose/day
- Cohort 6: 75mcg/kg/dose/day

If the MTD is not reached at or prior to completion of Cohort 6 (75 mcg/kg/day) then additional cohorts will be added in incremental increases based upon analysis of PK/PD data and all safety data for previous cohorts. Additional dose exploration may be required to more accurately identify an MTD.

Part 2: A maximum of 40 DLBCL subjects will be treated in Part 2 (MTD Expansion). The cohort designation for Part 2 is Cohort 7 (50 mcg/kg/dose/day). Three patients started in Part 2 on 75 mcg/kg/day.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All output will be incorporated into Rich Text Format (RTF) files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (Std Dev), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations.

This study is primarily descriptive in nature; therefore, there are no formal statistical hypothesis tests planned. Hypothesis testing may be employed if warranted.

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software v9.4, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v17.0. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version March 2014.

3.4. Baseline Definitions

For both the Main and Extension studies, unless noted otherwise, baseline will be defined as the most recent measurement prior to the first administration of MT-3724 in the Main Study.

3.5. Methods of Pooling Data

Subject data from all study centers will be combined for analysis.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation.

3.8. Subpopulations

All safety and efficacy analyses will be conducted in the following subsets in addition to the overall population:

1. DLBCL vs. "mixed" or "transformed" DLBCL histology (where data allows), designated as NHL histological subtype.
2. Patients with negative vs. positive serum rituximab (RTX) level at screening in the overall population, designated as serum rituximab status at screening.
3. Patients with negative vs. positive serum RTX levels at screening in the DLBCL subsets as defined in point #1 (where data allows).

For Part 1, subjects who have a reported disease histology of Follicular Lymphoma at their initial screening diagnosis and who subsequently have a DLBCL histology at their diagnosis screening review visit will be considered as "Mixed" or "transformed" DLBCL. For Part 2, "mixed" or "transformed" histology is an allowed entry on the disease histology field on the eCRF, and is reported as such.

The distinction between negative and positive serum RTX level is as follows:

- For subjects tested using the RUO assay with a quantitative readout in ng/mL, RTX status will be based on the Sponsor-preferred clinical cut off defined as: <500 ng/mL = negative; >=500 ng/mL = positive.
- For subjects tested using the GLP assay with a semi-quantitative readout of 'Negative', 'Low Positive' or 'High Positive', RTX status will be defined as Positive if the readout is either 'Low Positive' or 'High Positive', and Negative if the readout is 'Negative.

Both types of results will be pooled for the analyses by serum RTX status.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Subjects withdrawing from a cohort in Part 1/Core Study for reasons other than a DLT will be replaced. Subjects participating in Part 2 (MTD Expansion) who are withdrawn any time before Day 21 due to disease progression will be replaced. Subjects participating in Part 2 who withdraw prior to completion of the post-Cycle 4 tumor reassessment may be replaced at the Sponsor's discretion.

3.10. Missing, Unused, and Spurious Data

There will be no substitutions made to accommodate missing data points. All data recorded on the case report form will be included in data listings that will accompany the clinical study report.

When tabulating AE data, partial start dates will be handled as follows:

- If the year, month, and day are all missing, then set the onset day to the date of the first dose.
- If the month and day are missing, and the year is:
    - the same as the year of first dose, then set the onset day as the first day of the month of the first dose;
    - earlier than the year of first dose, then set the onset day as December 31;
    - after the year of the first dose, then set the onset day as January 1.
- If only the day is missing, then
    - if the month/year is the same as the first dose, then set the onset day as the date of first dose;
    - if the month/year is earlier than the month/year of the first dose, then set the onset day as the last day of the month;
    - if the month/year is later than the month/year of the first dose, then set the onset day as the first day of the month.

Partial end dates will only be imputed if the year is non-missing:

- If the month and day are missing, and the year is the same as the year of the last dose then set the end day as the last day of the month of the first dose. Otherwise, set the end date as December 31.
- If only the day is missing, then set the end day as the last day of the month.

If the imputed start date is later than the imputed/non-imputed end date then set the imputed start date to the imputed/non-imputed end date.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented.

3.12. Interim Analyses

There are no planned formal interim statistical analyses of the data. Interim safety data will be examined on an ongoing basis to ensure subject safety and to comply with the clinical trial dose escalation rules. Interim efficacy data may be examined on an ad hoc basis.

4. STUDY ANALYSES

All analyses will be presented by the following MT-3724 treatment groups:

- Cohort 1 (5 mcg/kg/dose)
- Cohort 2 (10 mcg/kg/dose)
- Cohort 3 (20 mcg/kg/dose)
- Cohort 4 (50 mcg/kg/dose)
- Cohort 5 (100 mcg/kg/dose)
- Cohort 6 (75 mcg/kg/dose)
- Cohort 7 / MTD Expansion Cohort (50 mcg/kg/dose)
    - Although 3 subjects enrolled in the original MTD of 75 mcg/kg/dose in Cohort 7, only those enrolled at a starting dose of 50 mcg/kg will be considered for the purpose of analysis
- A cohort which combines all patients with a starting dose of 75 mcg/kg, hereafter referred to as the 'Combined 75 mcg/kg/dose' Cohort
- A cohort which combines all patients with a starting dose of 50 mcg/kg, hereafter referred to as the 'Combined 50 mcg/kg/dose' Cohort

In addition, overall tabulations will be presented in appropriate analyses.

All analyses will be performed on integrated Main and Extention studies.

4.1. Subject Disposition

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented by MT-3724 treatment group. Frequency tables for qualitative data will be provided. If not otherwise mentioned the summary statistics will be based on all subjects who received at least one dose of any study medication, the safety analysis set.

Subject disposition will be tabulated and include the following:

- The number of subjects screened
- The number of subjects treated in total
- The number of subjects in each population for analysis, and the reasons for exclusion, as applicable
- The number of subjects who withdrew prior to completing the study and reason(s) for withdrawal
- The number of subjects who completed the core study, and the number continuing into the repeat cycles and/or extension study.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

4.2. Demographics and Baseline Characteristics

4.2.1. Demographic characterstics

The following baseline demographic characteristics will be summarized:

- age at enrollment
- gender
- race
- height
- weight

4.2.2. Medical history

Medical history findings include previous diagnoses, diseases and surgeries, excluding study indication, and meeting the following criteria: start before signing of the informed consent and considered relevant for the subject's study eligibility.

These data will be summarized using frequency tables for subject count by MedDRA v17.0 system organ class (SOC) and preferred term (PT). Summary statistics will be provided by MT-3724 treatment group and overall. Medical history will be provided in a by-subject data listing by treatment group.

4.2.3. Disease history

The following disease history parameters will be summarized:

- Age at diagnosis
    - In Part 1, the age at initial diagnosis will be assumed to be based on the first entry on the disease diagnosis field of the eCRF. In Part 2, the initial diagnosis will be indicated on the updated eCRF.The age at diagnosis will be computed as date of initial diagnosis – date of birth + 1. For patients enrolled under Protocol Version 7.0, the date of birth is not available; therefore, the year of birth will be used to approximate the age at diagnosis.
- Duration of disease
    - In Part 1, the duration of disease will be assumed to be based on the first entry on the disease diagnosis field of the eCRF.In Part 2, the initial diagnosis will be indicated on the updated eCRF.
- Tumor burden
- Tumor stage at diagnosis
- NHL histological diagnosis. If any data is missing from the initial disease diagnosis assessment, data will be taken from the disease diagnostic review assessment.

Disease history will be provided in by-subject data listings by treatment group.

4.2.4. Prior Medications

The prior medication will be analyzed using frequency tables based on the data classified by the WHO-DD ATC classification, version March 2014. The tables will include the corresponding name of the WHO DD code and the generic drug name. A medication is considered prior if the start date of the medication is before the date of first dose of MT-3724.

By-subject listings will be provided for all prior medications data by treatment group.

4.2.4.1. Prior Systemic Anti-Cancer Therapy

Descriptive summary statistics are not possible given the structure of the eCRF form that captured this data. Therefore, the individual prior systemic anti-cancer therapies (which include chemotherapy, hormonal therapy, immunotherapy and non-conventional therapy) will be presented in a by-subject listing for each treatment group.

Subjects who received anti-CD20 monoclonal antibody therapies will have their best response tabulated.

4.2.4.2. Prior Anti-Cancer Radiotherapy

Prior anti-cancer radiotherapy includes radiation therapy. Subjects who received radiation therapy will be tabulated. Individual prior anti-cancer radiotherapry will be presented in a by-subject listing for each treatment group.

4.2.4.3. Prior Anti-Cancer Surgeries

Prior anti-cancer surgeries include any prior diagnostic or therapeutic procedures. Subjects who underwent procedures will be tabulated. Individual prior anti-cancer surgeries will be presented in a by-subject listing for each treatment group.

4.2.5. Serum Rituximab levels

Subjects will be tabulated as positive or negative based on the clinical cut off value of 500 ng/mL. By-subject listings of serum Rituximab levels will be provided by treatment group.

4.2.6. Other baseline characteristics

Each subjects' functional status as measured by ECOG will be tabulated and listed in a by-subject data listing by treatment group.

Tumor imaging(MRI, CT, and chest radiography) and pregnancy test results will be provided in by-subject data listings by treatment group.

4.3. Exploratory Efficacy Evaluation

2. [redacted]

Descriptive statistics for all of the above endpoints will be summarized by treatment group. By-subject listings will be provided for each treatment group.

No formal hypothesis-tests are planned.

4.4. Pharmacokinetic Evaluation

Pharmacokinetic analyses will be conducted using the PAS.

Analysis of PK and PDn parameters will be described in a separate PK/PDn analysis document.

A by-subject listing with all sampling times will be presented.

4.5. Study Drug Exposure

Study drug exposure analyses will be conducted using the Safety Set.

All study drug exposure analysis will also be performed by subgroup as defined in Section 3.8.

Study drug exposure will be calculated as the number of days subjects were administered study drug, as determined below, and will be summarized by treatment group using descriptive statistics.

$$Duration\ of\ Study\ Drug\ Exposure\ (days) = (Date\ of\ last\ infusion - Date\ of\ first\ infusion) + 1$$

The number of dosing cycles completed will be tabulated for each treatment group.

Total drug received (both in mcg and mcg/kg), dose intensity (defined as total drug received divided by duration of exposure), number of doses taken, number of missed doses, number of dose interruptions, duration of dose interruption, and number of dose reductions will also be summarized.

Dosing information for each subject will be presented in a data listing by treatment group.

4.6. Safety Analyses

Study drug exposure analyses will be conducted using the Safety Set.

Safety will be evaluated from adverse events, laboratory results, vital signs, ECG parameters and the changes from baseline in physical examination and medical history.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All safety analysis will also be performed by subgroup as defined in Section 3.8.

4.6.1. Adverse Events

Adverse events (AEs) will be coded according to MedDRA Version 17.0 using system organ class (SOC) and preferred terms. Adverse events will be graded using the CTCAE v4.03. In the summary tables, subjects may be counted under multiple SOC and PT, but for each SOC and PT

category, subjects are only counted once. If a patient has the same AE on multiple occasions, the worst severity grade (fatal > life threatening > severe > moderate > mild) recorded for the event will be summarized.

Pre-treatment adverse events

All AEs that occurred before the first administration of MT-3724 are considered to be pre-treatment AEs.

Pre-treatment AEs will be summarized using frequency tables for subject count by CTCAE grade and worst CTCAE grade. Separate summary tables will be provided for serious and non-serious events. By-subject listings of pre-treatment AEs will be provided separately for serious and non-serious events. Summary statistics and listings of pre-treatment AEs will be provided for the overall safety population.

Treatment-emergent adverse events

All AEs that have started or worsened after the first administration of MT-3724 up until the last study assessment visit are considered to be treatment-emergent adverse events (TEAEs).

For each TEAE, the investigator will assess the causal relationship to MT-3724 as related and unrelated, where related = possibly, probably or definitely related, and unrelated = unlikely or definitely not related.

TEAEs will be summarized by treatment group using frequency tables for subject count by CTCAE grade and worst CTCAE grade. Separate tables will be provided for non-serious TEAEs, serious TEAEs and all TEAEs (non-serious and serious combined). The following tables will be provided for each of the above categories:

- TEAEs by MedDRA and Worst CTCAE Grade
- TEAEs by MedDRA and Worst CTCAE Grade, Only Grade 3/4/5 Events
- Related TEAEs by MedDRA and Worst CTCAE Grade
- Related TEAEs by MedDRA and Worst CTCAE Grade, Only Grade 3/4/5 Events
- Common TEAEs (occurring in ≥10% of subjects) by MedDRA and Worst CTCAE Grade – Only for the overall population and MTD expansion

The following additional tables will be provided for all TEAEs (non-serious and serious combined)

- TEAEs Leading to Permanent Discontinuation by MedDRA and Worst CTCAE Grade
- Related TEAEs Leading to Permanent Discontinuation by MedDRA and Worst CTCAE Grade
- TEAEs Leading to Dose Reduction by MedDRA and Worst CTCAE Grade
- Related TEAEs Leading to Dose Reduction by MedDRA and Worst CTCAE Grade
- TEAEs Leading to Dose Interruption / Delay by medDRA and Worst CTCAE Grade

- Related TEAEs Leading to Dose Interruption / Delay by medDRA and Worst CTCAE Grade

The following by-subject listings of TEAEs with the corresponding MedDRA PT, worst CTCAE grade, relatedness outcome and seriousness (where applicable) will be provided:

- Non-serious TEAEs Grade 3/4/5
- Serious TEAEs (all CTCAE grades)
- TEAEs Leading to Dose Interruption / Delay
- TEAEs Leading to Dose Reduction
- TEAEs Leading to Permanent Discontinuation
- TEAEs Declared as Dose Limiting Toxicities
- TEAEs Leading to Death

4.6.2. Laboratory Data

Clinical laboratory values will be expressed in SI units.

Quantitative laboratory data will be summarized by treatment group, parameter and scheduled time points using descriptive statistics. The summary tables will be presented for the original data as well as for the difference from baseline. In the event of repeat values, the average value per study day/time will be used. Local hematology lab results will be primarily considered for summary tables; if no local lab results are available, central lab results will be used. Non-negative results will be listed for qualitative variables. Microglobulin, immunology, and complement samples, as well as Serum cytokine results from the central lab will be included in the summary tables.

Shift tables will be produced that summarize the maximum shifts from baseline to worst value for hematology, chemistry, and coagulation lab categoriesusing CTCAE toxicity grades for relevant laboratory parameters. Scatter plots or box and whisker plots of selected lab tests over time may be presented where appropriate. Unscheduled visits may contribute to worst visits, as applicable. Both local and central hematology lab results will be considered for worst values.

All laboratory data will be provided in data listings, where laboratory values outside the normal range will be flagged with “H” (high) or “L” (low), as well as the CTCAE grade, if applicable.

Unscheduled visits will not be summarized in tabulations. They will only be included in data listings and/or shift tables, as appropriate.

4.6.3. Vital Signs

Vital signs parameters include systolic and diastolic blood pressure, heart rate, respiration rate, body temperature and body weight.

The actual value and change from baseline within each on-study evaluation will be summarized by treatment group. The pre-dose measurement will act as baseline for a given visit; post-dose measurements will be compared to pre-dose measurements within each visit.

Vital sign measurements will be presented for each subject in a data listing by treatment group.

4.6.4. Physical Examination

Physical examination results at each time point will be summarized using shift tables to indicate change in status (normal/abnormal) from baseline to each post-baseline assessment.

Those findings on physical examination that represented a changes from baseline will be presented in by-subjec tdata listing for each treatment group.

4.6.5. Electrocardiogram

Electrocardiogram (ECG) parameters include the heart rate, PR interval, QRS interval, QT interval, QT interval corrected for heart rate according to Fredericia's formula (QTcF), sinus rhythm (yes/no), overall ECG interpretation by the investigator or designee (normal, abnormal clinically not significant and abnormal clinically significant) and comments from the overall ECG interpretation by the investigator or designee.

The ECG recording obtained at screening will represent the baseline for all on-treatment observations.

Actual values and changes from baseline in ECG intervals and the heart rate will be summarized by descriptive statistics and presented in tables and by-subject listings for each treatment group. Categorical analysis of the QT and QTcF intervals (absolute value ≤450, 451-480, 481-500, and >500 msec and change from baseline <30, 31-60, and >60 msec) will also be performed and frequencies (number and percent of subjects) in each category will be presented in tables and by-subject listings for each treatment group. The specific value for each subject will be provided in the listing of categorical analysis results.

The overall ECG assessment results will be summarized by category (normal, abnormal clinically not significant, abnormal clinically significant) in frequency tables for each treatment group. In addition, the overall ECG assessment results will be listed by category for each treatment group. For abnormal clinically significant result, the corresponding AE term and CTCAE grade will be specified in the listing, if available.

4.6.6. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. Results will be tabulated by anatomic therapeutic class (ATC) and preferred term.

Concomitant medications will be tabulated by treatment group, where any medications that did not end prior to first dose will be included. If an end date is missing or the medication is ongoing, the medication will be included.

The concomitant medication dates and terms will be presented in by-subject listings for each treatment group.

4.6.7. ECOG Performance Status

ECOG performance status will be summarized using a shift table to indicate change in score from baseline to each post-baseline assessment.

All ECOG data will be presented in a by-subject data listing for each treatment group.

5. CHANGES TO PLANNED ANALYSES

Changes from Version 1.0 to Version 2.0 of this SAP was the result from a change in CRO providing biostatistical services to Molecular Templates for Study MT-3724_NHL_001_US.

Changes from Version 2.0 to Version 3.0 of this SAP are the result from the changes that occurred between Protocol Version 4.0 and Protocol Version 7.0 for Study MT-3724_NHL_001_US and between Protocol Version 1.0 and Protocol Version 2.0 for Study MT-3724_NHL_001_US_EXT.

6. REFERENCES

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579-86.