1. TITLE PAGE

Abbreviated Clinical Study Report

Safety, Pharmacodynamics and Efficacy of MT-3724 for the Treatment of Patients with Relapsed or Refractory DLBCL

Protocol Number	MT-3724_NHL_001 (Part 3); Version 8.0
Name of Investigational Drug:	MT-3724
Indication	Relapsed or refractory DLBCL
Developmental Phase of Study	1/2
First Subject Treated	14 October 2019
Date of Last Subject/Last Visit	21 March 2021
Sponsor Signatory	[redacted] Chief Medical Officer Molecular Templates, Inc. [redacted] Senior Vice President, Clinical Development Molecular Templates, Inc.
Responsible Medical Officer	Managed by CRO. Refer to the team contact list for the most up-to-date contact details.
Date of Report	16 November 2021

This study was conducted in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline E6, Guideline for Good Clinical Practice.

CLINICAL STUDY REPORT APPROVAL

Sponsor: Molecular Templates Inc

Clinical Protocol Number: MT-3724_NHL_001 Part 3

Drug Name: MT-3724

Protocol Title: Safety, Pharmacodynamics and Efficacy of MT-3724 for the Treatment of Patients with Relapsed or Refractory DLBCL

[redacted] 11/15/2021

Date

Chief Medical Officer
Molecular Templates, Inc.

[redacted] 11/16/2021

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Senior Vice President, Clinical Development
Molecular Templates, Inc.

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Director, Clinical Operations
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Date

Senior Director, Biostatistics
Molecular Templates, Inc.

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Date

Vice President, Regulatory Affairs
Molecular Templates, Inc.

2. STUDY SYNOPSIS

Name of Company:	Name of Finished Product:	Name of Active Ingredient:
Molecular Templates, Inc.	MT-3724	MT-3724 fusion protein

Title of Study:

Safety, Pharmacodynamics and Efficacy of MT-3724 for the Treatment of Patients with Relapsed or Refractory DLBCL

Investigators:

[redacted]

Publication (reference):

None

Studied Period:	Phase of Development: 1-2
Date first subject treated: 14 October 2019 Date of database lock: 25 May 2021	

Objectives:

Primary Objective:

The primary objective of Part 3 of this study was:

- To determine the efficacy of MT-3724 as monotherapy in subjects with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) based on the overall response rate (ORR) by the revised Lugano Classification for Lymphoma adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria), hereinafter referred to as "revised Lugano Criteria". ORR is defined as the proportion of subjects with either a complete response (CR) or a PR (partial response) as determined by independent, blinded central review.

Secondary Objectives:

The secondary objectives of Part 3 of this study were to determine the following for MT-3724 as monotherapy in subjects with r/r DLBCL:

- Safety
- Efficacy based on the duration of tumor response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS)
    - DOR: defined as time from initial documentation of tumor response (CR or PR) to disease progression
    - DCR: defined as the proportion of subjects who have achieved CR, PR, and stable disease (SD) (defined as SD for 3 months or longer)
    - PFS: defined as the time from study enrollment to the earliest date of disease progression or death from any cause
    - OS: defined as the time from study enrollment to death from any cause

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- Pharmacokinetics (PK)
- Pharmacodynamics (PD)
- Immunogenicity: anti-drug antibodies (ADA)
- Quality of life

Exploratory Objective:

The exploratory objective of this study was:

- To determine immunogenicity: neutralizing antibodies (NAb).

Methodology:

This was an open-label, Phase 1/2, study of MT-3724. This abbreviated clinical study report encompasses the third part, also known as the expansion cohort, to this study, which was closed prematurely after 11 patients were treated in Stage 1 of Part 3.

Part 1 of the protocol included evaluating escalating doses of MT-3724 in subjects r/r DLBCL or chronic lymphocytic leukemia (CLL) to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D).

Part 2 (implemented in Version 6.0 of the protocol) included an expansion of the MTD cohort to evaluate safety, tolerability, and potential efficacy at the MTD or RP2D. Implemented as Version 7.0 of the protocol, up to 40 additional subjects with DLBCL were treated with MT3724 at the MTD/ RP2D (50 µg/kg/dose).

The expansion cohort of this study (Part 3) implemented in amendment Version 8.0, was a multi-center, multinational, Phase 2 open-label, single-arm evaluation of MT-3724 given as monotherapy in repeat doses in subjects with relapsed or refractory DLBCL who have received 2 or more lines of prior therapy. The study was placed on clinical hold and then closed due to safety concerns.

Eligible subjects were identified and treated through competitive enrollment across multiple sites in North America and Europe; additional sites in other global regions may have been included if necessary to achieve optimal enrollment rate.

Part 3 was conducted in three stages, where the first two stages followed the Simon two-stage optimum design:

Stage 1: twenty-one (21) subjects were to be enrolled into the first stage. If there were ≤2 responses in the first 21 subjects, the study was stopped. If at least 3 responses were observed among the first 21 subjects, then the study would have proceeded to the second stage.

Stage 2: an additional 45 subjects were to be enrolled in the second stage for the total sample size of 66 subjects in the Simon 2-stage design. If at least 11 of 66 subjects responded at the end of the second stage, then MT-3724 as monotherapy would have moved forward to the third stage of clinical investigation, unless other considerations (*e.g.*, poor safety profile) indicated otherwise.

Stage 3: an additional 34 subjects were to be enrolled and treated for the total sample size of 100 subjects.

The total sample size of up to 100 was planned assuming positive outcomes, in terms of safety and efficacy, of the first two enrollment stages (target of 66 patients across stages 1 and 2).

Each treatment cycle was 21 days in length. The treatment with MT-3724 continued for up to 6 cycles or until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for

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withdrawal, or until study discontinuation. If the subject exhibited SD or PR after the end of Cycle 6 and the investigator determined that the benefit-risk ratio was favorable, treatment with MT-3724 may have continued for up to 6 additional cycles.

If a subject exhibited CR, dosing could have continued for two additional cycles.

Number of Subjects (planned/analyzed):

Up to 100 subjects with histologically confirmed r/r DLBCL who had received at least 2 standard of care (SOC) systemic non Hodgkin lymphoma (NHL) treatment regimens were planned to be enrolled.

A total of 11 subjects were enrolled; 11 subjects received study treatment. All subjects who received the study drug were included in the full analysis, PK, PD, immunogenicity, and safety data sets.

Diagnosis and Main Criteria for Inclusion:

Under Amendment 8, the study enrolled adult patients with r/r large B-cell lymphoma after two or more lines of systemic NHL therapy and who were not candidates for curative therapy. Subjects must have had at least one histologically confirmed diagnosis of DLBCL determined by excisional or core biopsy.

Inclusion Criteria:

Subjects who met all of the following inclusion criteria were considered eligible for participation:

1. Subjects must have been informed about the study and fully consent to participation as demonstrated by signing the written informed consent form (ICF) before any screening procedure.
2. Male and female subjects ≥ 18 years of age at the time of informed consent.
3. Subjects must have had r/r DLBCL according to the Revised European American Lymphoma/World Health Organization (REAL/WHO) classification. Subjects must have at least one documented, histologically confirmed diagnosis of DLBCL:
    a. Composite lymphoma (DLBCL and indolent histology in the same specimen) were also acceptable.
4. Subjects must have received at least 2 SoC for NHL treatment.
    a. Patients whose prior therapy included chimeric antigen receptor T-cell (CAR-T) therapy were eligible.
    b. Subjects who had previously received autologous stem cell transplant (SCT) must have been at least 100 days post-transplant before study drug administration and must have exhibited a full hematological recovery prior to relapse were eligible.
    c. Patients who were ineligible for SOC NHL treatment(s) may have been eligible at the investigator's discretion.
5. Subjects must have had at least one tumor lesion at screening that was measurable by fluorodeoxyglucose-positron emission tomography (FDG-PET) / computerized tomography (CT) (for FDG-avid tumors) or CT or magnetic resonance imaging (MRI) (for non-FDG-avid tumors) according to the revised Lugano criteria. Measurable tumor lesion was defined as longest diameter of > 1.5 cm for lymph nodes and > 1.0 cm for extranodal disease.
6. Subjects must have had life expectancy of > 3 months from the start of treatment.
7. Subjects must have had Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
8. Subjects must have met ALL the following laboratory criteria:
    a. Absolute neutrophil count ≥ 1.0×10^9/L
    b. Platelet count ≥ 50×10^9/L
    c. Peripheral blood total lymphocyte count of < 25,000/mm^3
    d. Hemoglobin ≥ 8.0 g/dL

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e. Creatinine clearance (CLcr) to be ≥ 50 ml/min either measured or estimated using the Cockcroft-Gault formula

f. Total bilirubin ≤ 2.0 × upper limit of normal (ULN), or ≤ 3.0 x ULN for subjects with Gilbert's Syndrome

g. Alanine transaminase (ALT) ≤ 2.5 × ULN (or ≤ 5.0 x ULN if liver involvement).

h. Aspartate aminotransferase (AST) ≤ 3.0 × ULN (or ≤ 5.0 x ULN if liver involvement).

i. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN (unless on therapeutic anticoagulants)

j. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN (unless on therapeutic anticoagulants)

9. Have had adequate serum albumin, as determined by:
   a. Albumin ≥ 3.0 g/dL
10. QTcF (Fridericia) ≤ 480 ms determined as the average of three QTcF values from the triplicate electrocardiogram (ECG) obtained at screening.
11. Left ventricular ejection fraction (LVEF) ≥45% by multi-gated acquisition (MUGA) or echocardiogram obtained at screening (inclusion of patients with LVEF ≥40% should have been discussed with the medical monitor).
12. Subjects of childbearing potential must have had a negative pregnancy test within 7 days before the start of treatment. Subjects of childbearing potential who were postmenopausal or permanently sterilized (*e.g.*, tubal occlusion, hysterectomy, bilateral salpingectomy) were considered as not of reproductive potential.
13. Subjects of reproductive potential must agree either to abstain continuously from heterosexual intercourse or to use a reliable birth control method from signing the informed consent until the post-study Follow-up visit. The following birth control methods were considered adequate:
    a. Condoms (male or female) with or without a spermicidal agent
    b. Diaphragm or cervical cap with spermicide
    c. Intrauterine device
    d. Hormone-based contraception: established use of oral, injected or implanted hormonal methods of contraception
    e. True abstinence
    f. Vasectomy was an acceptable method for a subject with the ability to father a child or the partner of a subject capable of fathering a child.
14. Subject must have been able to comply with all study-related procedures and medication use.

Exclusion Criteria:
Prior or current therapies

1. Received any amount of anti-CD20 monoclonal antibodies (mAbs) within the following periods before the start of treatment:
   a. Rituximab (Rituxan® or rituximab biosimilar): within 84 days; if a subject had received rituximab within 37 weeks before the start of treatment, then serum rituximab level must have been negative (< 500 ng/mL) at screening.
   b. Obinutuzumab (Gazyva®): 184 days
   c. Ofatumumab (Arzerra®): 88 days

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2. Received approved or investigational treatment for NHL (except anti-CD20 mAb and radioimmunoconjugates) within 4 weeks before the start of treatment. Radioimmunoconjugates were excluded within 12 weeks before the start of treatment.
3. Received radiation therapy to tumor lesions that would serve as target lesions (measurable disease) within 4 weeks before the start of treatment, unless the lesion exhibited objective progression between radiation therapy and screening according to the revised Lugano Classification.
    a. Palliative radiation therapy to non-target lesions may have been permitted at the investigator's discretion.
4. Received systemic immunosuppressive agents (except prescribed corticosteroids at doses ≤ 20 mg/day of prednisone equivalent) within 2 weeks before the start of treatment.
5. Received vaccines except injectable flu vaccine (inactivated or recombinant) within 4 weeks before the start of treatment, or likely to have required any vaccines except injectable flu vaccine at any time from the start of treatment until 28 days after the last dose of MT-3724.
6. Received allogenic stem cell transplant.

Medical history

7. Evidence of Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1 toxicity before the start of treatment, except for hair loss and those Grade 2 toxicities listed as permitted in other eligibility criteria. Subjects with Grade 2 neuropathy may have been eligible at investigator's discretion.
8. History or evidence of significant (CTCAE Grade ≥ 2) infection, systemic infection, or wound within 2 weeks before the start of treatment.
    a. Subjects with Grade 2 infection that had stabilized or improved with oral antibiotics before the start of treatment may have been eligible at the investigator's discretion.
9. Known or suspected hypersensitivity to the study drug or excipients contained in the study drug formulation.
10. Evidence of hypersensitivity or other underlying illness requiring systemic corticosteroids at doses > 20 mg/day prednisone equivalent.
11. Evidence of seropositive status for human immunodeficiency virus (HIV), hepatitis B virus (HBV) (positive for HBsAg or anti-HBcAG antibodies) or hepatitis C virus (HCV) (positive for anti-HCV antibody or HCV-RCV-RNA quantitation) at screening.
    a. Serology testing may have been omitted at the investigator's discretion if seronegativity was documented in the medical history and there were no clinic signs suggestive of HIV or hepatitis infections.
    b. Subjects with positive HBV serology were eligible if quantitative PCR for plasma HBV-DNA was negative and the subject was receiving prophylaxis for potential HBV reactivation.
    c. Subjects with positive HCV serology were eligible if quantitative PCR for plasma HCV RNA was negative.
12. Evidence of incomplete recovery from surgery or radiotherapy at screening, or planned surgery or radiotherapy from the start of treatment until the post-study follow-up visit, except minor elective surgery or palliative radiation therapy to non-target lesions deemed acceptable by the investigator.
13. History of cardiovascular, renal, hepatic or any other disease within ≤3 months before the start of treatment that in the investigator's opinion, may have increased the risks associated with study participation or required treatments that may have interfered with the conduct of the study or the interpretation of study results.

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14. History of another primary malignancy within the past 3 years (except for ductal breast cancer in situ, non-melanoma skin cancer, prostate cancer not requiring treatment, and cervical carcinoma in situ) that required systemic drug therapy or radiotherapy.
15. Evidence of new or growing brain or spinal metastases during screening. Subjects with known brain or spinal metastases may have been eligible if they:
    a. Had radiotherapy or another appropriate therapy for the brain or spinal metastases
    b. Had no neurologic symptoms (except Grade ≤2 neuropathy)
    c. Had stable brain or spinal disease on CT or MRI scan within 4 weeks before signing the informed consent
    d. Did not require steroid therapy (and, if applicable, have been stable off steroids for at least 4 weeks)
16. Patients who were pregnant or breastfeeding.
17. History of non-adherence to the schedule of procedures or medication use.

Test Product, Dose and Mode of Administration, Batch Numbers:
MT-3724 was supplied in 2.0 mL vials, which must have been stored until use at 20°C (10 to 25°C) in a secure facility. While the MT-3724 is stable at room temperature for up to 24 hours, it was recommended to use the thawed drug to prepare the final solution for infusion within 3 hours. All doses were administered over 1 hour through an IV line containing MT-3724 in 5% dextrose in water (D5W) or normal saline. Thawed drug vials with intact stoppers could have been stored at 2 -8°C for up to 1 month. After 1 month of storage at 2 - 8°C, unused drug vials should have been destroyed by the pharmacist according to local institutional standard procedures. MT-3724 was supplied at a dose of 50 µg/kg/dose/day with a maximum of 6000 µg/dose/day

The investigator may have modified the MT-3724 treatment in an individual subject by:

- Dose interruption defined as changes made during the current dose (*e.g.*, temporary or permanent stopping of the IV infusion).
- Dose delay was used for changes to dose schedule (*e.g.*, postpone the date of the next dose). A maximal dose delay of 14 days was allowed; a delay exceeding 14 days should have been discussed with the medical monitor.
- Dose reduction
    - Medical monitor must have been notified when dose was reduced.
- Permanent discontinuation.

Lot Numbers: 149-1014-007, AG3545, AK0582

Reference Therapy, Dose and Mode of Administration, Batch Numbers:
There were no positive or negative control groups in this study.

Duration of Treatment:
Duration of study participation for each subject was approximately 19 to 22 weeks or until the subject's disease is no longer responding or unacceptable side effects have developed. This included:

- A screening period of up to 35 days prior to the first dose of study drug
- Treatment cycles of 21 days until death, disease progression, unacceptable toxicity, withdrawal of consent, or any other reason for withdrawal prior to study discontinuation.
- Interim tumor status assessments every 6 weeks
- End of treatment (EoT) visit up to 14 days after the last dose of the study drug.

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- A short-term follow-up visit approximately 30 days after the last dose of the study drug.
- A long-term follow-up period, during which the study staff called the patient every 3 months after the last dose of study drug.

Criteria for Evaluation:

Primary Efficacy Endpoints:
The definitive treatment response assessment (*i.e.*, the tumor response used to derive the primary and secondary efficacy endpoints) was to be determined by response assessment using the revised Lugano Classification. The sponsor had the definitive treatment response assessment determined by the blinded, independent central review (ICR) service at the central imaging laboratory using the revised Lugano Classification. The primary efficacy variable was to be the ORR. The ORR was defined as the percent of subjects with CR or PR determined by the blinded, independent central review according to the revised Lugano Classification for Lymphoma adjusted according to LYRIC, relative to the full-analysis-set (FAS) population.

ORR was to be summarized by number and percentage of subjects meeting the definition of ORR along with the corresponding two-sided 95% binomial exact confidence intervals (CI). Further details were provided in the Statistical Analysis Plan (SAP).

Secondary Efficacy Endpoints:
The secondary efficacy variables were to be the PFS, DCR, DOR, and OS. All secondary efficacy variables were to be determined from the radiological tumor scans according to the revised Lugano Classification for Lymphoma adjusted according to LYRIC relative to the FAS population.

The DCR was defined as the percent of subjects with objective response of CR, PR or SD, (defined as SD for 3 months or longer). The DCR was to be analyzed using similar methods as the ORR. Further details were provided in the SAP.

The DOR was defined as the time from the first documented objective response (CR or PR) to the date of PD or death from any cause. Subjects who had not progressed or died at the time of data base lock were to be censored at the date of their last tumor assessment.

The PFS was defined as the time from the start of treatment with MT-3724 on C1D1 to the date of PD or death from any cause. Subjects who had not progressed or died at the time of data base lock were to be censored at the date of their last tumor assessment.

For both DOR and PFS, those subjects who had no data on progression (*e.g.*, subjects who discontinued the study due to other reasons than progression and who were not followed up until progression) and/or had no data on tumor assessment after baseline and were still alive were to be censored at the subject's date of first dose.

The OS was defined as the time from the start of treatment with MT-3724 until death from any cause.

The DOR, PFS and OS were to be summarized descriptively using the Kaplan-Meier methods (K-M median and corresponding 95% CI, quartiles, number of events, number censored, Kaplan Meier figure).

As a secondary sensitivity analysis for efficacy (*e.g.,* study drug exposure, lines or prior therapy, DOR to prior therapy, subject subsets), the Response Evaluable population was to be utilized. The same statistical techniques were to be applied on each efficacy endpoint on the Response Evaluable population.

Data listings were to be created to support each analysis and to present all efficacy data.

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The value for the percent change from baseline in the sum of product of perpendicular diameters (SPD) as the measurement of tumor lesion size in each individual subject was listed by time points. The values for the percent change from baseline in SPD values at each time point was to be plotted for individual subjects ("spider plot"). The largest value for the percent change from baseline in SPD was to be plotted on a histogram ('waterfall' plot).

Safety Endpoints

All subjects who received any dose (any amount) of MT-3724 monotherapy treatment were included in the summaries and listings of safety data. Overall safety profile was characterized by type, frequency, severity, timing, duration, AE relationship to study drug, laboratory abnormalities, and vital signs. All analyses were descriptive. Baseline values were defined as the last valid value prior to study drug administration. Baseline safety data was presented along with subsequent safety values assessed during or after drug administration.

AEs were classified using the MedDRA classification system and the severity of the toxicities was graded according to the NCI CTCAE v 5.0. In all summaries, emphasis was placed on treatment emergent AEs (TEAEs), namely, those with initial onset or those that worsened in severity after the first dose of MT-3724. AEs were summarized by the frequency of subjects experiencing TEAEs corresponding to MedDRA SOC and preferred term and by worst NCI CTCAE grade. Summaries were also provided for treatment related TEAEs, namely, those judged by the investigator to be related or likely related to MT-3724. AEs resulting in discontinuation of MT-3724 treatment or withdrawal from the study, Grade 3 or higher, serious adverse events, and deaths on-study were tabulated.

Laboratory data was summarized for the observed values at each scheduled assessment, together with the corresponding changes from baseline using descriptive statistics. For those analytes with CTCAE version 5.0 severity criteria are specified, abnormal laboratory values were to be summarized by shift tables displaying numerical values and percentages classified by baseline grade and maximum grade on treatment if appropriate. All laboratory data were presented in data listings.

Vital signs data was summarized by the observed valued at each scheduled assessment, together with the corresponding changes from baseline using descriptive statistics. Physical examination findings were presented in data listings.

Interim Analysis/Endpoints:

Because a three-stage design was employed, the response rate data was to be assessed after Stage 1 and Stage 2 to determine whether enrollment should proceed to the next sequential stage per the Simon two-stage stopping rules

PK Endpoints:

The PK parameters were to be estimated using standard noncompartmental methods as data permitted. PK parameters, where calculable, were to include: C_{max}, t_{max}, AUC_{0-4}, AUC_{0-inf}, AUC_{last}, $t_{1/2}$, V_z and CL. Actual sample collection times were to be used rather than scheduled collection times. It was planned that serum concentrations below the limit of quantification were to be treated as 0. Imbedded missing serum concentrations (*i.e.*, missing values between two observed values) were to be estimated using linear extrapolation. Other missing serum concentrations were to be excluded from calculations to estimate PK parameters.

PD Endpoints:

B-cell count and immunophenotyping results obtained by flow cytometry were to be presented as absolute values and percentage change from pre- to post-dose time points. The absolute values and changes from baseline by time point during the treatment were to be tabulated for the PD analysis set. The absolute values

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and change from baseline in PD data by time point during the treatment were to be listed and plotted for the PD analysis set.

Details of the descriptive statistical analyses of pharmacodynamic data were provided in a separate statistical analysis plan.

The exploratory exposure-response modeling to correlate the PD, safety or efficacy response with plasma concentrations of MT-3724 were to be investigated using population approaches. The details of the exposure-response modeling analysis were described in a separate Modelling and Simulation (M&S) Analysis Plan and the results will be presented in a separate M&S report.

Immunogenicity Endpoints:
Data for the ADA against MT-3724 was obtained. The ADA titer was determined for ADA samples confirmed as a positive result. The data for the NAb against MT-3724 was obtained as the positive or negative result.

The number and percent of subjects with a detectable ADA titer, and separately with a positive NA result, were to be summarized by time point for each treatment group/cohort. The individual subject's ADA and NA results were listed by time point during the treatment; the listings were presented for the pharmacodynamic analysis set. The individual subject's ADA titer was to be plotted by time point during the treatment.

Details of the descriptive statistical analyses of immunogenicity data were provided in a separate statistical analysis plan.

Statistical Methods:

Power and Sample Size:
Simon Stage 1: Twenty-one (21) subjects were to be enrolled into the first stage. If there were ≤ 2 responses in the first 21 subjects, the study would have been stopped. If at least 3 responses were observed among the first 21 subjects, then the study would have proceeded to the second stage.

Simon Stage 2: Assuming the positive outcome of the Simon Stage 1 (see above), an additional 45 subjects were to be enrolled in the second stage for the total sample size of 66 subjects in the Simon 2-stage design. If at least 11 of 66 subjects responded at the end of the second stage, then the conclusion could have been drawn that the MT-3724 monotherapy is promising and worthy of further clinical investigation in the third stage, unless other considerations (*e.g.*, poor safety profile) indicated otherwise.

Expansion Stage: Assuming the positive outcome of the Simon Stage 2 (see above), additional 34 subjects were to be enrolled and treated for a total sample size of 100 subjects in the three-stage expansion cohort. Assuming a true ORR (primary efficacy endpoint) was 25% among treated subjects, with a total sample size of 100 subjects, the 95% CI for the true ORR was between 16.5% and 33.5% (*i.e.*, CI width ±8.5% around the ORR point estimate). In addition, the lower bound of the 95% CI was >16.5%, which was deemed a clinically relevant ORR in this indication and patient population.

In addition, each subject was to undergo a LTFU Visit every 6 months (±14 days) after the last dose of MT-3724 until death or loss to follow up. The LTFU Visits were performed via a telephone call to collect the information about death (if any), the NHL status (relapsed or not) and the start of any new therapy for NHL or any other investigational drug since the last study visit/phone call. Subjects with CR, PR or SD were to also be followed for radiology assessment until progressive disease, death, new anticancer treatment or lost to follow-up. Radiology data were obtained from existing medical records if assessments were performed as standard of care between LTFU visits.

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Randomization:

No randomization was performed, and the study was open-label.

Tests of Hypotheses and Significance Levels:

When the true response rate of 25% (alternative hypothesis) was tested against the null hypothesis response rate of 10%, this Simon two-stage design with a total of 66 subjects yielded a Type I error rate of 0.05 and power of 90%.

Disposition:

A detailed description of subject disposition was provided. This description included the number of subjects who were included in the FAS, safety and efficacy evaluable analysis sets; a summary of subjects who completed the protocol; a summary of reasons for subject discontinuation, a summary of reasons for subjects with treatment failure, and an account of all identified protocol violations. All subjects enrolled in the study were accounted for in the summation.

Baseline Comparability:

Demographic characteristics, including age, gender, race, and ethnicity, were presented in the form of tabular summary statistics for all FAS subjects. Other subject baseline characteristics included weight, height, BMI, initial stage of disease, and performance status were presented similarly

Summary and Conclusions:

Subject Disposition:

A total of 29 subjects were screened at participating investigational sites worldwide. A total of 11 subjects received study drug.

Demographic and Baseline Characteristics:

Of the 29 subjects who were screened, 11 received at least one dose of MT-3724 monotherapy. Eighteen subjects failed the screening procedures and therefore did not receive study drug. For the subjects who received at least one dose of the study drug, the most common reason for treatment discontinuation was disease progression per radiographic assessment, N=7 (63.6%).

Exposure Results:

MT-3724 was administered at a dose of 50µg/kg/dose via IV infusion for all subjects, though dose reductions were required for Subject 2014-001 during Cycle 1 and 9201-002 during Cycle 1. Dosing was planned for Days 1, 3, 5, 8, 10, and 12 of each 21-day cycle. The median number of MT-3724 cycles received was 2 (range: 1 – 5), the median duration of exposure was 3.7 weeks (range: 1.4 weeks – 13.7 weeks), and the median total number of doses received was 7 (range: 4 - 30). MT-3724 dose intensity was similar across all cycles.

Safety Results:

- All 11 (100%) treated subjects in the safety analysis set experienced at least 1 treatment-emergent adverse events (AE) during the study. The most frequently reported TEAEs were myalgia, pyrexia, and anemia reported in 7 subjects (63.6%), 6 subjects (54.4%), and 5 subjects (45.5%), respectively.
- • The study drug was discontinued for one subject (9.1%), related to instances of CLS.
- The following serious AEs (SAEs) were reported: A Grade 1 fever was reported and was unlikely related to treatment. Another subject also experienced Grade 3 kidney injury and a Grade 4 edema. The edema was considered unlikely related to treatment, while the kidney injury was unrelated. All subjects reporting SAEs were receiving doses of 50 µg/kg.

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- One subject died during the study following a Grade 5 CLS, which occurred two days after receiving the study drug on Cycle 1, Day 10. Patient reported active conditions of hypertension, ischemic heart disease, hyperlipidemia, tremor (limbs), insomnia, constipation, and hernia at the time of the fatal event. Patient was a candidate for supportive oxygen and intubation but refused.
- One Suspected Unexpected Serious Adverse Reaction (SUSAR) was reported: the aforementioned case of Grade 5 CLS, which was considered related to MT-3724.

Conclusions:

Because only 11 subjects were treated with MT-3724 as a monotherapy and all experienced TEAEs, conclusions for efficacy and safety are limited in scope.

Although the PK concentration of MT-3724 was measurable in the serum of all 11 PK analysis patients, there was high variability in the data, small sample size, and inconsistent sampling. Therefore, PK-PD relationships were difficult to discern. Immunogenicity results were also complicated by the small sample size.

Potential risks of MT-3724 include capillary leak syndrome (CLS) with fatal outcome in one case, myalgia, pyrexia, anemia, diarrhea, hypoalbuminemia, peripheral edema, and dyspnea.

Given the limited safety data, including one fatal case of CLS and the absence of efficacy in this small sample size, it is not possible to adequately characterize the activity of MT-3724 as a monotherapy treatment in subjects with r/r DLBCL.

Date of the Report: 16 November 2021

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
BMI	Body Mass Index
BORR	Best Overall Response Rate
BP	Blood Pressure
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
CAR-T	Chimeric Antigen Receptor T-Cell
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine Kinase
CLcr	Creatinine Clearance
CLL	Chronic Lymphocytic Leukemia
CLS	Capillary Leak Syndrome
C_{max}	Maximum Concentration
CNS	Central Nervous System
CR	Complete Remission
CRF	Case Report Form
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CS	Clinically Significant
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
D5W	Dextrose (5%) in Water
DCR	Disease Control Rate
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose Limiting Toxicity
DOR	Duration of Tumor Response
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EoT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FLIPI	Follicular Lymphoma International Prognostic Index
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HBcAg	Hepatitis B Core Antigen
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council on Harmonisation
INR	International Normalized Ratio
IPI	International Prognostic Index
IRR	Infusion related reaction
IV	Intravenous
kDa	Kilodaltons
LTFU	Long Term Follow Up
LVEF	Left Ventricular Ejection Fraction
LYRIC	Lymphoma Response to Immunomodulatory therapy Criteria
MAbs	Monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
MUGA	Multigated Acquisition
N	Number
NAb	Neutralizing antibodies
NCS	Not Clinically Significant
NHL	non-Hodgkin's Lymphoma
NK	Natural Killer
NSAID	Non-Steroidal Anti-Inflammatory Drug
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic

PET	Positron Emission Tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial remission
PRBC	Packed Red Blood Cell
PT	Prothrombin Time
r/r	Relapsed/refractory
REAL	Revised European American Lymphoma
RP2D	Recommended Phase 2 Dose
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCT	Stem cell transplantation
SD	Stable disease
SIRS	Systemic inflammatory response syndrome
SOC	Standard of Care
SPD	Sum of product of perpendicular diameters
STFU	Short Term Follow Up
SUSAR	Suspected Unexpected Serious Adverse Events
t½	Half-life
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
T_{max}	Time to maximum plasma concentration
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

9. INVESTIGATION PLAN

9.1 Overall Study Design and Plan

This abbreviated clinical study report investigates the study results only for Part 3, the expansion cohort of the MT-3724-001 study, which was designed as a multi-center, multinational, Phase 2 open-label, single-arm evaluation of MT-3724 given as monotherapy in repeat doses in subjects with relapsed or refractory DLBCL who have received two or more prior lines of systemic NHL therapy.

As discussed in Listing 16.1.1, Part 1 and Part 2 (reported separately) were comprised of B-cell NHL or chronic lymphocytic leukemia patients (median prior therapies of 4.5) treated at doses between 5 and 100 μg/kg/dose while Part 3 was planned to be a continuation of the expansion of the MTD cohort with the intention to verify the safety, dose and dosing schedule in approximately 66 subjects with DLBCL.

As protocol Versions 9-11 were not approved and implemented at any site, implementation of the protocol occurred under Version 8.0.

Eligible subjects were identified and treated through competitive enrollment across multiple sites in North America and Europe. Sites in other global regions may have been included, if necessary, to achieve optimal enrollment rate.

This expansion cohort was to be conducted in three stages, where the first 2 stages were designed to follow the Simon two-stage optimum design (Simon, 1989).

In each stage, the long-term follow-up (LTFU) was be performed every 6 months after the last dose of MT-3724 until death or lost to follow-up.

The primary efficacy variable was the best overall response rate (BORR). The secondary efficacy variables are the DCR, DOR, PFS, and OS.

If the pre-specified targets for the primary efficacy endpoint (BORR) were met at the end of each of the first 2 stages, then the third stage (Expansion) would have continued to enroll subjects. A response was defined as the BORR of CR or PR according to the Lugano Classification (Cheson 2014, 2016).

In order to support ongoing enrollment of the study through all stages, the Sponsor, following DSMB review and recommendations, may have approved enrollment into the next stage of the study before all subjects in the previous stage were enrolled in the event that the pre-specified response rate that would support further expansion of enrollment had been achieved prior to fully enrolling the current stage. The total sample size of up to 100 was planned assuming positive outcomes, in terms of safety and efficacy, of the first two enrollment stages (target of 66 subjects across stages 1 and 2).

<u>Simon Stage 1</u>

Twenty-one (21) subjects were to be enrolled into the first stage. If there were ≤2 responses in the first 21 subjects, the study would have been stopped. If at least 3 responses were observed among the first 21 subjects, then the study would have proceeded to the second stage.

Simon Stage 2

Assuming the positive outcome of the Simon Stage 1, an additional 45 subjects were to be enrolled in the second stage for the total sample size of 66 subjects in the Simon 2-stage design. If at least 11 of 66 subjects responded at the end of the second stage, then the conclusion could have been drawn that the MT-3724 monotherapy is promising and worthy of further clinical investigation in the third stage, unless other considerations (*e.g.*, poor safety profile) indicated otherwise.

Expansion Stage

Assuming the positive outcome of the Simon Stage 2, additional 34 subjects were to be enrolled and treated for the total sample size of 100 subjects in this three-stage expansion cohort. Assuming a true ORR (primary efficacy endpoint) was 25% among treated subjects, with a total sample size of 100 subjects, the 95% CI for the true ORR would have lain (or been) between 16.5% and 33.5% (*i.e.*, CI width ±8.5% around the ORR point estimate) (Colosia 2014; Crump 2017). In addition, the lower bound of the 95% CI was >16.5%, which was deemed a clinically relevant ORR in this indication and patient population.

In addition, each subject underwent a LTFU Visit every 6 months (±14 days) to collect the information about death, the NHL status (relapsed or not) and the start of any new therapy for NHL since the last study visit/phone call. This information was used to assess the secondary efficacy endpoints (PFS and OS).

9.2 Discussion of Study Design

9.2.1 Rationale for Selection of Subject Population

Non-Hodgkin's Lymphomas:

Epidemiology: According to American Cancer Society statistics, 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. Although some of this increase may be attributable to earlier detection resulting from *e.g.*, improved diagnostic techniques and access to medical care, or possibly to the new emergence of HIV-associated lymphomas, for the most part the rise in incidence is unexplained. The median age at presentation for most subtypes of NHL is greater than 50 years. The exceptions are high-grade lymphoblastic and small non-cleaved lymphomas, which are the most common types of NHL observed in children and young adults. According to the Leukemia and Lymphoma Society of the United States (US) an estimated 69,740 new NHL patients were diagnosed in 2013.

Pathology: NHL represents a progressive clonal expansion of a lymphoid cell line arising from an accumulation of lesions affecting proto-oncogenes or cancer suppressor genes, resulting in

cell immortalization. Although a variety of laboratory and imaging studies are used in the evaluation and staging of suspected NHL, a well-processed section of an excised lymph node is the mainstay of pathologic diagnosis. NHL subtypes are characterized by the level of differentiation, the size of the cell of origin, the originating cell's rate of proliferation, and the histologic pattern of growth. Several cytogenetic lesions are associated with specific NHLs, reflecting the presence of specific markers of diagnostic significance in sub-classifying various NHL subtypes.

Lymphoma includes a heterogeneous group of malignancies originating from lymphoid tissues (mainly of lymph nodes) with different biology and prognoses divided into two large groups of neoplasms: (1) NHL and (2) Hodgkin's disease. Various neoplastic malignant cell lines correspond to each of the cellular components of antigen stimulated lymphoid follicles. Almost 85% of NHLs are of B-cell origin; only 15% are derived from T-cells or Natural Killer (NK) cells, and the small remainder arises from macrophages. For many of the B-cell NHL subtypes, the pattern of growth and cell size may be important determinants of NHL tumor aggressiveness. NHL tumors that grow in a nodular pattern are generally less aggressive than lymphomas that proliferate in a diffuse pattern. Lymphomas of small lymphocytes generally have a more indolent course than those of large lymphocytes, which may have intermediate-grade or high-grade aggressiveness. However, some subtypes of high-grade lymphomas are characterized by small cell morphology.

NHL Classification: The Working Formulation classification categorizes the subtypes of NHL by clinical behavior (low-, intermediate-, and high-grade). Because the Working Formulation is limited to classification based upon morphology, it does not encompass the complex spectrum of NHL disease, excluding important subtypes such as mantle cell lymphoma or T/NK-cell lymphomas. In the 1990s, the REAL Classification supplanted the Working Formulation in its attempt to apply immunophenotypic and genetic features in identifying distinct clinicopathologic NHL entities. The WHO classification further elaborates upon the REAL approach. This classification divides NHL into those of B-cell origin and those of T-cell and NK-cell origin.

Clinical NHL Management: The treatment of B-cell NHL varies greatly, depending on tumor stage, grade, and type as well as several clinical factors. The 5-year relative survival rate of patients with NHL is approximately 63%. The survival rate has steadily improved over the last 2 decades, due to improvements in medical and nursing care, the advent of mAbs, including CD20-targeting therapies, validation of biomarkers of response, and the implementation of tailored treatment.

The prognosis for patients with newly diagnosed NHL depends on the following factors:

- Tumor histology (based on Working Formulation classification)
- Tumor stage
- Patient age
- Tumor bulk
- Performance status

- Serum lactate dehydrogenase (LDH) level
- Beta2-microglobulin level
- Presence or absence of extra-nodal disease

In general, these clinical characteristics are thought to reflect the following host or tumor characteristics:

- Tumor growth and invasive potential (*e.g.*, LDH, stage, tumor size, beta2-microglobulin level, number of nodal and extra-nodal sites, bone marrow involvement)
- Patient's response to tumor (*e.g.*, performance status, symptoms)
- Patient's tolerance of intensive therapy (*e.g.*, performance status, patient age, bone marrow involvement)

The International Prognostic Index (IPI), which was originally designed as a prognostic factor model for aggressive NHL, also appears to be useful for predicting the outcome of patients with low-grade lymphoma and mantle cell lymphoma. This index is also used to identify patients at high risk of relapse, based on specific sites of involvement, including bone marrow, central nervous system (CNS), liver, testis, lung, and spleen. For patients with follicular lymphoma—the second most common subtype of NHL—the Follicular Lymphoma International Prognostic Index (FLIPI) more accurately scores prognosis. Patients who do not achieve CR by the third cycle of chemotherapy have a worse prognosis than those who achieve rapid CR. Patients with lymphomas with 1, 7, and 17 chromosomal abnormalities have worse prognoses than those with lymphomas without these changes. Low-grade lymphomas have indolent clinical behavior and are associated with a comparatively prolonged survival (median survival is 6 to 10 years), but they have little potential for cure when the disease manifests in more advanced stages. They also tend to transform to high-grade lymphomas. Approximately 70% of all patients with intermediate- and high-grade NHL relapse or never respond to initial therapy. Most recurrences are within the first 2 years after therapy completion. Patients with relapsed or resistant NHL have a very poor prognosis (< 5-10% are alive at 2 years with conventional salvage chemotherapy regimens).

Rational for New Drug Development: Although there has been a slight decline in mortality over the past decade, in 2013 just over 19,000 people died from NHL, and the reported five-year survival rate (2003 - 2009) was 69%. Thus, while the addition of anti-CD20 MAbs to subtype specific chemotherapeutic regimens or as single agents has improved the outcome for patients with both indolent and aggressive subtypes of NHL, relapses are still common, and the current regimens employed to salvage those patients are not always effective. A substantial proportion of NHL patients are still never cured.

9.2.2 Rationale for Dose Selection

The starting MT-3724 dose in each subject was 50 µg/kg/dose, which was determined to be the RP2D of MT-3724 in Part 2. The total administered dose of MT-3724 must not have exceeded

6000 µg per infusion in all treatment cycles. Therefore, subjects weighing more than 120 kg would have their dose capped at 6000 µg/kg/dose.

The dose of MT-3724 was calculated based on the subject's baseline body weight (in kilograms [kg]). For MT-3724 dose calculation, the body weight was measured before the first dose of MT-3724 in Cycle 1 (baseline for all subsequent assessments) and again before the first dose of MT-3724 in each subsequent cycle. If body weight changed by >10% from the baseline value, a re-calculation of MT-3724 dose at investigator's discretion may have been required.

9.2.3 Stratification and Randomization

The expansion cohort was conducted as a single-arm, open-label, non-randomized study, where all eligible subjects were assigned to MT-3724 treatment.

Assignment of the screening slots and treatment slots was performed on the basis of competitive enrollment across multiple sites.

The assignment to MT-3724 treatment occurred only after the investigator declared the subject eligible and the Medical Monitor acting on behalf of the Sponsor had reviewed the screening results and acknowledged the investigator's eligibility decision.

9.2.4 Control Arm information

There were no positive or negative control groups in this study.

9.8 Changes in the Conduct of Study or Planned Analyses

Resulting from a serious adverse event of capillary leak syndrome in study MT-3724_001 with fatal outcome, all ongoing MT-3724 trials including this trial were placed on Partial Clinical Hold, on 04 November 2020. The Sponsor conducted a thorough investigation into the clinical event and the available investigational product lots of MT-3724. It was determined that the lot of MT-3724 study drug that was used to treat subjects enrolled in the study may have presented a risk of increased immunogenic adverse effects as the lot used to treat the subject who experienced the Grade 5 CLS event. As additional lots of MT-3724 were unavailable, the study was prematurely closed.

9.8.1 Protocol Amendments

There was a total of 12 global Amendments to the original protocol, dated 30 July 2014. The substantive changes have been summarized below. However, only 9 global Amendments were implemented *i.e.*, approved by regulatory agencies and subsequently employed for patient consent and enrollment. Three additional amendments (not detailed in this CSR) were developed but not implemented.

9.8.1.1 The primary purpose of protocol Version 1.1, dated 18 August 2014, was:

- To add information and instructions for the repeat dosing study.

9.8.1.2 The primary purpose of protocol Version 1.2, dated 05 September 2014, was:

- To make non-substantive changes to the Schedule of Events in response to FDA Medical Reviewer comments.

9.8.1.3 Protocol Version 2.0

The primary purposes protocol Version 2.0, dated 16 January 2015, were:

- To clarify humoral and cellular immune status in the secondary objectives
- To add clarifying information for the Phase 1 Cohort Expansion Trial design and scheme.
- To include the procedure for Investigators to file a request for waiver of inclusion/exclusion.
- To correct information for collection of data for laboratory parameters and sample collection.
- To revise instructions for PK parameter assessment.
- To add and reorganize instructions for stopping rules.
- To correct instructions for documentation and reporting of AEs and SAEs, including timing of non-serious AEs.
- To correct the instructions for removal of subjects from the trial and study drug source documentation using the Case Report Form (CRF) (see Listing 16.1.2 for a sample CRF and 16.3 for individual patient CRFs).
- To correct the study activities in the Core Study and Repeat Dosing Study schedules of events.
- To correct the information listed in the PK, PD, and safety analyses.
- To add information regarding protocol violations or deviations.
- To revise information for data quality auditing and CRF entries.
- To clarify baseline assessments, study visit information, performance status assessments, and tumor assessment guidelines.

9.8.1.4 Protocol Version 3.0

The primary purposes of protocol Version 3.0, dated 15 May 2015, were:

- To update platelet counts in laboratory requirements and inclusion criteria.
- To update pre-infusion treatment instructions.

9.8.1.5 Protocol Version 4.0

The primary purposes of protocol Version 4.0, dated 08 July 2015, were:

- To remove requirements for a sentinel subject in each cohort to allow staggered subjects at the discretion of the medical monitor and/or Data Monitoring Committee (DMC).
- To update the schedule of events and timing windows.

9.8.1.6 Protocol Version 5.0

The primary purposes of protocol Version 5.0, dated 07 January 2016, were:

- To include throughout the document an indication for B-Cell CLL and associated instructions.
- To include further instructions for study withdrawal, completion/continuation of treatment, dose escalation/de-escalation due to a dose-limiting toxicity (DLT) in both the Core Study and the Repeat Dosing Study.

- To add instructions for the timing of procedures and tests as part of local SOC.
- To add information related to HIPAA, prior malignancy, and hepatitis in the inclusion/exclusion criteria.
- To include information for dose administration for Cohorts 5, 6, and 7 and planned dose de-escalations.
- To clarify reporting requirements for SAEs in relation to study duration.
- To revise the PK analysis plans and endpoints.
- To add information based on the first 11 subjects who received MT-3724 and the associated findings.
- To clarify early subject withdrawal procedures.
- To clarify the time windows allowed for infusions in the first and repeat dosing cycles.
- To remove the timing requirements for DMC review and evaluation of cumulative safety data.
- To clarify the grading system for stopping rules and the stopping rule for suspected hypersensitivity reactions.
- To clarify guidance regarding prior treatments and allowed vaccinations.

9.8.1.7 Protocol Version 6.0

The primary purposes of protocol Version 6.0, dated 05 January 2017, were:

- To define additional objectives and endpoints for exploratory efficacy in Part 2 (MTD expansion).
- To revise enrollment in Part 2 to allow only subjects with relapsed/refractory DLBCL
- To revise the dose cohorts in Part 1 to reflect findings related to the MTD.
- To revise the timing of dosing in each cycle for Parts 1 and 2.
- To clarify the determination of an SAE with respect to DLTs.
- To modify the enrollment/inclusion, design, study activities, timing, duration, withdrawal procedures, dosing, and sample size based on the changes made to split the study into Part 1 and Part 2.
- To explain and clarify the role of the DMC in Part 2 (MTD expansion).
- To clarify the definition of a DLT.
- To define the requirements for suspending study treatment, reducing the dose of study treatment, withdrawing a subject, and premature discontinuation in Part 1 versus Part 2.

9.8.1.8 Protocol Version 7.0

The primary purposes of protocol Version 7.0, dated 08 February 2018, were:

- To explain rationale for increasing study population and changing the MT-3724 dose in Part 2.
- To correct the requirements for previous treatment with rituximab in the inclusion criteria.

- To add information to the efficacy analysis and endpoints for subjects with DLBCL treated with MT-3724 in Part 2.
- To revise subject dosing schedules, infusion treatment windows, and administration instructions.
- To update laboratory assessments for safety and AE management.
- To revise AE grading and the role of the internal DMC review of safety and efficacy data in Part 2.
- To add information inclusive of cytokine release syndrome or capillary leak syndrome.
- To add the capping of MT-3724 dose at 6000 µg/dose.

9.8.1.9 Protocol Version 8.0

The primary purposes of protocol Version 8.0, dated 15 April 2019, were:

- To update the study phase to include an expansion cohort designed to confirm efficacy.
- To update the study indication to include DLBCL and remove CLL in the study population for Part 3.
- To update theoretical safety and efficacy data with first in human experience.
- To describe adverse events of special interest (AESI) seen in Part 1 of the study and management thereof including potential adverse events of special interest not yet reported.
- To add efficacy of MT3724 as monotherapy in subjects with relapsed or refractory DLBCL based on the ORR as a primary objective.
- To add Part 3 secondary objectives to explore safety, efficacy, PK, PD, and effect of treatment on quality of life.
- To add an additional exploratory objective for efficacy to assess immunogenicity through NAb.
- To revise study plan to adjust the total number of treatment cycles, define the STFU, and add a LTFU.
- To replace the DMC with a DSMB (Data Safety Monitoring Board).
- To update the inclusion/exclusion criteria to clarify requirements for histology, prior therapies, tumor lesions, CNS metastases, platelet counts, hemoglobin, creatinine clearance, total bilirubin, INR, PT, aPTT, albumin, QTcF, LVEF, birth control, systemic corticosteroid use, vaccinations, serology testing, infections, pre-existing AEs, and pre-existing malignancies.
- To add information for treatment and prevention of potential infusion reactions.
- To adjust dosing duration, schedule, premedication, and dose/treatment modification instructions.
- To update assessment instructions for cardiac monitoring, Quality of Life, follow-up phone calls, disease activity measurements, optional tumor biopsy collection, and radiological evaluations.

9.8.1.10 Local Amendments:

Five (5) local protocol versions were developed and executed in specific study countries as described below.

The primary purpose of protocol Version 7.1, dated 15 April 2019, was:

- To add MT-3724 to be administered until disease progression, unacceptable toxicity, death, withdrawal of consent or other reason for withdrawal.

The primary purpose of protocol Version 8.1, dated 02 April 2019, was:

- To updated study objectives and procedures for Parts 1, 2, and 3 (instead of only Part 3 as in protocol Version 8.0).

The primary purpose of protocol Version 8.2, dated 15 April 2019, was:

- To add administrative amendment to incorporate an editorial change to the protocol title to make it consistent with the title in protocol Version 7.0.

The primary purpose of protocol Version 8.3, dated

- To update the anticipated start date and duration of the study.

The primary purpose of protocol Version 8.4, dated 20 November 2019, was:

- To update inclusion criteria related to contraception and pregnancy testing/reporting.

9.8.2 Changes in the Planned Analyses

The changes from Version 1.0 to Version 2.0 of the Statistical Analysis Plan (SAP) were implemented as a result of a change in the clinical research organization (CRO) providing biostatistical services to the sponsor for this study.
Changes from Version 2.0 to Version 3.0 of the SAP were the result of changes that occurred between Protocol Version 4.0 and Protocol Version 7.1.

10. STUDY SUBJECTS

10.1 Disposition of Study Subjects

10.1.1 Summary of Study Enrollment

A total of 29 subjects were screened from the participating investigational sites worldwide. Complete information regarding inclusion and exclusion criteria can be found in Listing 16.2.1.2.2. The most common reason for screen failure was detection of rituximab (9 subjects).

10.1.2 Summary of Subject Disposition

Subject disposition and baseline characteristics are summarized in Table 10-1 and in Listing 16.2.1.1.1. Of the 29 subjects who were screened, 11 received at least one dose of MT-3724 monotherapy. Eighteen subjects were screened but did not receive study drug. Ten treated subjects were included in the modified full analysis set, which included all full analysis subjects with at least one post-baseline efficacy assessment and subjects who discontinued due to disease progression or death prior to disease assessment. For the subjects who received at least one dose of the study drug, the most common reason for treatment discontinuation was disease progression per radiographic assessment, N=7 (63.6%).

Table 10-1: Subject Disposition

Subject Disposition: All Subjects		
		All Subjects (N = 11)
Full Analysis Set		
	Yes	11 (37.9%)
	No	18 (62.1%)
Modified Full Analysis Set		
	Yes	10 (34.5%)
	No	19 (65.5%)
PK Analysis Set		
	Yes	11 (37.9%)
	No	18 (62.1%)
Immunogenicity Analysis Set		
	Yes	11 (37.9%)
	No	18 (62.1%)
PD Analysis Set		
	Yes	11 (37.9%)
	No	18 (62.1%)
Safety Analysis Set		
	Yes	11 (37.9%)
	No	18 (62.1%)
Primary Reason for Early Termination (safety analysis set)		
	Adverse Event	1 (9.1%)
	Consent Withdrawn	1 (9.1%)
	Disease Progression (Radiographic per Lugano)	7 (63.6%)
	Clinical Disease Progression	2 (18.2%)

Note: (1) Full Analysis Set (FAS) includes all subjects who received at least 1 dose of MT-3724 monotherapy treatment.
(2) Modified Full Analysis Set (mFAS) includes all FAS subjects with at least 1 post-baseline efficacy assessment, and subjects who discontinued due to disease progression or die, prior to disease assessment.
(3) PK Analysis Population includes all FAS subjects with on-treatment PK data.
(4) Immunogenicity Analysis Population includes all FAS subjects with valid post-baseline immunogenicity assessment.
(5) PD Analysis Population includes all FAS subjects with at least 1 valid post-baseline pharmacodynamic assessment.
(6) Safety Analysis Population includes all subjects who received at least 1 dose of MT-3724 monotherapy treatment.
(7) End of Treatment %s are calculated from FAS subjects. All other %s are calculated from all subjects with informed consent.

Source: Table 14.1.1.

Demographic data for the 11 treated subjects are summarized in Listing 16.2.1.2.1 and summarized in Table 10-2. At baseline, the mean and median ages were 57.5 years and 64.0 years, respectively. The majority of treated subjects were male [8 (72.7%) subjects] and all subjects were white [11 (100%) subjects] and one subject was Hispanic (9.1%). Of the 3 female subjects (27.3%) on treatment, 1 (11.1%) was of reproductive potential.

Baseline mean and median weight were 75 kg and 83.7 kg, respectively; baseline mean and median height were 173.1 cm and 174 cm, respectively (Listing 16.2.3.2.1). The majority of subjects had an ECOG performance status of 1 [7 (63.6%)]. ECOG assessments for all subjects are presented in Listing 16.2.3.2.5. Quality of life information is presented in Listing 16.2.3.2.7 and showed a slight depreciation in overall quality of life over time, as expected with progressive advanced cancer. Smoking and alcohol consumption are noted for all subjects in Listing 16.2.1.2.10. Five (5) subjects (45.5%) reported a history of smoking greater than 2 years.

Cancer-related surgical histories are outlined for each patient in Listing 16.2.1.2.8. Only one subject reported a prior cancer-related surgery in addition to the diagnostic biopsy, which was an incisional biopsy for Subject 9201-001.

Table 10-2: Summary of Baseline Demographic Characteristics

Demographics: All Subjects		
		FAS (N = 11)
Age		
	N	11
	Mean (SD)	57.5 (14.77)
	Median	64.0
	Min, Max	28, 71
Gender		
	Male	8 (72.7%)
	Female	3 (27.3%)
Race		
	American Indian or Alaska Native	0 (0.0%)
	Asian	0 (0.0%)
	Black or African American	0 (0.0%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)
	White	11 (100.0%)
	Other	0 (0.0%)
	Multiple	0 (0.0%)
Ethnicity		
	Hispanic	1 (9.1%)
	Non-Hispanic	9 (81.8%)
	Not Reported	1 (9.1%)
	Unknown	0 (0.0%)

Source: Table 14.1.2.

Complete physical examination information can be found in Listing 16.2.1.2.11. The physical exam findings are consistent with advanced disease for all 11 subjects. Medical history is provided for all subjects in Listing 16.2.1.2.5. All 11 subjects had substantial ongoing or prior medical conditions that may have complicated study results in this report. Three subjects (27.3%) reported musculoskeletal and connective tissue disorders. Three subjects (27.3%) also reported dyspnea. Prior NHL therapies and prior radiotherapies are summarized in 16.2.1.2.6 and 16.2.1.2.7, respectively. Ten (10) subjects (90.9%) reported prior multi-agent therapy with rituximab. Seven (7) subjects (63.6%) reported prior radiotherapy with a highly variable dosage and response.

Baseline disease history is presented in Listing 16.2.1.2.3. All 11 (100%) treated subjects were previously diagnosed with DLBCL cancer at Screening, which was confirmed by histology and is presented in histological confirmation and disease assessment Listing 16.2.1.2.4. Ann Arbor Staging at screening ranged from Stage I (involvement of a single lymph node region or lymphoid structure) to Stage IV [involvement of extra nodal site(s) beyond the designated “E”]. Genetic abnormalities for each subject’s cancer at screening are outlined in Listing 16.2.1.2.9. Double hits were indicated for Subject 4805-002 and triple hits were indicated for both Subjects 1006-002 and 1006-003.

Radiological tumor assessments are detailed in Listing 16.2.2.1.1 and improvements in FD-PET/CT scans, CT MRI scans, or splenic and bone marrow assessments were not observed for any subjects throughout the trial. Target Lesion assessments and Non-Target Lesion Assessments are presented in Listing 16.2.2.1.2 and Listing 16.2.2.1.3, respectively. Information presented for both target and non-target lesions also demonstrated complex, advanced disease states for all patients. Non-target lesion information is available for 8 of 11 (72.7%) patients. New Lesions are presented in Listing 16.2.2.1.4. New lesions were observed for 7 of 11 (63.6%) treated patients during the study. Tumor tissue biopsy reports are presented in 16.2.2.1.5, but only one subject (2014-005) provided this information.

Deaths and treatment withdrawals due to AEs are summarized in Section 12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events. Treatment discontinuations and the reason for discontinuation are presented by subject in Listing 16.2.1.1.2. Notably, Subject 9201-002 discontinued the study due to a fatal adverse event of CLS.

12. SAFETY EVALUATIONS

12.1 Extent of Exposure

The 11 treated subjects were included in the safety analysis set.

12.1.1 Extent of Exposure

The extent of exposure for MT-3724 is summarized in Listing 16.2.1.3.1. MT-3724 was administered at a dose of 50µg/kg/dose via IV infusion for all subjects. Dosing was planned for Days 1, 3, 5, 8, 10, and 12 of each 21-day cycle. The median number of MT-3724 cycles received was 2 (range: 1 – 4), the median duration of exposure was 3.7 weeks (range: 1.4 weeks – 15.0 weeks), and the median total number of doses received was 7 (range: 4 - 30).

12.1.2 Study Drug Modifications

Study drug dispensation and modifications for MT-3724 are recorded in Listing 16.2.1.3.2. Dosages were recalculated due to changes in weight for 3 subjects. One subject (2014-001) formally reported a dose change due to an AE.

12.1.3 Concomitant Medications

As summarized in Listing 16.2.1.3.3, all subjects received some type of premedication, most commonly in the form of an anti-pyretic, antihistamine [intravenous (IV) or oral], and corticosteroid. All prior and concomitant medications are listed in Listing 16.4.3.2.6. Vitamin and mineral supplements and analgesics were the most commonly prescribed classes of concomitant medications.

12.2 Adverse Events
12.2.1 Brief Summary of Adverse Events

Table 12-1: Overview of Subjects with Treatment-Emergent Adverse Event (TEAE)

Overview of Subjects with Treatment-Emergent Adverse Event (TEAE): Safety Population			
		Safety Analysis Set	
		Subjects (N = 11)	Events (N = 133)
Any Treatment-Emergent Adverse Events (TEAEs)		11 (100.0%)	133 (100.0%)
	TEAEs Related to Study Treatment, i.e., Definitely, Probably, or Possibly Related to Study Treatment	11 (100.0%)	82 (61.7%)
	Severe TEAEs, i.e., TEAEs with Grades 3, 4, or 5	8 (72.7%)	19 (14.3%)
	Severe TEAEs Related to Study Treatment	6 (54.5%)	9 (6.8%)
	Treatment-Emergent Serious Adverse Events (TESAEs)	3 (27.3%)	6 (4.5%)
	TESAEs Related to Study Treatment	1 (9.1%)	3 (2.3%)
	TEAEs of Special Interest	4 (36.4%)	11 (8.3%)
	TEAEs Leading to Drug Withdrawn/Permanent Discontinuation	1 (9.1%)	3 (2.3%)
	TEAEs Leading to Study Discontinuation	3 (27.3%)	5 (3.8%)
	TEAEs Leading to Death	1 (9.1%)	1 (0.8%)
Note: (1) Treatment-emergent adverse event (TEAE) is defined as AEs with initial onset or AEs that worsen in severity after the first dose of MT-3724. (2) AE of special interest includes neutropenia, acute kidney injury, capillary leak syndrome, cytokine release syndrome, systemic inflammatory response syndrome, infusion related reactions, tumor lysis syndrome, and immunogenicity. (3) Any change in severity grade is counted as a separate event.			

Source: Table 14.1.3.

12.2.2 Analysis of Adverse Events

12.2.2.1 Treatment Emergent Adverse Events

TEAEs are summarized in Table 12-1. All 11 (100%) treated subjects experienced at least 1 AE during the study that was assessed as treatment emergent. Of the 8 (72.7%) subjects who experienced a Grade ≥ 3 TEAE, 6 subjects (54.5%) had a TEAE that was assessed as related to study treatment. Three (27.3%) subjects experienced at least 1 treatment emergent serious adverse event (TESAE); 1 (9.1%) subject experienced a TESAE that was assessed as related to MT-3724. Only 1 (9.1%) subject experienced a TEAE which resulted in drug withdrawal and permanent discontinuation.

A summary of TEAEs categorized by MedDRA Preferred Term for the safety population is presented in Table 12-2. The most frequently reported TEAEs were myalgia in 7 subjects (63.6%) and pyrexia in 6 subjects (54.4%). Diarrhea, hypoalbuminemia, and peripheral edema were reported in 4 subjects (36.4%) each, and dyspnea in 3 subjects (27.3%). Capillary leak syndrome (CLS), decreased appetite, dizziness, fatigue, hypoproteinemia, and muscular weakness were reported in 2 subjects each (18.2%).

Table 12-2: Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term

Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term: Safety Population Safety Analysis Set		
	Subjects	Events
	(N = 11)	(N = 133)
MedDRA Preferred Term		
Subjects with Any Treatment-Emergent Adverse Events Or Number of Events	11 (100.0%)	133 (100.0%)
Myalgia	7 (63.6%)	14 (10.5%)
Pyrexia	6 (54.5%)	8 (6.0%)
Anemia	5 (45.5%)	5 (3.8%)
Diarrhea	4 (36.4%)	8 (6.0%)
Hypoalbuminemia	4 (36.4%)	9 (6.8%)
Oedema peripheral	4 (36.4%)	5 (3.8%)
Dyspnea	3 (27.3%)	4 (3.0%)
Capillary leak syndrome	2 (18.2%)	8 (6.0%)
Decreased appetite	2 (18.2%)	3 (2.3%)
Dizziness	2 (18.2%)	3 (2.3%)
Fatigue	2 (18.2%)	6 (4.5%)
Hypoproteinemia	2 (18.2%)	3 (2.3%)
Muscular weakness	2 (18.2%)	4 (3.0%)
Abdominal distension	1 (9.1%)	2 (1.5%)
Abdominal pain	1 (9.1%)	1 (0.8%)
Acute kidney injury	1 (9.1%)	1 (0.8%)
Arthralgia	1 (9.1%)	1 (0.8%)
Ascites	1 (9.1%)	1 (0.8%)
Asthenia	1 (9.1%)	1 (0.8%)
Cancer pain	1 (9.1%)	1 (0.8%)
Cellulitis	1 (9.1%)	1 (0.8%)
Coronary artery disease	1 (9.1%)	1 (0.8%)
Deep vein thrombosis	1 (9.1%)	1 (0.8%)
Diplopia	1 (9.1%)	1 (0.8%)
Dysphagia	1 (9.1%)	1 (0.8%)
Epistaxis	1 (9.1%)	1 (0.8%)

Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term: Safety Population Safety Analysis Set		
	Subjects	Events
	(N = 11)	(N = 133)
Eye irritation	1 (9.1%)	1 (0.8%)
Eye swelling	1 (9.1%)	1 (0.8%)
Granulocytopenia	1 (9.1%)	1 (0.8%)
Headache	1 (9.1%)	1 (0.8%)
Horner's syndrome	1 (9.1%)	1 (0.8%)
Hyperesthesia	1 (9.1%)	1 (0.8%)
Hypotension	1 (9.1%)	1 (0.8%)
Insomnia	1 (9.1%)	1 (0.8%)
Iron deficiency anemia	1 (9.1%)	1 (0.8%)
Leukopenia	1 (9.1%)	2 (1.5%)
Lymphocyte count decreased	1 (9.1%)	2 (1.5%)
Lymphopenia	1 (9.1%)	2 (1.5%)
Muscle spasms	1 (9.1%)	1 (0.8%)
Nausea	1 (9.1%)	1 (0.8%)
Neck pain	1 (9.1%)	2 (1.5%)
Neuropathy peripheral	1 (9.1%)	1 (0.8%)
Neutropenia	1 (9.1%)	2 (1.5%)
Oedema	1 (9.1%)	1 (0.8%)
Pain	1 (9.1%)	1 (0.8%)
Pleural effusion	1 (9.1%)	1 (0.8%)
Swelling face	1 (9.1%)	2 (1.5%)
Thrombocytopenia	1 (9.1%)	2 (1.5%)
Tumor pain	1 (9.1%)	1 (0.8%)
Vertigo	1 (9.1%)	2 (1.5%)
Vision blurred	1 (9.1%)	3 (2.3%)
Weight increased	1 (9.1%)	1 (0.8%)
Note: (1) Treatment-Emergent Adverse Event (TEAE) is defined as AEs with initial onset or AEs that worsen in severity after the first dose of MT-3724 (2) AE of Special Interest includes neutropenia, acute kidney injury, capillary leak syndrome, cytokine release syndrome, systemic inflammatory response syndrome, infusion related reactions, tumor lysis syndrome, and immunogenicity. (3) All results are ordered by descending frequency of MedDRA Preferred Term in all subjects. (4) Any change in severity grade is counted as a separate event.		

Source: Table 14.1.4.

12.2.2.2 Grade ≥ 3 Adverse Events

All Grade ≥ 3 AEs are summarized in Listing 16.4.3.1.4. One death occurred on study, due to an AE of capillary leak syndrome.

To summarize all treatment-related Grade ≥ 3 AEs, Subject 1006-003 reported a Grade 4 incident of decreased lymphocyte count that was possibly related to the study treatment at Study Day 8, which resolved on Study Day 27 with a study drug dose reduction. Subject 2014-005 experienced generalized myalgia Grade 3, considered definitely related to study treatment, on Study Day 37, which resolved on Study Day 44 and managed with concomitant medications and study drug dose reduction. The same subject reported an incidence of asthenia Grade 3, possibly related to study treatment reported on Study Day 38 and resolved on Study Day 77. Subject 3703-001 experienced Grade 3 lymphopenia, possibly related to the study treatment, on Study Day 29 and resolved on Study Day 49 with a dose reduction in study drug. Subject 4805-002 reported leucopoenia and granulocytopenia on Study Day 22 and was ongoing until the dose was interrupted, and concomitant medication was prescribed.

Complete SAE reports can be found in Listing 16.4.3.1.9, where details for fever, edema, acute kidney injury, and capillary leak syndrome in three subjects are presented. SAE criteria for these events are summarized and outlined in Listing 16.4.3.1.5. Relevant laboratory, imaging, and diagnostic testing information can be found in Listing 16.4.3.1.8. Criteria for reporting and relevant testing information are consistent with descriptions of the SAEs.

12.2.3 Listing of Adverse Events by Subject

Adverse events are presented by subject in Listing 16.4.3.1.1.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Serious adverse events are presented by subject and MedDRA SOC and PT in Listing 16.4.3.1.2. SAE are presented by criteria and subject Listing 16.4.3.1.3.

12.3.1.1 Deaths

Deaths are included in Listing 16.4.3.1.4. A total of 1 death due to an AE occurred on study. Subject 9201-002 experienced a fatal incident of CLS on Study Day 20, which the investigator considered probably related to the study drug.

12.3.1.2 Other Serious Adverse Events

The last study treatment prior to SAE occurrences can be found in Listing 16.4.3.1.6. Of the 11 subjects, 4 (36.4%) subjects experienced at least one SAE. One subject experienced two separate SAEs. Reports on CLS, systemic inflammatory response syndrome (SIRS)/ cytokine release syndrome (CRS), and infusion related reactions (IRR) are summarized in Listings 16.4.3.1.10,

16.4.3.1.11, and 16.4.3.1.12 respectively. Seven (7) line listings are presented for CLS. No incidences of SIRS, CRS, or IRR are recorded.

Serious AEs assessed as related to MT-3724 were as follows:
Subject 2014-001 experienced a Grade 1 SAE of fever on Study Day 13. The SAE was assessed as unlikely related to MT-3724. The subject recovered and continued on treatment with a reduced dose.

Subject 2014-005 experienced a Grade 4 SAE of edema on Study Day 33. The SAE was assessed as unlikely related to MT-3724, and the dose of MT-3724 was modified. The same subject experienced a Grade 3 SAE of acute kidney injury also on Study Day 33. This SAE was assessed as unrelated to MT-3724.

Subject 9201-002 experienced a Grade 5 SAE of capillary leak syndrome on Study Day 10. The SAE was assessed as definitely related to MT-3724, and the subject discontinued study treatment due to the SAE. The subject died 11 days after SAE onset.

12.3.1.3 Withdrawals due to Adverse Events
Adverse events resulting in the discontinuation of MT-3724 are summarized in Listing 16.4.3.1.7. One subject (9.1%) experienced an AE that resulted in a discontinuation of MT-3724 (CLS).

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Narratives for deaths, other SAEs, and other significant AEs are provided in Section 14.3.3 and summarized by Table 14-1.

12.4 Clinical Laboratory Evaluation
All local and central laboratory test results were compared with each laboratory's normal range and to any applicable CTCAE grades. Reference ranges were provided for each analyte. No inter-laboratory standardization was performed.

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Serum measurements for PK and PD are summarized in Listing 16.2.2.2.1 and Listing 16.2.2.2.2 respectively. MT-3724 was measurable in serum samples in all subjects, but concentrations were highly variable. Notably, Subject 1112-001 did not have measurable drug concentrations beyond Cycle 1. PD analysis was complicated, as ADAs were detected in serum samples from 5 out of 11 subjects (45.5%). Notably, one subject was positive for ADAs at screening (Subject 1601-002).

Local laboratories were used for all analyses in Listing 16.4.3.2.8.1. Values that were outside of the reference range were flagged and assessed as normal, abnormal clinically significant (CS), or abnormal, not clinically significant (NCS). Listing 16.4.3.2.8.2 presents 24-hour urine collection

for creatinine clearance, but only one subject was able to provide this sample. A central lab was used for analyses presented in Listing 16.4.3.2.9.1 and Listing 16.4.3.2.9.2. Values that were outside of the reference range are listed as “HIGH” or “LOW”.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Vital Signs

Vital signs are summarized in Listing 16.4.3.2.1.

No notable changes in pre- and post-dose systolic blood pressure (BP), diastolic BP, heart rate (HR), respiratory rate (RR), and temperature were observed across time points evaluated during the study. Changes in weight and body mass index (BMI) were unremarkable throughout the study.

12.5.2 Electrocardiograms and Cardiovascular Findings

Overall, ECG findings were normal and presented no clinical concern, as no clinically significant abnormalities were detected in the safety population. The 12-lead ECG data were consistent and of high quality and are presented in Listing 16.4.3.2.2.

Additional cardiac findings are presented in Listing 16.4.3.2.3 for NYHA Functional Classification information and Listing 16.4.3.2.4 for LVEF functionality. Subjects 2014-002 and 2014-005 were both scored as having Class I – mild impairment at both the Screening and End of Study visits.

12.5.3 Physical Findings and Follow-Up

Physical examination findings are presented in Listing 16.2.1.2.11. Clinically significant lymphatic abnormalities were noted for Subject 2014-002 on Study Day 46 at the End of Treatment Visit. Clinically significant findings for general appearance, respiratory system, and abdominal system were noted for Subject 2014-005 on Study Day 43 at the End of Treatment Visit. Surgical and all other procedures are summarized in Listing 16.4.3.2.10, though no notable findings are listed.

Follow-up phone calls for safety are presented in Listing 16.4.3.2.11, which shows that all subjects were deceased [5 (45.5%)] or had progressive disease and were pursuing alternative treatment options [5 (45.5%)] at the time of the long-term phone call. As one subject died during the study, only ten subjects had follow-up procedures.

12.5.4 Pregnancy

No pregnancies were reported during this study.

12.6 Safety Summary

The following conclusions are based on the results of the safety analyses:

- All 11 (100%) treated subjects in the safety analysis set experienced at least 1 TEAE during the study. The most frequently reported TEAE was myalgia in 7 subjects (63.6%),

pyrexia in 6 subjects (54.4%), anemia in 5 subjects (45.5%), diarrhea, hypoalbuminemia, and peripheral edema in 4 subjects (36.4%) each, and dyspnea in 3 subjects (27.3%).

- The study drug was discontinued for the one subject (9201-002), all related to instances of CLS.
- The following SAEs were reported: A Grade 1 fever was reported and was unlikely related to treatment. Another subject also experienced Grade 3 kidney injury and a Grade 4 edema. The edema was considered unlikely related to treatment, while the kidney injury was unrelated. All subjects reporting SAEs were receiving doses of 50 μg/kg of the study drug.
- One SUSAR was reported: a case of Grade 5 CLS, which was considered related to MT-3724. This CLS, which started as Grade 3, occurred approximately one week having experienced a Grade 2 CLS event on Cycle 1, Day 5, from which the subject had recovered, and two days after receiving the study drug on Cycle 1, Day 10. The subject was initially hospitalized on Cycle 1, Day 10 with CLS Grade 3, hypoalbuminemia, dyspnea and hypoxia being the lead signs and symptoms. Immediate cardiac distress was excluded by lab tests and ECHO. The subject's condition worsened 5 days later, and CLS became Grade 4. High dose steroids and an IL-6 mAb (Tocilizumab) were added to the treatment regimen along with albumin substitution. Despite this, the clinical situation of the subject further deteriorated further. The subject was a candidate for supportive oxygen and intubation but refused. The subject passed away 11 days after the onset of the CLS event. He became unconscious with drip morphine.

13. DISCUSSION AND CONCLUSIONS

The expansion cohort of this study (Part 3) was a multi-center, multinational, Phase 2 open-label, single-arm evaluation of MT-3724 given as monotherapy in repeat doses in subjects with relapsed or refractory DLBCL who have received 2 or more lines of prior therapy.

The objectives of this final Part 3 of the study (the results of the initial dose-escalating and expansion parts reported separately in Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Multiple Doses of MT-3724 for the Treatment of Patients with Relapsed Non-Hodgkin's B-Cell Lymphoma and B-Cell Chronic Lymphocytic Leukemia – Clinical Study Report MT-3724 NHL 001, 22 Jan 2021) in subjects with relapsed or refractory DLBCL, were to assess the safety (frequency and nature of clinical and laboratory AEs both reported and observed) and efficacy (based on the ORR by the Lugano classification for lymphoma) of repeated cycles of MT-3724 given at a dose of 50 µg/kg (the MTD determined in parts 1 and 2 of the study) on days 1, 3, 5, 8, 10, and 12 define the PK and PD profiles of MT-3724.

Eleven (11) subjects received treatment with MT-3724. Of these, 4 subjects (36.4%) experienced at least 1 SAE and 2 (18.2%) subjects experienced multiple AEs that were Grade ≥ 3 in severity. One subject reported both edema (Grade 4) and acute kidney injury (Grade 3). One subject reported an SAE of CLS, which started as a Grade 3, progressed to Grade 4, and then Grade 5. All 11 (100%) treated subjects experienced at least 1 TEAE during the study that was assessed as related to MT-3724. Of the 8 (72.7%) subjects who experienced a Grade ≥ 3 TEAE, 6 subjects (54.5%) had a TEAE that was assessed as study treatment. Three (27.3%) subjects experienced at least 1 TESAE; 1 (9.1%) subject each experienced a TESAE that was assessed as related to MT-3724. One (1) (9.1%) subject experienced a TEAE which resulted in drug withdrawal and permanent discontinuation.

Potential safety risks of MT-3724 include capillary leak syndrome with possibly fatal outcome, myalgia, pyrexia, anemia, diarrhea, hypoalbuminemia, peripheral edema, and dyspnea. It is important to note that this study was placed on clinical hold because of a Grade 5 CLS event. Following internal investigations into the possible root causes including product quality and discussion with FDA, the Sponsor decided to terminate the study. As no patients in this Part 3 had shown a response at that point in time it was felt that potential risks outweighed potential benefits.

The plasma concentration of MT-3724 was measurable in the serum of all 11 patients included in the PK Analysis set. However, data were highly variable, sample size was small, and sampling was not always complete, complicating the analysis and interpretation of the PK data. In addition, the concurrence of ADAs in some subjects (see below) may have impacted the observed PK results.

ADAs were found in 5 of the 11 subjects. Almost all ADA-positive results were also associated with detection of NAb.

Data with regards to changes of CD19+ B lymphocyte counts as a pharmacodynamic parameter were sparse (only 6 of 11 subjects had follow-up data after screening) since most subjects discontinued the study early for lack of objective or clinical response to treatment; also, many subjects (3 of 6) had low or undetectable CD19+ B lymphocyte counts already before start of treatment with MT-3724. Thus, paucity and variability of PD data do not allow conclusions.

Due to high variability in the data, small sample size, and inconsistent sampling, PK-PD relationships were difficult to discern.

Regarding efficacy, no notable improvements in radiographic evaluations, including FD-PET/CT scans, CT MRI scans, or splenic and bone marrow assessments were noted for any subjects. Information presented for both target and non-target lesions demonstrate complex, advanced disease states for all patients and no improvements were noted for any subjects. As new lesions were observed for the majority of the treated patients during the study, efficacy was not observed.

Given the limited safety data and absence of efficacy in this small sample size, it is not possible to adequately characterize the activity and tolerability of MT-3724 as a monotherapy treatment in subjects with r/r DLBCL. However, it should be noted that for subjects diagnosed with r/r DLBCL, relatively few efficacious and tolerable treatment options exist, and the research landscape continues to evolve.

14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Summary Data

The following summary data are included in this section

14.2 Efficacy Summary Data

The following summary data are included in this section

14.3 Safety Summary Data

14.3.1 Listings of Deaths, Other Serious Adverse Events, and Significant Adverse Events

The following summary data are included in this section

14.3.2 Narratives of Deaths, Other Serious Adverse Events, and Significant Adverse Events

Three classifications of safety narratives are included in this section. The first group (Narratives of Deaths) presents descriptions of all subject deaths during the treatment-emergent period (defined as the first dosing day of study treatment up to 30 days after the last study drug administration) and deaths after the treatment-emergent period that were considered related to MT-3724. The second group (Narratives of Other Serious Adverse Events) includes narratives for SAEs for all subjects during the treatment-emergent period and SAEs after the treatment-emergent period that were considered related to MT-3724. The last group (Narratives of Other Significant Adverse Events) presents narratives for all subjects who withdrew from the study because of an AE or other event.

The narrative presents information on all applicable categories of events. The header information in the narrative includes the MedDRA® preferred term for each event; however, the text includes the investigator term. Narratives are not duplicated within each group but are prioritized by the primary category of safety event. For example, the narrative for a subject who had a serious adverse event and also discontinued the study due to an adverse event would be located in the second group (i.e., Other Serious Adverse Events); however, the narrative would describe both events.

Table 14-1: List of Subjects with Safety Narratives

	Safety Event Category		
Subject Number	**Death**	**Other Serious Adverse Event**	**Withdrawal due to Adverse Event**
2014-001		X	
2014-005		X (2 SAEs)	X
9201-002	X		

15. REFERENCES

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16. APPENDICES

16.1 Study Information

16.2 Subject Data Listings