Official Title:	A Phase 2 Study to Evaluate the Efficacy and Tolerability of Debio 1562 in Combination with Rituximab in Patients with Relapsed and/or Refractory Diffuse Large B-Cell Lymphoma and Other Forms of Non-Hodgkin's Lymphoma
NCT Number:	NCT02564744
Document Date:	Protocol Version 7: 11 May 2020

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Study to Evaluate the Efficacy and Tolerability of Debio 1562 in Combination with Rituximab in Patients with Relapsed and/or Refractory Diffuse Large B-Cell Lymphoma and Other Forms of Non-Hodgkin's Lymphoma
Study Number:	Debio 1562-201
Study Phase:	2
Product Name:	Debio 1562
IND Number:	109,517
EudraCT Number:	2015-004061-87
Clinicaltrial.gov NCT Number:	NCT02564744
Indication:	Diffuse Large B-Cell Lymphoma, B-cell Non-Hodgkin's Lymphoma
Investigators:	Multicenter
Sponsor:	Debiopharm International S.A. Forum "après-demain" Case Postale 5911, Chemin Messidor 5-7, 1002 Lausanne, Switzerland Contact: [redacted], MD Title: [redacted] Telephone: [redacted] E-mail: [redacted]
Current version:	7, dated 24 April 2020, integrating amendments 1-6
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SPONSOR SIGNATURE PAGE

[redacted]

11-MAY-2020

Company/Sponsor signatory | Date

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INVESTIGATOR'S AGREEMENT

I have received and read the Investigational Brochure for Debio 1562. I have read protocol Debio 1562-201 and agree to conduct the study as outlined and in conformance with Good Clinical Practices (GCPs) and applicable regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse event
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT / SGPT	Alanine aminotransferase / Serum glutamic pyruvic transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST / SGOT	Aspartate aminotransferase/ Serum glutamic oxaloacetic transaminase
AUC	Area under the time-concentration curve
β-hCG	beta-human chorionic gonadotropin
BID	Twice daily
BUN	Blood urea nitrogen
C_{max}	Maximum plasma drug concentration
C7D1	Cycle 7 Day 1
Ca	Calcium
CDC	Complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CIP	Cancer Imaging Program
Cl	Chloride
CL	Clearance
CLL	Chronic Lymphocytic Leukemia
COVID-19	Coronavirus Disease 2019
CR	Complete response/remission
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or Specialist Term	Explanation
CTEP	Cancer Therapy Evaluation Program
DCP	Division of Cancer Prevention
DD	Drug Dictionary
DLBCL	Diffuse Large B-Cell Lymphoma
DME	Dose modifying event
[redacted]	
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
FACT-G	Functional Assessment of Cancer Therapy-General
FDA	Food and Drug Administration
FIH	First-in-human
FL	Follicular Lymphoma
FNA	Fine Needle Aspiration
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GVHD	Graft versus host disease
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hct	Hematocrit
HD-ASCT	High dose chemotherapy with autologous stem cell transplantation
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Explanation
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
[redacted]	
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
K	Potassium
[redacted]	
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MALT	Mucosa-associated lymphoid tissue
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimal Important Difference
MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic acid
MTD	Maximum tolerated dose
MZL	Marginal Zone Lymphoma
Na	Sodium
NA or N/A	Not available
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NK	Natural killer
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission testing

Abbreviation or Specialist Term	Explanation
PFS	Progression-free survival
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PO	By mouth
PR	Partial response/remission
Prn	As needed
PT	Prothrombin time
Q3W	Once every three weeks
Q4h	Every four hours
Q6h	Every six hours
QW	Once every week
RBC	Red blood cell
R-CHOP	Rituximab-Cyclophosphamide, doxorubicin Hydrochloride, vincristine (Oncovin), and Prednisone
R/R	Relapsed/Refractory
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SCID	Severe combined immunodeficient
SD	Stable disease
SOC	System Organ Class
SPD	Sum of the product of the diameters
SRC	Safety Review Committee
STD_{10}	Severely toxic dose to 10% of animals
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life
T/C	Ratio of Median Tumor Volume for Treated and Control groups
TEAEs	Treatment emergent adverse events
TLS	Tumor Lysis Syndrome
ULN	Upper limit of normal
US	United States
V_{ss}	Volume of distribution at steady state

Abbreviation or Specialist Term	Explanation
WBC	White blood cell
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title of Study: A Phase 2 Study to Evaluate the Efficacy and Tolerability of Debio 1562 in Combination with Rituximab in Patients with Relapsed and/or Refractory Diffuse Large B-Cell Lymphoma and Other Forms of Non-Hodgkin's Lymphoma	
Study center(s): Approximately 55 centers globally	
Studied period (months): Approximately 48 months (including follow-up)	**Phase of development:** Phase 2

Purpose/rationale: Debio 1562 is an antibody drug conjugate (ADC) consisting of the humanized anti-CD37 antibody, K7153A, conjugated via a stable thioether-based linker to the cytotoxic maytansinoid DM1. Once released within the target cell, DM1 acts as an anti-mitotic agent that inhibits tubulin polymerization and microtubule assembly. Cells treated with maytansinoids arrest in the G2/M phase of the cell cycle, and eventually die by apoptosis (Remillard 1975). Debio 1562 binds with high affinity and specificity to the leukocyte antigen CD37, found on the surface of malignant human B lymphocytes, and to some extent, normal B cells (Moore 1987, Barrena 2005, Deckert, 2013).

Nonclinical studies demonstrated that Debio 1562 has potent cytotoxic activity against CD37-positive lymphoma cell lines *in vitro* and anti-tumor activity in a variety of mouse tumor xenograft models of Non-Hodgkin's Lymphoma (NHL).

In a first-in-human (FIH) Phase 1 study, treatment with single agent Debio 1562 was shown to elicit objective responses, including a complete response, in patients with relapsed/refractory (R/R) NHL (Stathis 2014). In the FIH, single agent study, the most common adverse events (AEs) were: neutropenia, thrombocytopenia, fatigue, pyrexia, nausea, and diarrhea. The dose of 1.4 mg/kg with granulocyte growth factor support was determined to be the maximum tolerated dose (MTD) after reviewing the data for 49 patients across 8 dose levels. Additionally, a dose of 1.0 mg/kg was determined to be the MTD without prophylaxis of granulocyte growth factor in this study.

Rituximab is a CD20-directed, monoclonal antibody that induces antibody-dependent cell mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. Rituximab, in combination with other agents, is currently approved for the treatment of newly diagnosed or R/R B-cell NHL, including diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). Preclinical studies indicate that the anti-tumor activity of Debio 1562 is enhanced when combined with rituximab.

In this Phase 2 study, we propose to investigate the safety and anti-tumor activity of Debio 1562 in combination with rituximab for the treatment of patients with R/R DLBCL and other forms of B-cell NHL.

Objectives:

- **Primary**

The primary objectives of the study are to:

1) Determine the safety and tolerability of the proposed Debio 1562 dose regimens in combination with rituximab
2) Determine the anti-tumor activity of the proposed Debio 1562 dose regimens in combination with rituximab

- **Secondary**

Secondary objectives are to:

1) Characterize the pharmacokinetics (PK) of Debio 1562 in combination with rituximab
2) Determine time to event outcomes (progression-free survival [PFS], time to response, duration of response [DoR], and overall survival [OS])
3) Assess the immunogenicity of Debio 1562 (anti-drug antibody [ADA]) when administered in combination with rituximab

- **Exploratory**

Exploratory objectives are to:

1) Correlate the extent of CD37 and CD20 antigen expression in tumor samples with anti-tumor activity of the Debio 1562 and rituximab combination

[redacted]

5) Assess health-related quality of life (HRQoL)

The study objectives, and corresponding study endpoints are fully defined in the body of the protocol.

Number of patients (planned): It is estimated that approximately 75 patients will be enrolled into the study, which consists of three parts:

- **Part 1 (Safety run-in):** Approximately 15 patients with a diagnosis of R/R DLBCL, Follicular Lymphoma (FL), Marginal Zone Lymphoma (MZL)/Mucosa-associated lymphoid tissue (MALT), Mantle Cell Lymphoma (MCL) or other NHL subtypes with the Sponsor's approval will be enrolled.
- **Part 2 (Initial assessment of safety and efficacy of once every three weeks [Q3W] and once every week [QW] dosing regimens):** Approximately 30 patients, with a diagnosis of relapsed DLBCL as defined below will be enrolled.
- **Part 3 (Expansion):** Approximately 30 patients with a diagnosis of relapsed DLBCL will be enrolled

The estimated duration of the study is approximately 48 months for patient accrual, dosing, and follow up.

Study Design Overview: This is an open label, multicenter, adaptive Phase 2 clinical study. For each patient, the study will include a screening period, a treatment period, and a follow-up period. The study consists of three parts:

- Safety run-in (Part 1)
- Initial assessment of safety and efficacy of Q3W and QW dosing regimens (Part 2)
- Expansion (Part 3)

Safety Run-In (Part 1)

Patients with DLBCL, FL, MCL, MZL/MALT or other NHL subtypes (with Sponsor's approval) will be eligible for enrollment in the safety run-in part of the study. During the safety run-in, at least six DLBCL and six FL NHL patients will be enrolled.

Patients will be given Debio 1562 and rituximab on the same day (i.e., Day 1) Q3W intravenously (IV). Debio 1562 will be given at a dose of 0.7 mg/kg, followed by 375 mg/m^2 of rituximab.

Following review of safety and PK data by a Safety Review Committee (SRC - comprised of the Sponsor's Medical Director and Investigators from participating sites) once the last patient of the safety run-in has completed 1 cycle of treatment, the SRC will make a recommendation to either stop the study for unacceptable safety, or to continue the Q3W dosing schedule with the 0.7 mg/kg dose of Debio 1562 or an alternate higher (1.0 mg/kg) or lower dose of Debio 1562.

This part of the study has been completed and the SRC recommended continuation of the study.

Initial Assessment of Safety and Efficacy of Q3W and QW Dosing Regimens (Part 2)

During Part 2 of the study, only patients with relapsed DLBCL will be enrolled into two parallel cohorts according to the dosing regimen of Debio 1562: cohort A (21-day treatment cycle with a Q3W dosing schedule) and cohort B (21-day treatment cycle with a QW dosing schedule).

Patients in **cohort A** will receive Debio 1562 and rituximab IV on the same day (Day 1) on a Q3W dosing schedule. Debio 1562 will be given at a dose of 0.7 mg/kg (unless recommended otherwise by the SRC), followed by 375 mg/m^2 of rituximab.

Cohort B will explore a QW dosing schedule of Debio 1562: 0.4, 0.2, and 0.2 mg/kg of Debio 1562 will be administered IV to patients on Day 1, Day 8 and Day 15 of a 21-day treatment cycle, respectively. Rituximab will be administered IV at a dose of 375 mg/m^2 on Day 1 of each treatment cycle (following Debio 1562 administration). After amendment # 6, patients receiving the QW regimen were allowed to switch to the Q3W regimen

An Independent Data Monitoring Committee (IDMC - comprised of independent experts in the field of hematology, oncology, and biostatistics) will perform regular reviews of cumulative safety, efficacy, and PK data in both cohorts A and B (Section 4.1.3.2).

In summary: for cohort A, a futility analysis will be performed after 10 patients are evaluable for efficacy (i.e., patients should have performed at least one post baseline objective response assessment- *unless there is earlier clear evidence of Progressive Disease [PD]*). Additionally, the totality of the safety data for this dose regimen will be reviewed by the IDMC who can recommend to terminate or modify the dosing regimen in case of unacceptable safety. If futility is met and/or the safety profile is unacceptable (as determined by the IDMC), the enrollment of this cohort will be stopped. Otherwise, an additional 5 patients will be enrolled and a subsequent futility analysis will be performed after 15 patients are evaluable for efficacy. Similarly, the cumulative safety data for this dose regimen will be reviewed by the IDMC. If futility is met and/or the safety profile is unacceptable, this cohort will be stopped. Otherwise, a recommendation may be made by the IDMC to continue with the expansion (study Part 3) using the same dosing regimen as described in cohort A.

For cohort B, there will be no futility analysis, however an intense safety oversight by the IDMC will be performed. At minimum, the IDMC will conduct data reviews at the following points:

1) An initial review of safety data once the third patient has completed one cycle of treatment.
2) A subsequent review of safety, available PK and efficacy data once the sixth patient has completed 2 cycles of treatment, with a recommendation to:
    a. Stop this cohort in case of unacceptable safety
    b. Enroll 6 more patients in order to obtain more data, or
    c. Explore a new QW dosing schedule (which will not exceed the total cumulative Q3W dose of 1.0 mg/kg)
3) In case the IDMC recommends to enroll 6 more patients, a review of safety, available PK and efficacy data once the twelfth patient has completed 2 cycles of treatment. The IDMC will then make a recommendation to:
    a. Stop this cohort in case of unacceptable safety
    b. Explore a new QW dosing schedule (which will not exceed the total cumulative Q3W dose of 1.0 mg/kg)
    c. Continue with enrollment of patients in cohort B in the expansion part (study Part 3), depending on evaluation of the totality of data in both cohorts A and B

Assignment of patients to cohorts A and B will be done through a central allocation system (Interactive Web Response System [IWRS]) as follows:

- 1:1 randomization when both cohorts are open for recruitment
- Automatic allocation to cohort A when enrollment to Cohort B is paused during IDMC review for 6 patients of cohort B

Expansion (Part 3)

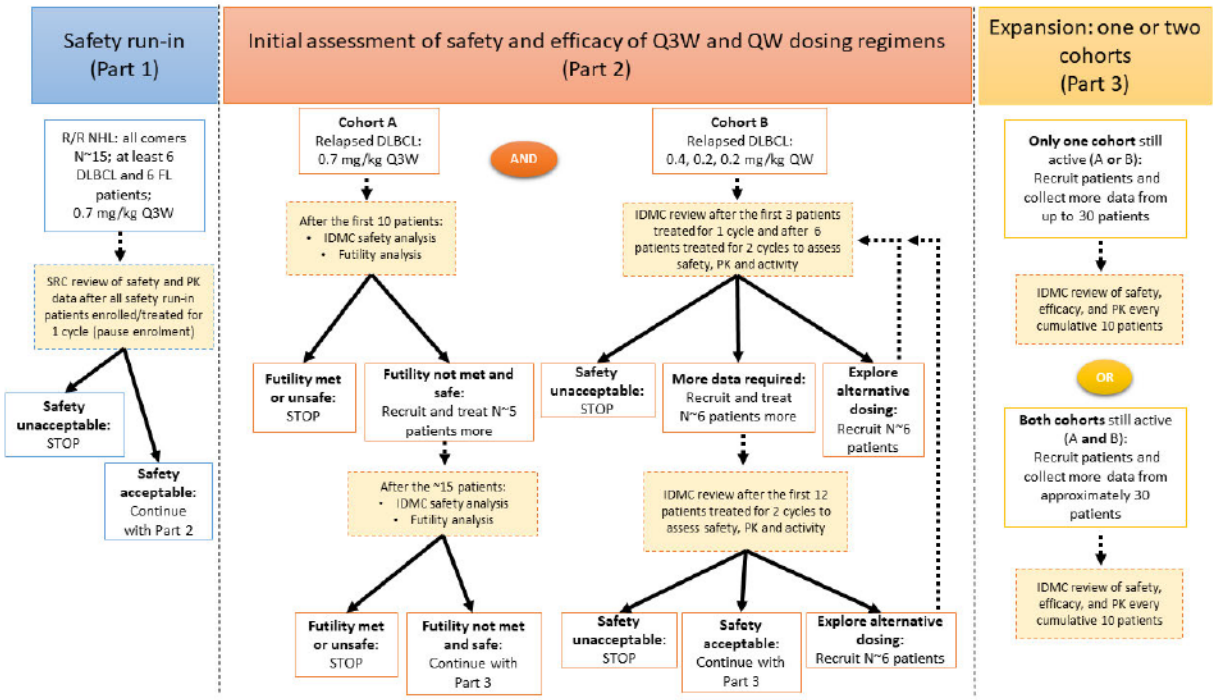
Part 3 of the study will enroll additional patients with relapsed DLBCL to further assess safety, efficacy and PK of the selected dosing schedule(s) investigated in Part 2 of the study (i.e., six 21-day cycles of Q3W and/or QW Debio 1562 dosing), as recommended by the IDMC.

In this part of the study, the IDMC will continue to review safety, efficacy and PK data available after every 10 patients are enrolled and treated for at least 2 cycles. (Section 4.1.3.2).

A schematic overview of the study design is shown in Figure 1 below.

In this study, the anti-tumor activity will be assessed following the recommendations from the International Conference on Malignant Lymphomas Imaging Working Group 2014 (Appendix I) and AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Figure 1: Schematic Overview of the Study Design



The study design and methodology are detailed in the full protocol.

Main Criteria for Study Eligibility (Refer to Section 3 for a complete list of eligibility criteria):

Diagnosis and allowable prior therapy and disease measurability:

1) For the safety run-in, patients must have histopathologically confirmed diagnosis of relapsed and/or refractory DLBCL, FL, MZL/MALT, MCL, or other Sponsor approved NHL subtypes according to the World Health Organization (WHO) classification 2008 for which standard measures do not exist or are no longer effective.

2) For Part 2 and Part 3 of the study, patients must have histopathologically and clinically confirmed diagnosis of relapsed DLBCL. Patients will be considered to have a relapsed disease if they showed a duration of response of at least 24 weeks after their first line of therapy. The following patients with relapsed DLBCL will be enrolled:

   i. Patients who received only one line of previous therapy and achieved either complete response (CR) or partial response (PR) for at least 24 weeks (from the last day of the last cycle) after their first line of therapy, **but** who are not eligible for high dose chemotherapy with autologous stem cell transplantation (HD-ASCT)

   ii. Patients who received more than one line of previous therapy (including HD-ASCT), and have achieved a duration of response (CR or PR) of at least 8 weeks (from the last day of the last cycle) after their last line of therapy

3) All patients in the study must have:

a. Received no more than six prior treatment regimens. Prior treatment with an anti-CD20 agent, either alone or in combination, is allowed.

b. Evaluable or measurable disease in accordance with the International Working Group Guidelines for Lymphoma (Cheson 2014).

Main Eligibility Criteria for All Patients:

1) Adult patients with Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
2) Patients must have adequate blood counts and organ function
3) Patients must have available a pathology-informed fresh or archived tumor tissue biopsy reflecting the current DLBCL disease. If the tissue biopsy is older than 18 months from the screening visit and a fresh one cannot be available, patients should provide fine needle aspiration (FNA) samples.
4) Patients who have received prior allogeneic stem cell transplantation will be excluded from the safety run-in part of the study; however they may be allowed to enroll in Part 2 and Part 3 of the study if their graft versus host disease (GVHD) is controlled and the Sponsor approves.
5) Patients with ≥ Grade 2 peripheral neuropathy will be excluded.
6) Patients with active hepatitis A, B or C infection or other uncontrolled intercurrent illness will be excluded.
7) Women of child bearing potential who are pregnant or breast feeding will be excluded.
8) Patients who have received prior other anti-CD37-targeting therapy will be excluded.

Investigational product, dosage, and mode of administration: Debio 1562 and rituximab will be administered IV. During the safety run-in Part 1 and in cohort A of Part 2, Debio 1562 will be given on Day 1 of a 21-day cycle at a dose of 0.7 mg/kg. Patients in cohort B of Part 2 will receive Debio 1562 at doses of 0.4, 0.2 and 0.2 mg/kg at Day 1, Day 8 and Day 15 of a 21-day cycle, respectively. During the entire study, 375 mg/m^2 of rituximab will be administered on Day 1 of each 21-day cycle.

In an effort to minimize the risk of Coronavirus Disease 2019 (COVID-19) infection for patients participating in the study, the Sponsor decided that in the interest of patient safety it is best to allow to switch patients who are on the QW Debio 1562 dosing regimen to the Q3W. The switch from the QW to Q3W regimen is not expected to result in any detrimental effect on safety or efficacy for these patients, based on recent analysis of preliminary study data.If a switch to the Q3W regimen is considered by the treating physician to be in the best interest of a given patient to mitigate the COVID-19 risk, the following should be observed:

- the patient must terminate his/her ongoing weekly administration cycle before switching to the Q3W regimen. For instance, if the patient received his/her first weekly administration of 0.4 mg/kg (D1), he/she should continue to receive weekly treatment until the end of that cycle. Only then, the patient can start the Q3W dosing regimen (0.7 mg/kg);
- patients who switch should continue to receive the Q3W regimen for the remainder of the study.

This will reduce the number of visits to the hospital. Therefore, reducing the exposure of patients to a potential risk of contamination, while ensuring adequate treatment. The measure taken will also reduce the burden at the trial sites during the pandemic.

Treatment and study duration: Patients will receive study treatment for six 21-day cycles, or until they develop unacceptable toxicity, withdraw consent, or the Sponsor terminates the study. Permission to prolong the study treatment could be exceptionally granted by Study Sponsor if patients are deriving benefit from the study treatment and after complete presentation of the individual case by the Study Investigator, particularly the medical justification for extending the treatment and the re-assessment of the risk/benefit balance. The Sponsor's decision will consider the availability of the Investigational Medicinal Product (IMP) at the time of the request. A report of the discussions with the Sponsor must be filed in the source documentation.

Patients who display intolerability to the combination regimen may be eligible to continue treatment with single agent Debio 1562.

Patients who discontinue the study treatment for reasons other than PD (including treatment completion) will be followed by radiographic scan, every 12 weeks (± 4 weeks) from the time of their last on-study tumor assessment until PD, start of any new anti-cancer therapy, or death.

For patients who are exceptionally granted continued study treatment after completion of 6 cycles, repeat radiographic tumor response assessments can be performed as per local institutional care practice. Ideally, repeat assessments should continue at 6-week (± 1 week) intervals and should not be longer than 12-weeks (± 4 weeks). Periodic tumor assessment will be conducted using the same imaging modality of prior cycles of treatment until PD, start of any new anti-cancer therapy, or death.

All patients will be contacted every 12 weeks (± 4 weeks) from the time of the 30-day safety follow-up visit until one year from last patient's first study treatment.

Statistical methods: All statistical analyses will be performed using the most recently released and available Statistical Analysis Software (SAS) statistical software, unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be calculated. For continuous variables, the sample size (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated. There will be a summary of patient disposition, patient demographics, and baseline characteristics. PK parameters will be computed and presented in tables and listings. Plasma concentrations will be presented in graphs for each patient and by cohorts. Latest version of SAS or WinNonlin will be used for the PK analyses.

No formal interim analysis for efficacy will be performed; however, futility analyses will be conducted after 10 patients and, if deemed necessary, 15 patients in cohort A are evaluable for efficacy (i.e., patients should have performed at least one post baseline objective response assessment- *unless there is earlier clear evidence of PD*), as well as cumulative after enrollment of every 10 evaluable patients for efficacy (if deemed necessary) in study Part 3. At each analysis, futility will be evaluated using a Bayesian approach with a non-informative conjugate prior. The decision rule will be to recommend stopping for futility if there is sufficiently low probability (20% or less) that Objective Response Rate (ORR) exceeds the pre-specified (historical) control response of 40%. The primary analysis will be conducted after all enrolled patients reached their 3rd on-treatment scheduled response assessment or have discontinued from treatment. The final analysis will be triggered one year after the last accrued patient's first dose date. In the exceptional

case that after the final analysis a patient(s) might continue to receive study treatment under the protocol, any subsequent data generated from this patient(s) will be summarized in an addendum report to be issued after the last treatment of the last patient.

A statistical analysis plan (SAP) will fully describe the planned analyses for this study, including sensitivity analysis related to patients who might switch dose regimen during the COVID-19 pandemic.

[redacted]

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1. INTRODUCTION

Debio 1562 is an ADC consisting of the humanized anti-CD37 antibody, K7153A, conjugated via a thioether-based linker to the cytotoxic maytansinoid, DM1 (Deckert, 2013). The ADC is stable in blood such that the cytotoxic potency of DM1 is restored only after Debio 1562 is bound to its cell surface target then internalized and released from the conjugate within the cell. Once released within the target cell, DM1 acts as an anti-mitotic agent that inhibits tubulin polymerization and microtubule assembly. Cells treated with maytansinoids arrest in the G2/M phase of the cell cycle, and eventually die by apoptosis (Remillard 1975). Debio 1562 binds with high affinity and high specificity to the leukocyte antigen, CD37. The selective expression of CD37 on the surface of B-cell derived lymphocytes and malignant cells makes CD37 a suitable target for a maytansinoid ADC as a potential treatment for patients with B-cell derived malignancies such as NHL and CLL.

1.1. Target Background

The target antigen for Debio 1562 is the leukocyte antigen CD37, also known as GP52-40, tetraspanin-26, or TSPAN26. CD37 is a heavily glycosylated transmembrane protein of the tetraspanin superfamily with a molecular weight of approximately 40-50 kD (Maecker 1997). Normal tissue expression is highly restricted, with strong expression limited to B-cells during the pre-B to peripheral B-cell stages (Link 1986, Barrena 2005) and only weak expression on T-cells, myeloid cells and granulocytes (Link 1986, Schwartz-Albiez 1988). CD37 is absent on other hematopoietic cells including hematopoietic stem cells, pro-B-cells and normal plasma cells (Link 1986). There is also no expression of CD37 in non-lymphoid tissue (Link 1986). In contrast, the CD37 antigen is highly expressed on B-cell NHL including DLBCL, FL, MCL, as well as CLL (Moore 1987, Barrena 2005). This pattern of restricted expression in normal tissue but high expression in malignant tissue suggests that CD37 represents a promising therapeutic target for B-cell malignancies.

Immunohistochemical (IHC) studies conducted at ImmunoGen, Inc. (ImmunoGen) using human tumor tissue microarrays have demonstrated CD37 expression in the majority of NHL cores including FL, MALT, DLBCL, MCL and Burkitt's lymphoma. As expected, non-specific staining was observed in T-cell lymphoma and multiple myeloma cores. These data are consistent with previously published studies, which demonstrated that CD37 is widely expressed on B-cell malignancies such as NHL and B-cell CLL (Link 1986, Moore 1987, Schwartz-Albiez 1988, Barrena 2005).

1.2. Debio 1562

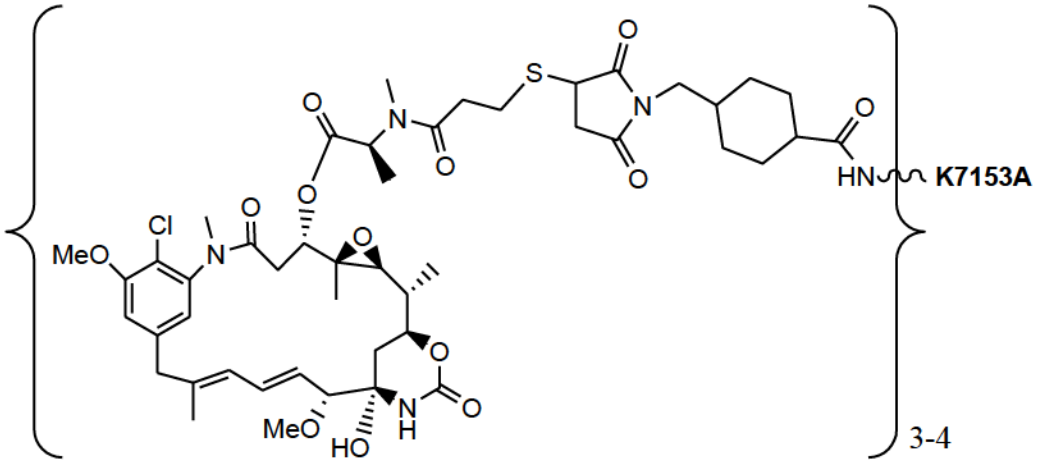
Debio 1562 is synthesized by conjugating the maytansinoid DM1 to the humanized monoclonal antibody K7153A, using the heterobifunctional crosslinking agent SMCC. The nomenclature and structure of Debio 1562 are shown in Table 1 below.

Table 1: Product Description

Chemical Name(s):	K7153A humanized monoclonal antibody tetraamide with N2'-[3-[[1-[(4-carboxycyclohexyl)methyl]-2,5-dioxo-3-pyrrolidinyl]thio]-1-oxopropyl]-N2'-deacetylmaytansine
Generic Name:	Not assigned
CAS Registry Number:	1607824-64-5
Investigational Code Number:	Not assigned
Synonyms:	Debio 1562 N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-Maytansine-Conjugated Humanized Monoclonal Antibody (K7153A) Maytansinoid-Conjugated Humanized Monoclonal Antibody against CD37 • huCD37-3-DM1 huCD37-3-DM1 conjugate huCD37-3-SMCC-DM1 huCD37-3-MCC-DM1
Antibody Synonyms:	K7153A huCD37-3

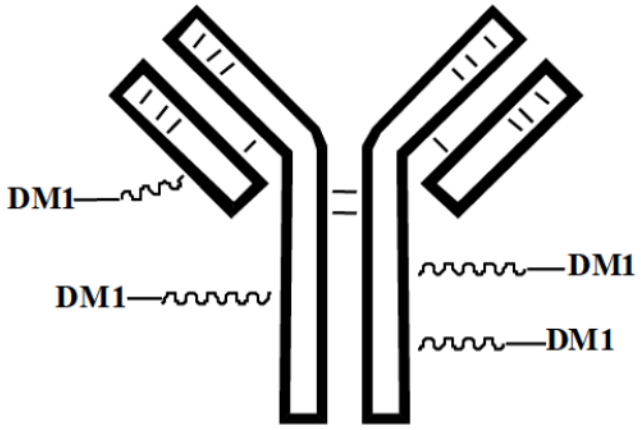
The chemical structure of Debio 1562 is shown in Figure 2. On average, there are 3.5 molecules of DM1 linked via disulfide bonds to each antibody molecule providing a stable conjugate. A schematic representation of DM1 bound to the humanized CD37-3 antibody (K7153A) is shown in Figure 3.

Figure 2: Chemical Structure of Debio 1562



DM1 is ~1.8% weight by monoclonal antibody

Figure 3: Schematic Representation of Debio 1562



For illustration only – not intended to represent exact conjugation sites

1.2.1. Mechanism of Action

The development of monoclonal antibody (mAb) specific to surface antigens expressed on tumor cells makes it possible to enhance the selectivity of anti-cancer cytotoxic agents by binding these agents to antibodies. Debio 1562 is a stable ADC that is inactive in blood plasma; the killing potency of its cytotoxic component, DM1, is restored only after binding, internalization, and intracellular release of DM1 from the conjugate. This specificity is anticipated to result in lower systemic toxicity and less damage to healthy tissue than other non-conjugated chemotherapeutic agents. DM1 is a structural analog of maytansine, a potent cytotoxic maytansinoid that was evaluated in Phase I and Phase II human clinical trials from 1978-1984 (Blum 1978, Cabanillas 1978, Chabner 1978, Eagan 1978, Issell 1978). Maytansinoids induce G2/metaphase arrest in dividing cells by inhibiting tubulin polymerization and microtubule assembly, resulting in cell death (Remillard 1975), similar to the vinca alkaloids (Kupchan 1972, Rao 1979, Remillard 1975). *In vitro* evaluation of the comparative cytotoxic potential of DM1 with other common cytotoxic agents shows that DM1 is a highly potent cytotoxic agent, with approximately 100-1000 fold greater potency than chemotherapy agents such as doxorubicin, etoposide, or cisplatin (Blattler 2001).

The activity of Debio 1562 is mediated by the selective binding to the CD37 antigen. *In vitro* studies have demonstrated that cell death is induced by several mechanisms including cell cycle arrest, induction of apoptosis and effector-mediated cytotoxicity (

Beckwith 2014, Deckert 2013).

1.3. Non-Hodgkin Lymphoma (NHL): Medical Need

NHL is one of the most common cancers in the United States (US), accounting for about 4% of all cancers. In the US there was an estimated 70,800 new cases in 2014 (SEER 2015). NHL consists of a heterogeneous group of cancers of the lymphatic system arising from B-lymphocytes, T lymphocytes or natural killer (NK) cells. B-cell lymphomas represent 80-85% of all lymphoma cases in the US (National Comprehensive Cancer Network 2011). Per WHO criteria, there are more than 30 subtypes of NHL which can be grouped in one of two categories; indolent or aggressive. Indolent forms include FL, CLL and MZL; while aggressive forms include DLBCL

and MCL. Aggressive lymphomas are often curable with intensive chemotherapy regimens, whereas indolent lymphomas are usually incurable in advanced clinical stages.

Anti-cancer treatment for this diverse disease is dependent on the specific subtype and stage but may include radiation, chemotherapy, biologic therapy, chemotherapy plus radiation or stem cell transplantation. The introduction of the CD20-directed Mab rituximab has had a significant effect on patient outcomes. Rituximab induces ADCC, CDC and apoptosis. Rituximab is currently approved for the treatment of newly diagnosed or R/R B-cell NHL, including the treatment of newly diagnosed DLBCL in combination with chemotherapy, as well as CLL. Combination regimens containing rituximab and chemotherapeutic agents have been shown to increase overall response rates and the rate of complete remissions as well as to delay time to progression (Leonard 2008, Cheson 2008). However, patients may show primary and secondary resistance. The five-year survival rate of NHL patients has risen from 47% (1975-1977) to approximately 71% (2004-2010) (Leukemia, Lymphoma, Myeloma Facts 2015); these survival statistics highlight the continued need for improved therapeutic strategies.

1.4. Non-Clinical Studies of Debio 1562

A brief summary of Debio 1562 nonclinical data is provided here. Additional information can be found in the Debio 1562 Investigator's Brochure (IB).

1.4.1. Pharmacology

Debio 1562 binding affinity and capacity

Debio 1562 has been shown to bind with high affinity and specificity to B-cells (apparent K_D: ~0.2 – 0.5 nM) with no evidence of non-specific binding at concentrations as high as 100 nM. Flow cytometry experiments using a fluorescently labelled CD37 antibody show that the number of antigen binding sites on B-cells is at least an order of magnitude higher than that of other cell types in normal peripheral blood.

Debio 1562 mode of action

The cytotoxic activity of Debio 1562 is mediated by the selective binding of the ADC to the CD37 antigen. Cell death is induced by several mechanisms, including cell cycle arrest, induction of apoptosis and effector-mediated cytotoxicity (ADCC and CDC).

In vivo anti-tumor activity of single agent Debio 1562 in severe combined immunodeficient (SCID) mice xenograft models

The anti-tumor activity of Debio 1562 has been demonstrated in several NHL xenograft models using SCID mice. A single IV dose (10 mg/kg) was active (ratio of median tumor volume for treated and control groups [T/C] = 16%) in female SCID mice bearing established DoHH2 (FL) tumors with 4/9 animals showing partial regression, 2/9 complete regression and 1/9 remaining tumor free by the end of the study. In a DLBCL mouse model (SU-DHL-4), Debio 1562 demonstrated dose-dependent anti-tumor activity with T/C values of 24%, 2% and 0% at doses of 2.5, 5 and 10 mg/kg, respectively. In addition, at the 10 mg/kg dose, Debio 1562 induced complete regressions and tumor free survivors in all of the mice (8/8). In a JVM-3 (B-CLL) model, Debio 1562 demonstrated anti-tumor activity with T/C values of 16% and 26% at doses of 5 and 10 mg/kg, respectively. Activity was also observed in mice bearing BJAB (BL) xenograft tumors.

In vitro cytotoxic activity of Debio 1562 in combination with rituximab

Debio 1562 in combination with rituximab demonstrated synergistic pro-apoptotic activity in a panel of cell lines representative of diverse NHL subtypes, including activated B-cell-like and germinal center B-cell–like DLBCL, CLL and MCL.

In vivo anti-tumor activity of Debio 1562 in combination with rituximab

Debio 1562 in combination with rituximab demonstrated synergistic anti-tumor activity in xenograft models of NHL established from [redacted] or [redacted] cells (Figure 4). In both models the combination of Debio 1562 and rituximab was compared with standard-of-care (R-CHOP. In the [redacted] model, the anti-tumor activity of Debio 1562 ([redacted] mg/kg) in combination with rituximab ([redacted] mg/kg) was comparable to that of R-CHOP with extended, complete tumor regressions in all mice. In addition, the combination regimen was [redacted] fold more active than single agent Debio 1562 or rituximab at the same dose (Figure 4). In the [redacted] model, the Debio 1562 ([redacted] mg/kg) and rituximab (10 mg/kg) combination was more active than R-CHOP, with [redacted]% percent of the animals achieving a complete response and remaining tumor free for the duration of the study compared to only [redacted]% in the R-CHOP group. Similarly, the combination regimen was more potent (T/C = [redacted]%) than either Debio 1562 (T/C = [redacted]%) or rituximab (T/C = [redacted]%) alone (Figure 4).

[redacted]

[redacted]

1.4.2. Pharmacokinetics

Nonclinical studies with Debio 1562 non-cross reactive (mouse) species were conducted to define PK parameters and to determine the stability of the linker and impact of conjugation on antibody clearance. The studies are summarized here and further detailed in the Debio 1562 IB.

1.4.2.1. Single Dose Pharmacokinetics of Debio 1562 in CD-1 Mice

Debio 1562 showed biphasic PK disposition upon single IV administration in CD-1 mice with a distribution phase of ~[redacted] hours and mean elimination half-life of Debio 1562 of about [redacted] days for

conjugate and [redacted] days for the K7153A antibody component. These results indicate that Debio 1562 is stable in circulation of the mouse.

1.4.3. Toxicology

Due to lack of CD37 sequence homology and/or Debio 1562 binding in animal species, ImmunoGen generated a mouse [redacted] model expressing the human CD37 antigen. Analysis of CD37 distribution and expression levels demonstrated similar tissue distribution but lower expression than that observed in human cells. Debio 1562 given at doses known to deplete human B cells [redacted]

Two Good Laboratory Practice studies evaluated the non-targeted toxicity [redacted] of Debio 1562 in [redacted] mice.

[redacted] Debio 1562 (doses [redacted]) caused reversible and non-reversible changes including [redacted]

The majority of Debio 1562-related alterations demonstrated a significant restoration towards normal [redacted]. Under the conditions of these studies, the STD_{10} for Debio 1562 was determined [redacted] (see Debio 1562 IB).

1.5. Clinical Studies of Debio 1562

1.5.1. First-in-Human Phase 1 Study

Safety

During the escalation phase of the FIH study with Debio 1562 (IMGN0301, NCT01534715), infusion reactions and early onset neutropenia were observed and this resulted in the implementation of peri-infusional and pre-dose steroid prophylaxis at the 0.4 mg/kg dose to successfully mitigate these occurrences. In subsequent dose escalations, later onset Grade 4 neutropenia and Grade 3 febrile neutropenia required the implementation of granulocyte growth factor prophylaxis, per institutional practice. Overall, the most common treatment emergent AEs (TEAEs), i.e., occurring in more than 10% of patients, include neutropenia, fever, fatigue, thrombocytopenia, nausea, diarrhea, hypokalemia, asthenia, aspartate aminotransferase (AST) increased, dyspnoea, alanine aminotransferase (ALT) increased, peripheral oedema, febrile neutropenia, decreased appetite, muscle weakness, and anemia. Grade 3 or greater TEAEs, regardless of relationship to Debio 1562, that have been reported by more than one patient include neutropenia, febrile neutropenia, leukopenia, thrombocytopenia, anemia, ALT increased, diarrhea, hyponatraemia, leukopenia, lymphophenia, and pneumonia. One patient suffered Grade 3 myocardial infarction and Grade 5 cardiac arrest that was considered to be unrelated to study treatment.

Anti-tumor activity

Of the forty-nine patients evaluated, four PR and one CR have been reported in patients with DLBCL or FL. Responses have been observed in patients with three or greater prior lines of therapy including autologous stem cell transplant relapses.

1.6. Rationale for Debio 1562 dosing regimens

The MTD of Debio 1562 in the FIH single agent study IMGN0301 was 1.4 mg/kg IV Q3W with granulocyte growth factor support and 1.0 mg/kg IV Q3W without prophylaxis of granulocyte growth factor.

The selected dose of Debio 1562 in combination with rituximab in the safety run-in (study Part 1) of this study will be 0.7 mg/kg IV Q3W (in a 21-day treatment cycle), with the dose calculated using total body weight. This dose level was deemed tolerable in the FIH study without the use of growth factor support.

In Part 2 of this study, the same 0.7 mg/kg IV Q3W Debio 1562 dosing regimen in combination with rituximab will be further assessed in cohort A. In parallel, a new QW Debio 1562 dosing schedule will be explored in cohort B. In this cohort, Debio 1562 will be administered at a dose of 0.4 mg/kg on Day 1, 0.2 mg/kg on Day 8 and 0.2 mg/kg on Day 15 (in a 21-day treatment cycle).

This additional weekly dosing regimen is aimed to maximize the synergistic effects of the combination of Debio 1562 and rituximab that was observed in prior non-clinical studies, which in turn may translate into a greater efficacy of the combination treatment in humans while maintaining or improving the safety profile of the study treatment. This hypothesis is based on the pre-clinical models showing improved Debio 1562 internalization when combined with rituximab, and the preliminary pharmacokinetic characterization of Debio 1562 that have shown a relatively short half-life of Debio 1562 compared with rituximab. Analyses of available PK data from the completed FIH single agent phase 1 trial and the completed safety run-in of this currently ongoing Phase 2 study suggest that a QW administration of Debio 1562 would prolong the exposure of Debio 1562 to the CD37 antigen, and improve the synergistic effect with rituximab.

The Sponsor has conducted several modeling simulations of Debio 1562 plasma concentration versus time, which suggest a lower peak concentration (C_{max}) and an extended drug exposure with the QW regimen compared to the Q3W regimen, which may result in a sustained target receptor occupancy (CD37). Additionally, preliminary PK modelling and simulation analyses suggest that the C_{max} of Debio 1562 may be associated with the onset of neutropenia, which has been shown to be the most common adverse reactions in the clinical setting so far.

The proposed QW dosing schedule of Debio 1562 will likely reduce the peak concentration while maintain the overall exposure. Without exceeding the MTD, this could be achieved with the administration of 0.4 mg/kg at the beginning of the treatment cycle, followed by two consecutive doses of 0.2 mg/kg each, the second and third week respectively. The total cumulative dose of 0.8 mg/kg per cycle is below the MTD defined in the single agent FIH study 0301(1.0mg/kg). Therefore, the weekly regimen is hypothesized to limit the risk of neutropenia while maintaining the exposure of Debio 1562 to malignant B-cells via the CD37 antigens. Additional information can be found in the IB.

Rituximab will be given at 375 mg/m^2 IV Q3W (in a 21-day treatment cycle) throughout the study, consistent with dosing of rituximab with concurrent chemotherapy in NHL, (Rituxan® (rituximab) Package Insert 2014).

From the data thus far, the toxicity profiles of Debio 1562 and rituximab are generally non-overlapping, although neutropenia, infusion reactions and fever have been observed with both Debio 1562 monotherapy and single agent rituximab, with neutropenia being a dose limiting event for Debio 1562.

1.7. Rationale for the Study Plan

This is an open label, Phase 2, clinical study that consists of three parts: 1) Safety run-in, 2) Initial assessment of safety and efficacy of Q3W and QW dosing regimens and 3) Expansion. For each patient, the study will include a screening period, a treatment period, and a follow-up period. The study is designed to determine the safety, tolerability and anti-tumor activity of Debio 1562 in combination with rituximab. The PK of Debio 1562 and rituximab as well as the immunogenicity of Debio 1562 will be evaluated.

Based on the broad expression of CD37 in B-cell NHL and the initial anti-tumor activity seen with Debio 1562 in DLBCL, this trial will initially include a broad range of B-cell NHL subtypes, in an effort to seek signals of safety and activity for the combination of Debio 1562 with rituximab. Patients with DLBCL, FL, MCL, or MZL/MALT or other NHL subtypes (with Sponsor's approval) are eligible for enrollment in the safety run-in. At least six DLBCL and six FL NHL patients will be enrolled in this part of the study. TEAEs occurring during Cycle 1 in patients enrolled into the safety run-in will be reviewed and taken into consideration when confirming the suitability of the combination treatment for continuation with the second part of the study. This part of the study has been completed and the SRC recommended continuation of the study.

In Part 2 and Part 3 of the study, enrollment will be focused on patients with relapsed DLBCL, for the following reasons:

1. DLBCL patients represent the largest group of NHL patients (about 40% of all NHL cases), with a significant unmet medical need.
2. DLBCL patients showed the highest response rate compared to patients with other NHL subtypes in a clinical study with another anti CD37 ADC, AGS67E (Sawas, 2017).
3. Relapsed DLBCL patients could benefit more than refractory patients from the treatment with Debio 1562: efficacy data obtained so far indicates that response rate in relapsed DLBCL patients is encouraging (approximately 43%).
4. Focusing on relapsed DLBCL patients will improve the homogeneity of the study population and facilitate data interpretation.
5. The primary mechanism of action of Debio 1562 (anti-CD37 antibody linked with the tubulin-disrupting payload agent DM1) is well suited for the more aggressive, rapidly dividing NHLs, such as relapsed DLBCL.

1.8. Clinical Pharmacology

Debio 1562 concentrations in plasma were obtained by using a validated enzyme-linked immunosorbent assay ligand binding assay.

Debio 1562 PK parameters from the FIH study 0301 were determined for Cycle 1 for each patient. In most cases, t_{max} coincided with the end of infusion, as expected. Overall results were fairly consistent across cycles, suggesting that the PK of Debio 1562 does not change upon repeat dosing. On average, C_{max} and $AUC_{0\text{-}inf}$ increased with an increase in dose. Greater than proportional increases occurred at doses of 0.8 mg/kg and above when compared to the 0.1 to 0.7 mg/kg doses, most likely due to an increase in the mean clearance (CL) in the lower dose range. [redacted] These changes in terminal elimination rate are consistent with target mediated drug disposition at low doses, with saturation of this mechanism occurring at higher doses. [redacted] in each group, the values for V_{ss} were consistent with plasma volume [redacted] There was no apparent accumulation of Debio 1562 in repeated dosing.

[redacted]

1.9. Risk Minimization Measures

Based on the currently available information, the most commonly reported severe adverse reactions were hematological events, including neutropenia, febrile neutropenia, leukopenia, and thrombocytopenia. Febrile neutropenia is the only expected Serious Adverse Reaction of Debio 1562. In this clinical trial, specific measures are implemented to minimize and monitor this risk and other identified risks during treatment with Debio 1562 and rituximab.

For the management of occurring cytopenia or preventing the re-emergence of serious ones including febrile neutropenia, specific treatment modification guidelines are provided in Section 5.8.2 of this protocol. The safety measures include dose reduction, use of bone marrow supportive measures, and discontinuation of study treatment. In addition to routine AE reporting, vital signs and hematology assessments including White Blood Cell (WBC) count and differential cell counting are planned along the treatment cycle, and more frequent for cycles 1 and 2.

To minimize the risk of serious infections, patients presenting with active hepatitis or human immunodeficiency virus (HIV) infection, or having received attenuated vaccination within 30 days prior to first study treatment are excluded for participation. As patients will receive rituximab in addition to Debio 1562, they are required to receive antiviral treatment per institutional guidelines.

To minimize the risk of emergence of serious infusion-related reaction or to mitigate its potential severity in case of occurrence, the study protocol defines the pre- and post-infusion prophylaxis (Section 5.7.1) as well as specific guideline to manage serious infusion-related reactions (Section 5.7.5). Patients who have had a prior anaphylactic or other serious infusion-related reactions are excluded from the study. As an additional precautionary measure, patients will remain in the clinic under monitoring for four hours after completion of the rituximab infusion during the first cycle. Patients receiving Debio 1562 only, i.e., on Day 8 and Day 15 for the QW dosing schedule or due

to rituximab intolerability, will also remain in the clinic under monitoring for one hour for all cycles. In addition, trained medical personnel, appropriate prophylactic medication and other resources is mandatory to have available at participating sites before starting to infusion in case of anaphylaxis.

To minimize the risk of tumor lysis syndrome (TLS), patients with high tumor burden and/or high circulating lymphocyte counts should be adequately hydrated prior to the infusion. Serum chemistry assessments will be conducted at each visit, including at Day 2 and Day3 after the first two cycles.

As pneumonitis has been reported with the use of ADCs, including one fatal case in a patient receiving treatment with Debio 1562, despite the absence of a casual dose and temporal relationship with Debio 1562, the current protocol excludes the enrollment of patients with current diagnosis of interstitial lung disease or with clinical history of severe parenchymal lung disorders.

In an effort to minimize the risk of Coronavirus Disease 2019 (COVID-19) infection for patients participating in the study, the sponsor decided that in the interest of patient safety it is best to allow to switch patients who are on the QW Debio 1562 dosing regimen to the Q3W. The switch from the QW to Q3W regimen is not expected to result in any detrimental effect on safety or efficacy for these patients, based on recent analysis of preliminary study data.

This will reduce the number of visits to the hospital. Therefore, reducing the exposure of patients to a potential risk of contamination, while ensuring adequate treatment. The measure taken will also reduce the burden at the trial sites during the pandemic.

As of April 14, 2020, three patients are on treatment with QW dose regimen. All were granted permission to switch to the Q3W regimen by Study Sponsor in the best interest of the patients. Study enrollment has been completed.In addition to the specific risk minimization measures, safety will be closely evaluated throughout the study until the 30-day safety follow-up visit. The safety assessments include AE reporting, laboratory assessments, electrocardiogram (ECG), physical exams, and vital signs. An IDMC will monitor the safety data regularly throughout the study, and provide recommendations at the pre-defined timepoint based on the data (see Section 4.1.3.2).

1.10. Amendment History

1.10.1. Amendment 1

The reasons for amending the protocol are as follows:

1. The document was edited to clarify protocol procedures, improve internal consistency and, consequently, readability and understanding.
2. Some of the details were removed from the synopsis as they are detailed in the main body of the protocol, thereby reducing duplication and risk of error.
3. The Safety Review Committee composition and function is described in the synopsis as it is referenced early in the document.
4. The following sections of the protocol were revised and edited for clarification purposes:
    a. The rationale for the starting doses of Debio 1562 (formerly IMGN529) and rituximab

b. The rationale for the study plan
c. The Study Design
d. Study Drug Administration
e. Management guidelines for infusion reaction
f. PK Assessments
g. ECG procedures
h. Radiologic imaging and tumor response assessment guidelines

5. The objectives and endpoints were edited for clarity and one of the exploratory objectives was expanded [redacted]; the corresponding endpoint was revised accordingly.
6. Revisions were made to the Inclusion and Exclusion Criteria.
7. The Toxicity Management Guidelines, including the sections of the protocol describing dose modifications and AE assessments, were revised to improve internal consistency and to define "Dose Modifying Events".
8. The guidelines for patient discontinuation and collection of subsequent anti-cancer therapy were revised.
9. The hematology and serum chemistry assessments were streamlined.
10. The section of the protocol detailing the study activities was deleted entirely.
11. The section of the protocol describing records retention was streamlined.
12. Missing references were added to the protocol.
13. The Schedule of Events was revised.
14. The Ann Arbor Staging Criteria (with Cotswold Modifications) were added to the protocol.

1.10.2. Amendment 2

The protocol was amended for administrative reasons as the ownership of IMGN529 was transferred from ImmunoGen Inc. to Debiopharm International S.A.

As a result, the following changes were made:

- The Sponsor name and address were updated
- The contact medical director's name and address were updated
- Product identifier was changed from IMGN529 to Debio 1562 throughout the document
- Study number was changed from 0302 to Debio 1562-201 throughout the document

1.10.3. Amendment 3

The reasons for amending the protocol are as follows:

- To confine the patient population to those with relapsed DLBCL in study Part 2 (cohorts A and B) and study Part 3, to have a more homogeneous population for data analysis.

- To add an arm to investigate a new QW Debio 1562 dosing schedule (cohort B) while maintaining the current Q3W Debio 1562 dosing arm (cohort A), without increasing the cumulative Debio 1562 dose currently allowed in the protocol (i.e., 0.7 mg/kg – 1.0 mg/kg Q3W).
- To change the fixed study design to an adaptive design in order to utilize the generated data to establish a dosing regimen associated with optimal benefit-risk.
- To add blood sampling time points to improve evaluation of PK disposition.
- [redacted]
- To add HRQoL assessment.

1.10.4. Amendment 4

The main reason for amending the protocol was to reflect the following changes requested by regulatory health authorities during the review process of the previous protocol.

- To update eligibility criteria to exclude patients currently presenting interstitial lung disease, diffuse parenchymal lung disease, or with a past history of severe/Grade 3 parenchymal lung disorder
- To extend the period of monitoring to 4 hours after completion of the rituximab infusion for the first cycle
- To introduce a new section of risk minimization measures for the expected serious adverse reactions

In addition, Section 5.9 was revised for clarification purposes. Some minor changes are also included in other sections of the protocol for clarification and to improve consistency.

1.10.5. Amendment 5

The main reason for amending the protocol is to address the potential for exceptional individual patients' study treatment prolongation beyond 6 cycles, provided the patient is benefitting from the study treatment and after discussing and agreement with the Study Sponsor.

Furthermore, this protocol amendment also addresses the following:

- To clarify study treatment duration and the conditions under which treatment duration may be prolonged for patients who exceptionally continue study treatment beyond 6 cycles (Section 4.1.1)
- To clarify the frequency and imaging modality of radiologic tumor response assessments for patients who exceptionally continue study treatment beyond 6 cycles (Section 8.14)
- To clarify last timepoint of PK, Immunogenicity [redacted] Assessments at Cycle 7 Day 1 (C7D1), instead of End of Treatment (EOT) visit and with no additional samples taken at 30-day follow-up visit for patients who exceptionally continue with treatment beyond 6 cycles (Sections 6.1; Section 6.2; Section 6.3; Appendix E, Appendix F [redacted])

- To clarify last timepoint of assessments of HRQoL at C7D1: instead of EOT visit and with no additional HRQoL assessment to be completed at 30-day follow-up visit for patients who exceptionally continue with treatment beyond 6 cycles (Section 8.8)
- To clarify that primary analysis will be conducted after all enrolled patients reach their 3rd on-treatment scheduled response assessment or have discontinued from treatment. The final analysis will be triggered one year after the last accrued patient's first dose date. In the exceptional case that after the final analysis a patient(s) might continue to receive study treatment under the protocol, any subsequent data generated from this patient(s) will be summarized in an addendum report to be issued after the last treatment of the last patient (Section 10).
- APPENDICES A-C: Schedule of events were revised for clarification purposes.
- Clarification was made regarding the separate tubes used for blood draw for PK assessment and for anti-drug antibodies (ADA).
- Clarification that the potential immunogenicity against rituximab will be assessed.
- Some minor changes are also included in other sections of the protocol to improve clarity and consistency.

Based on the changes above, this amendment is considered substantial, requiring approval by Ethics Committees and Regulatory Authorities before implementation.

1.10.6. Amendment 6

In an effort to minimize the risk of COVID-19 infection for patients participating in the study, the Sponsor decided that in the interest of patient safety it is best to allow to switch patients who are on the QW Debio 1562 dosing regimen to the Q3W. The switch from the QW to Q3W regimen is not expected to result in any detrimental effect on safety or efficacy for these patients, based on recent analysis of preliminary study data.

If a switch to the Q3W regimen is considered by the treating physician to be in the best interest of a given patient to mitigate the COVID-19 risk, the following should be observed:

- the patient must terminate his/her ongoing weekly administration cycle before switching to the Q3W regimen. For instance, if the patient received his/her first weekly administration of 0.4 mg/kg (D1), he/she should continue to receive weekly treatment until the end of that cycle. Only then, the patient can start the Q3W dosing regimen (0.7 mg/kg). patients who switch should continue to receive the Q3W regimen for the remainder of the study.
- This will reduce the number of visits to the hospital. Therefore, reducing the exposure of patients to a potential risk of contamination, while ensuring adequate treatment. The measure taken will also reduce the burden at the trial sites during the pandemic.

As of April 14, 2020, patients who are on treatment with QW dose regimen were granted permission to switch to the Q3W regimen by the Sponsor in their best interest. Study enrollment has been completed.

A potential switch of ongoing patients receiving QW regimen to a Q3W is not anticipated to impact the primary analysis. Nonetheless, a sensitivity analysis will be performed to identify any potential impact.
Considering that COVID-19 presents an imminent potential risk for the patients, this change was already implemented as an Urgent Safety Measure, of immediate effect. In order to comply with relevant regulations, this substantial protocol amendment is being submitted to all relevant Regulatory Agencies and Ethic Committees, following local regulations.
As access to study sites by study/sponsor monitors could be difficult or impossible during the COVID-19 pandemic, remote monitoring will be allowed, if possible, and according to local requirements.
Some minor edits are also included in Appendix E and Appendix F to improve the clarity and consistency of PK and ADA assessments in the protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

- Determine the safety and tolerability of the proposed Debio 1562 dose regimens in combination with rituximab
- Determine the anti-tumor activity of the proposed Debio 1562 dose regimens in combination with rituximab

2.1.2. Secondary Objectives

- Characterize the PK of Debio 1562 in combination with rituximab
- Determine time to event outcomes [PFS, time to response, DoR, and OS]
- Assess the immunogenicity of Debio 1562 (ADA) when administered in combination with rituximab.

2.1.3. Exploratory Objectives

- Correlate the extent of CD37 and CD20 antigen expression in tumor samples with anti-tumor activity of the Debio 1562 and rituximab combination.

[redacted]

[redacted]

[redacted]

- Assess HRQoL.

2.2. Endpoints

2.2.1. Primary Endpoints

- TEAEs, clinically significant changes in clinical laboratory test results, ECG and vital sign measurements
- Number of patients with clinical responses (ORR) as assessed by the Lugano Classification of response assessments (Appendix I)

2.2.2. Secondary Endpoints

- PK parameters (evaluated as deemed appropriate but not limited to): C_{max}, AUC_{0-t}, AUC_{inf}, terminal half-life ($t_{½}$), CL, V_{ss}, T_{max}, for both Debio 1562 and rituximab
- Calculation of time to event parameters:

- PFS and OS
- Time to response and duration of response

- Immunogenicity of Debio 1562: presence of human ADA

2.2.3. Exploratory Endpoints

- Expression levels of CD37, CD20 by IHC (protein) and/or mRNA detection and correlation of these measures to clinical response criteria.

- HRQoL will be assessed through analysis of patient reported Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) scores.

3. STUDY POPULATION

3.1. Criteria for Selection of Patient Population

Inclusion Criteria

1) For Part 1 of the study, patients must have histopathologically confirmed diagnosis of R/R DLBCL, FL, MZL/MALT, MCL, or other Sponsor approved NHL subtypes according to the WHO classification 2008 for which standard measures do not exist or are no longer effective.
2) For Part 2 and Part 3 of the study, patients must have histopathologically and clinically confirmed diagnosis of relapsed DLBCL. Patients will be considered to have a relapsed disease if they showed a duration of response of at least 24 weeks after their first line of therapy. The following patients with relapsed DLBCL will be enrolled:
    i. Patients who received only one line of previous therapy and achieved either complete response (CR) or partial response (PR) for at least 24 weeks (from the last day of the last cycle) after their first line of therapy, **but** are not eligible for high dose chemotherapy with autologous stem cell transplantation (HD-ASCT)
    ii. Patients who received more than one line of previous therapy (including HD-ASCT), and have achieved a duration of response (CR or PR) of at least 8 weeks (from the last day of the last cycle) after their last line of therapy.
3) Patients must have received no more than six prior treatment regimens. Prior treatment with an anti-CD20 agent, either alone or in combination, is allowed.
4) Patients must be ≥ 18 years.
5) Patients must have ECOG Performance Status 0 - 2.
6) Patients must meet the following laboratory criteria:
    - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L (1000/mm^3)
    - Platelet count ≥ 50 x 10^9/L (50,000/mm^3; patients must not have been transfused within 10 days previous of blood drawn for laboratory assessment)
    - Patients receiving therapeutic anticoagulation are eligible provided their anticoagulation parameters are within range (e.g. International Normalized Ratio [INR] 2-3 on Coumadin if applicable) and they have no history of ≥ Grade 2 bleeding while on anticoagulation therapy
    - ***For patients receiving therapeutic doses of anticoagulation:*** Platelet count ≥ 100 x 10^9/L (100,000/mm^3; must not have been transfused within previous 10 days)
    - Hemoglobin ≥ 8.0 g/dL (may have been transfused)
    - Serum creatinine ≤ 2.0 x upper limit of normal (ULN) or 24-hour creatinine clearance of ≥ 60 mL/minute
    - AST ≤ 2.5 x ULN; ALT ≤ 2.5 x ULN and

- Total bilirubin ≤ 1.5 x ULN; patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin ≤ 3.0 x ULN.

7) Patients must have evaluable or measurable disease in accordance with the International Working Group Guidelines for Lymphoma (Cheson 2014).
8) Patients who are Hepatitis B surface antigen (HBsAg) + (must be polymerase chain reaction [PCR] negative) who are taking antivirals are allowed to enroll.
9) Male patients and female patients of child bearing potential participating in this study must agree to use two highly effective methods of contraception throughout the study and for at least 12 weeks after the last dose of Debio 1562 and 12 months after the last dose of rituximab. Examples of acceptable birth control methods include but are not limited to the following methods: (e.g., oral, parenteral, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; partner's latex condom or vasectomy).
10) Patients must be willing to provide informed consent and be willing to comply with the study protocol.
11) Patients must have available a pathology-informed fresh or archived tumor tissue biopsy reflecting the current DLBCL disease. If the tissue biopsy is older than 18 months from the screening visit and a fresh one cannot be available, patients should provide fine needle aspiration (FNA) samples.

Exclusion Criteria

1) Patients with a diagnosis of CLL or Small Lymphocytic Lymphoma.
2) For Part 2 and Part 3 of the study, patients with primary refractory DLBCL (defined as progression of disease within 24 weeks after first line of treatment).
3) For Part 2 and Part 3 of the study, patients that are eligible to undergo first time HD-ASCT.
4) For Part 2 and Part 3 of the study, patients with R/R FL, MZL/MALT, MCL, or any other NHL subtypes according to the WHO classification
5) The following exclusions, with regard to prior therapy apply:
    - Not recovered from prior chemotherapy or radiation as per Investigator's judgment.
    - Anti-CD20 monoclonal antibody therapy within 14 days of starting study treatment.
    - Prior therapy with other anti-CD37-targeting therapy.
    - Radioimmunotherapy within two months prior to starting study treatment.
    - Small molecule anti-cancer therapeutic agent, and all investigational agents within 5 x $t_{1/2}$ or 14 days whichever is shorter.
    - Allogeneic stem cell transplantation in the safety run-in period. In Part 2 and Part 3 of the study, patients who have had an allogeneic stem cell transplant may be eligible if their GVHD is controlled, after investigator/Sponsor discussion.

- Chronic, systemic treatment with corticosteroids unless the dose has been stable for >7 days and is equivalent to ≤ 10 mg of prednisone per day.
- Patients who have not recovered from prior surgery. Patients must have recovered or stabilized from the side effects of any major or minor surgical procedures prior to study treatment.

6) Patients who have had a prior anaphylactic or other severe infusion reaction such that the patient is unable to tolerate antibody administration.
7) Patients who have known central nervous system, meningeal, or epidural disease including brain metastases.
8) Patients who have received or are to receive vaccination with live viruses within 30 days of Cycle 1 Day1.
9) Impaired cardiac function or clinically significant cardiac disease such as:
   - New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy;
   - Unstable angina pectoris ≤ 6 months prior to starting study treatment;
   - Acute myocardial infarction ≤ 6 months prior to starting study treatment; or
   - Other clinically significant heart disease e.g., ≥ grade 3 hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen.
10) Patients with ≥ Grade 2 peripheral neuropathy.
11) Patients with active hepatitis A, B or C infection.
12) Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, psychiatric illness that would limit compliance with study requirements, active autoimmune disease requiring immunosuppressive therapy, severe immune deficiency.
13) Known diagnosis of HIV infection.
14) Patients with a concurrent primary malignancy that requires treatment or that would confound the disease response interpretation for the disease under study.
15) Women of child bearing potential who are pregnant or breast feeding.
16) Patients currently presenting interstitial lung disease, diffuse parenchymal lung disease, or with a past history of severe/Grade 3 parenchymal lung disorders.

4. INVESTIGATIONAL PLAN

4.1. Study Design

4.1.1. Overview

This is an open label, multicenter, adaptive Phase 2 clinical study of Debio 1562 in combination with rituximab in patients with DLBCL and other subtypes of B-cell NHL.

For each participating patient, the study will include a screening period, a treatment period, and a follow-up period.

The study consists of three parts:

Safety Run-In (Part 1)

Patients with DLBCL, FL, MCL, MZL/MALT or other NHL subtypes (with Sponsor's approval) will be eligible for enrollment in the safety run-in part of the study. During the safety run-in, at least six DLBCL and six FL NHL patients will be enrolled.

Patients will be given Debio 1562 and rituximab IV on the same day (i.e., Day 1) Q3W. Debio 1562 will be given at a dose of 0.7 mg/kg, followed by 375 mg/m^2 of rituximab.

Following review of safety and PK data by a SRC (comprised of the Sponsor's Medical Director and Investigators from participating sites) once the last patient of the safety run-in has completed 1 cycle of treatment, the SRC will make a recommendation to either stop the study for unacceptable safety, or continue the Q3W dosing schedule with the 0.7 mg/kg dose of Debio 1562 or an alternate higher (1.0 mg/kg) or lower dose of Debio 1562 (Section 4.1.3.1).

This part of the study has been completed and the SRC recommended continuation of the study.

Initial Assessment of Safety and Efficacy of Q3W and QW Dosing Regimens (Part 2)

During Part 2 of the study, only patients with relapsed DLBCL will be enrolled into two parallel cohorts according to the dosing regimen of Debio 1562: cohort A (21-day treatment cycle with a Q3W dosing schedule) and cohort B (21-day cycle treatment cycles with a QW dosing schedule).

Patients in **cohort A** will receive Debio 1562 and rituximab IV on the same day (Day 1) on a Q3W dosing schedule. Debio 1562 will be given at a dose of 0.7 mg/kg (unless recommended otherwise by the SRC), followed by 375 mg/m^2 of rituximab.

Cohort B will explore a QW dosing schedule of Debio 1562: 0.4, 0.2, and 0.2 mg/kg of Debio 1562 will be administered IV to patients on Day 1, Day 8 and Day 15 of a 21-day treatment cycle, respectively. Rituximab will be administered IV at a dose of 375 mg/m^2 on Day 1 of each treatment cycle (following Debio 1562 administration). After amendment #6 (Section 1.10.6), patients receiving a QW regimen were allowed to switch to Q3W regimen.

An IDMC (comprised of independent experts in the field of hematology, oncology, PK and biostatistics) will perform regular reviews of cumulative safety, efficacy, and PK data in both cohorts A and B (Section 4.1.3.2).

In summary: for cohort A, a futility analysis will be performed after 10 patients are evaluable for efficacy (i.e., patients should have performed at least one post baseline objective response assessment- *unless there is earlier clear evidence of PD*). Additionally, the totality of the safety data for this dose regimen will be reviewed by the IDMC who can recommend to terminate or modify the dosing regimen in case of unacceptable safety. If futility is met and/or safety profile is unacceptable as determined by the IDMC, this cohort will be stopped. Otherwise, an additional 5 patients will be enrolled and a subsequent futility analysis will be performed after 15 evaluable patients for efficacy. Similarly, the cumulative safety data for this dose regimen will be reviewed by the IDMC. If futility is met and/or safety profile is unacceptable, this cohort will be stopped. Otherwise, depending on the evaluation of the totality of data in both cohorts (A and B), a recommendation may be made by the IDMC to continue with the expansion (study Part 3) using the same dosing regimen as in cohort A.

For cohort B, there will be no futility analysis, however an intense safety oversite by IDMC will be performed. At minimum, IDMC will conduct reviews at the following time points:

1) An initial review of safety data once the first 3 patients have received at least one cycle of treatment
2) A subsequent review of safety, available PK and efficacy data after 6 patients will have completed 2 cycles of treatment, with a recommendation to:
    a. Stop this cohort in case of unacceptable safety
    b. Enroll 6 more patients in order to obtain more data, or
    c. Explore a new QW dosing schedule (which will not exceed the total cumulative Q3W dose of 1.0 mg/kg)
3) Review of safety, available PK and efficacy data after 12 patients will have completed 2 cycles of treatment in case data of an additional 6 patients are deemed necessary (see point 2b above). The IDMC will then make a recommendation to:
    a. Stop this cohort in case of unacceptable safety
    b. Explore a new QW dosing schedule (which will not exceed the total cumulative Q3W dose of 1.0 mg/kg)
    c. Continue with enrollment of patients in cohort B in the expansion part (study Part 3), depending on evaluation of the totality of data in both cohort A and B

If the IDMC recommend to explore a different dose, only one new dose regimen will be investigated. In such case, the three IDMC reviews described above will occur for this new regimen.

Assignment of patients to cohorts A and B will be done through an IWRS as follows:

- 1:1 randomization when both cohorts are open for recruitment
- Automatic allocation to cohort A during IDMC review of cohort B

Based on evaluation of the totality of data available from the safety run-in Part 1 and Part 2 of the study, the IDMC will make a recommendation on continuation with enrollment of patients in either cohort A, cohort B or both cohorts.

Expansion (Part 3)

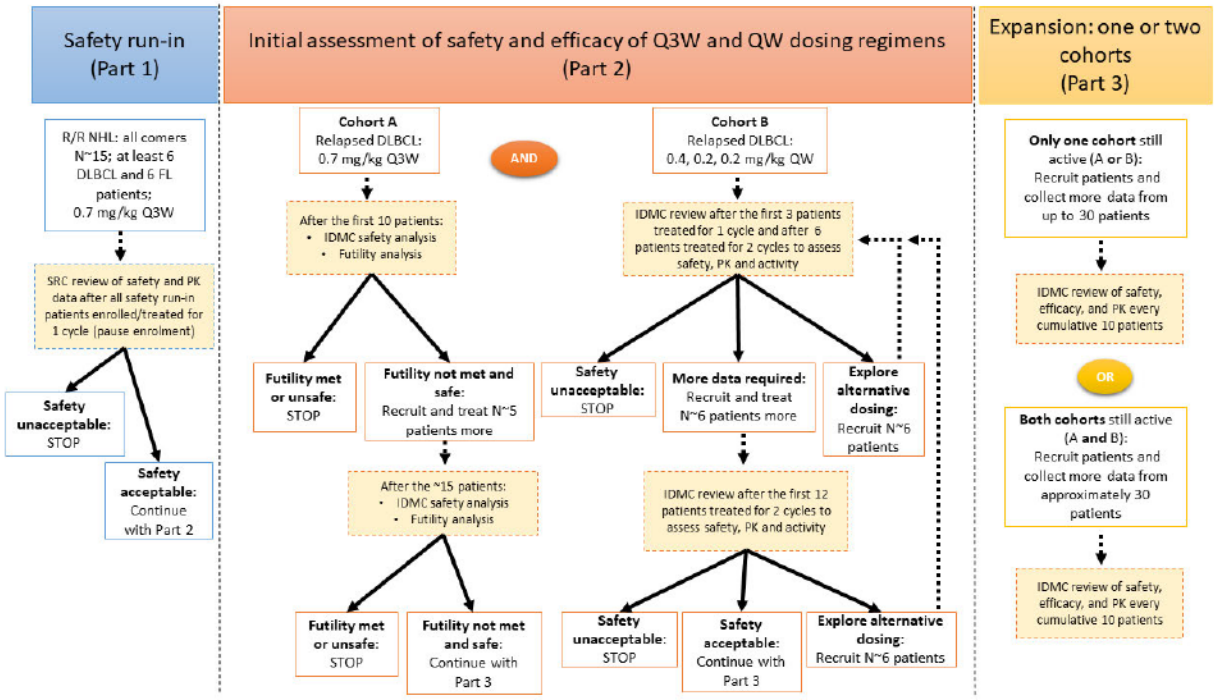
Part 3 of the study will enroll additional relapsed DLBCL patients to further assess safety, efficacy and PK of the selected dosing schedule(s) investigated in Part 2 of the study (i.e., six21-day cycles of Q3W and/or QW Debio 1562 dosing), as recommended by the IDMC.

In this study part, the IDMC will continue to review safety, efficacy and PK data available after every 10 patients enrolled and treated for at least 2 cycles (Section 4.1.3.2).

A schematic overview of the study design is provided in Figure 5 below.

In this study, the anti-tumor activity will be assessed by the Lugano Classification (Appendix I) and AEs will be graded using CTCAE version 4.03

Figure 5: Schematic Overview of the Study Design



Study treatment duration

Patients will receive study treatment for six 21-day cycles, or until they develop unacceptable toxicity, withdraw consent, or the Sponsor terminates the study. Permission to prolong the study treatment could be exceptionally granted by Study Sponsor if patients are deriving benefit from the study treatment and after complete presentation of the individual case by the Study Investigator, particularly the medical justification for extending the treatment and the re-assessment of the risk/benefit balance. The Sponsor's decision will consider the availability of investigational medicinal product (IMP) at the time of the request. A report of the discussions with the Sponsor must be filed in the source documentation.

Patients who display intolerability to the combination regimen may be eligible to continue treatment with single agent Debio 1562.

4.1.2. Replacement of Patients

Patients who will not be evaluable for safety may be replaced if they:

- Withdrew consent before at least one cycle of study treatment is completed
- Are discontinued due to hypersensitivity reaction on Day 1 of Cycle 1
- Discontinue before the end of Cycle 1 due to:
  - AEs unrelated to study treatment
  - Development of rapid disease progression
  - Death, unrelated to study treatment

4.1.3. Safety Review Committee (SRC) and Independent Data Monitoring Committee (IDMC)

4.1.3.1. Safety Review Committee (SRC)

The SRC, comprised of the Sponsor's Medical Director and Investigators from participating sites, is responsible for safety data review during the course of the safety run-in (Part 1). During the safety run-in, the SRC will meet every 2-4 weeks by teleconference to review patient safety updates.

Safety Review Following the Safety Run-in - Part 1: Once the last patient in the safety run-in has completed one cycle of study treatment, enrollment will be paused and an SRC meeting will be convened to review all available safety and PK data. The SRC will determine whether the Debio 1562 dose of 0.7 mg/kg should be evaluated in the next part of the study, or whether an alternative dose should be evaluated. During the safety run-in, the SRC will review the available safety and PK data and may decide to escalate the Debio 1562 starting dose from 0.7 mg/kg to 1.0 mg/kg, which is one dose level lower than the MTD defined in the monotherapy study, with granulocyte growth factor support. If the SRC determines at any time that the dose should be reduced for safety reasons, a lower dose of Debio 1562 will be explored.

4.1.3.2. Independent Data Monitoring Committee (IDMC)

The IDMC, comprised of independent experts in the field of hematology, oncology, and biostatistics, will be responsible for the review of safety, efficacy and PK data during the course of Part 2 and Part 3 of the study.

At multiple time points during these study parts, available safety, (preliminary) PK and anti-tumor activity data will be provided for review by the IDMC:

For cohort A (Part 2):

1. Once 10 patients are evaluable for efficacy (i.e., patients should have performed at least one post baseline objective response assessment- *unless there is earlier clear evidence of PD*). Enrollment in this cohort will continue during the IDMC review.
2. Once 15 patients are evaluable for efficacy (i.e., patients should have performed at least one post baseline objective response assessment- *unless there is earlier clear evidence of PD*). Enrollment in this cohort will continue during the IDMC review.

For cohort B (Part 2):

1. Once the 3rd patient has completed one cycle of treatment. Enrollment in this cohort will continue during the IDMC safety review.
2. Once the 6th patient has completed two cycles of treatment. Enrollment in this cohort will be paused during the IDMC safety review.
3. Once the 12th patient has completed two cycles of treatment. Enrollment in this cohort will continue during the IDMC safety review.

For any cohort (Part 3):

After every 10 patients have completed two cycles of treatment and are evaluable for efficacy (i.e., patients should have performed at least one post baseline objective response assessment- *unless there is earlier clear evidence of PD*). Enrollment will continue during the IDMC safety review.

Clinical safety, efficacy and PK data that will be provided for SRC and IDMC review will include, but are not limited to the following: AEs, laboratory data, ECG results, dose modifications, a summary of serious adverse events (SAEs), tumor assessments, overall tumor response and DoR. Based on their expertise and experience in treating DLBCL patients, the IDMC members will establish all the criteria necessary to take the decision of stopping or continuing the study.

IDMC Safety, Efficacy and PK Review - Part 2

Cohort A: Once the first 10 patients evaluable for efficacy (i.e., patients should have performed at least one post baseline objective response assessment- *unless there is earlier clear evidence of PD*) during Part 2 of the study are available for futility analysis, the IDMC will review the totality of the safety data for the Q3W dosing regimen and can recommend to terminate or modify the dosing regimen in case of unacceptable safety. If futility is met and/or safety profile is unacceptable as determined by the IDMC, this cohort will be stopped. Otherwise, an additional 5 patients will be enrolled and a subsequent futility analysis will be performed after 15 evaluable patients for efficacy. Similarly, the cumulative safety data for this dose regimen will be reviewed by the IDMC. If futility is met and/or safety profile is unacceptable, this cohort will be stopped. Otherwise, depending on the evaluation of the totality of data in both cohorts (A and B), a recommendation may be made by the IDMC to continue with the expansion (study Part 3) using the same dosing regimen as in cohort A.

Cohort B: An initial IDMC review of safety data will be performed once the first 3 patients have received at least one cycle of treatment. A subsequent review of safety, available PK and efficacy data will be performed by the IDMC once 6 patients will have completed 2 cycles of treatment, and a recommendation will be made to either:

1. Stop the cohort in case of unacceptable safety
2. Enroll 6 more patients in order to obtain more data
3. Explore an alternative QW dosing regimen

In case the IDMC deems it necessary to enroll 6 more patients (point 2 above), the IDMC will review safety, available PK and efficacy data again once 12 patients have completed 2 cycles of treatment, and will decide whether to:

1. Stop the cohort, in case of unacceptable safety

2. Explore an alternative QW dosing regimen
3. Continue with the expansion (Part 3 of the study)

The IDMC may recommend deviation from the planned patient numbers following review of the cumulative safety, efficacy and PK data. If the IDMC recommend to explore a different dose, only one new dose regimen will be investigated. In such case, the three IDMC reviews described above will occur for this new regimen.

Based on evaluation of the totality of data available from the safety run-in, Part 1 and Part 2 of the study, the IDMC will make a recommendation on continuation with enrollment of patients in either cohort A, cohort B or both cohorts.

IDMC Safety, Efficacy and PK Review - Part 3

The IDMC will continue to review safety, efficacy and PK data available after every 10 patients are enrolled and treated for at least 2 cycles.

In general, if the SRC or the IDMC determine at any time that the dose should be reduced for safety reasons, a lower dose of Debio 1562 will be explored.

5. STUDY TREATMENT

5.1. Description of Study Treatment

The investigational study drug, Debio 1562, will be provided by the Sponsor in 20 mL glass vials each containing 5 mL of a protein concentration of 8.0 mg/mL Debio 1562 [redacted]

Rituximab will be supplied as a commercially available formulation. Please refer to the rituximab prescribing information.

5.2. Debio 1562 Packaging and Labeling

The Debio 1562 container [redacted] The label [redacted] will include the necessary information as required by the country in which it is being used.

5.3. Storage, Handling, and Accountability

Specific details regarding storage and handling of Debio 1562 and rituximab can be found in the Pharmacy Manual.

Additionally, please refer to the rituximab prescribing information regarding the proper storage and handling of this drug.

Accountability and shipping documents for all drugs supplied by the Sponsor must be maintained by the Principal Investigator or designee (e.g., the study pharmacist). The Investigator or designee must maintain an accurate record of the receipt and dispensing of Debio 1562 in a drug accountability log. These records must always be available for inspection, and a copy will be supplied to the Sponsor, on request. Information recorded on these accountability and shipping documents will include quantities received, dates and amount dispensed, the recorder's initials, patient number to whom the drug was administered, lot number of drug administered, and drug lost, damaged, or destroyed.

Upon completion of the study, all Debio 1562 dispatched to a site must be accounted for and unused supplies destroyed according to the site's Standard Operating Procedures upon Sponsor approval. If the site cannot destroy onsite, return of unused supplies to the Sponsor can be arranged. The original drug reconciliation records shall be maintained at the site and a copy collected and sent to the Sponsor once a representative of the company has confirmed the drug accountability. The pharmacy shall maintain accurate records of all study drugs that have been received, stored, dispensed, destroyed, and used. The electronic Case Report Form (eCRF) shall also record details of study drug administration such as date and time of administration.

Drug accountability will be monitored regularly.

5.4. Study Treatment Compliance

Debio 1562 and rituximab supplied for the study may not be used for any purpose other than the study or administered other than as described in this protocol.

Source documents must capture the dates when drug is dispensed and the initials of the person preparing the dose as well as the volumes and doses dispensed, patient number, lot number, and expiration date if available of the drug administered.

Under no circumstances is the Investigator allowed to release Debio 1562 supplies to any physician not named as part of the study (e.g., not named in the FDA Form 1572) or to administer these supplies to a patient not enrolled in this study. If investigational supplies are to be dispensed from any facility other than that supervised directly by the Principal Investigator (i.e., hospital pharmacy, satellite pharmacy), it is the responsibility of the Principal Investigator to ensure that all Debio 1562 is maintained in the manner described in the Pharmacy Manual.

For Debio 1562, two different drug lots cannot be mixed in a single dose administration.

5.5. Assignment of Patient Number

Patient numbers are assigned in sequential order as patients sign informed consent to participate.

Patients who have consented to the study and who have received at least one dose of study treatment will be considered enrolled.

Patients who are issued a patient number, but who do not successfully complete the screening process and who do not receive a dose of study treatment will be considered a screen failure.

A patient number that has been issued for a given patient who failed screening will not be re-issued for another patient, but can be re-issued to the same patient if he/she is re-screened for the study at a later date.

5.6. Blinding

Not applicable as this is an open-label study.

5.7. Drug Preparation and Administration

Debio 1562 is an experimental anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling this compound. It is recommended that gloves and protective garments be worn during preparation. Similar precautions should be taken when handling rituximab. Refer to the Pharmacy Manual and rituximab package insert for more information.

For logistical reasons (such as holidays, weekends, etc.), changes of ± 3 days in the start of any cycle of study treatment are permitted. Similarly, intra-cycle administrations on Day 8 and Day 15 in Cohort B patient can have a window of -1 day to +3 days for logistical reasons; however, every two administrations need to have a minimal interval of 5 days.

5.7.1. Pre- and Post -Infusion Prophylaxis

Prior to receiving treatment with Debio 1562 and rituximab, patients will be given dexamethasone IV at 8 mg (or equivalent), acetaminophen PO or IV 325 – 650 mg, and an antihistamine (e.g. 25-50 mg diphenhydramine or equivalent) approximately 30-60 minutes prior to the Debio 1562 infusion. Patients will be instructed to take oral dexamethasone at 8 mg/day on Days 2 and 3, following the infusion. If any patient requires more intensive treatment to prevent infusion reaction, investigators may modify the regimen accordingly.

In patients with poor bone-marrow functional reserve or as part of the management of previously occurring cytopenias treatment (See Section 5.8.2), granulocyte colony-stimulating factor support could be used in accordance with either the American Society of Clinical Oncology (Smith 2015), or European Society of Medical Oncology guidelines (Crawford 2010), as determined by institutional or regional practice.

Any patient experiencing TLS or at risk for TLS should be managed according to institutional practice. Patients with high tumor burden and/or high circulating lymphocyte counts ($> 25 \times 10^9$/L) are at greater risk for TLS and should be adequately hydrated beginning 12 - 24 hours prior to the infusion of Debio 1562 (e.g. 2 L within 12 - 24 hours prior to infusion – roughly 170 cc every two hours).

Patients should receive prophylactic antiviral treatment as per institutional guidelines.

5.7.2. Debio 1562 Preparation

The total dose of Debio 1562 will be calculated based on each patient's body weight. The weight used for calculation should be obtained prior to first treatment and thereafter should only be modified for significant (≥ 10%) changes in body weight (not influenced by weight gain or loss attributed to fluid retention). Further information about dosing requirements is outlined in the Pharmacy Manual.

5.7.3. Rituximab Preparation

Rituximab will be prepared per label. Body weight at Cycle 1 Day 1 is to be used to calculate the body surface area (Appendix J), which will be used to determine the required rituximab dose. No dose modifications are foreseen unless the patient's body weight changes by ±10% from baseline.

5.7.4. Administration

5.7.4.1. Debio 1562

After the pre-infusion prophylaxis regimen is given, Debio 1562 will be administered as follows:

- At 0.7 mg/kg, or other applicable dose as determined by the SRC, as an IV infusion on Day 1 of a 21-day cycle for safety run-in (study Part 1);
- At 0.7 mg/kg, or other applicable dose as determined by the IDMC, as an IV infusion on Day 1 of a 21-day cycle for cohort A (study Part 2);
- At 0.4, 0.2, 0.2 mg/kg, or another applicable dosing regimen as determined by the IDMC, as an IV infusion on Day 1, Day 8 and Day 15, respectively, of a 21-day cycle for cohort B (study Part 2);
- During Part 3 of the study, Debio 1562 will be administered according to the selected dosing regimen(s) studied in Part 2.
- During the COVID-19 pandemic, patients on the Debio 1562 QW regimen can be switched to the Q3W regimen. If a switch to the Q3W regimen is considered by the treating physician to be in the best interest of a given patient to mitigate the COVID-19 risk, the following should be observed:

- the patient must terminate his/her ongoing weekly administration cycle before switching to the Q3W regimen. For instance, if the patient received his/her first weekly administration of 0.4 mg/kg (D1), he/she should continue to receive weekly treatment until the end of that cycle. Only then can the patient start the Q3W dosing regimen (0.7 mg/kg), as an IV infusion on Day 1 of a 21-day cycle – similarly as for cohort A);
- patients who switch should continue to receive the Q3W regimen, following Cohort A treatment schedule for the remainder of the study.

Debio 1562 should be administered first at Day 1 of each cycle, followed by rituximab. An IV tubing administration set with a 0.22 micron in-line filter will be used for infusion.

Initially, Debio 1562 should be administered at a rate of 1 mg/min; after a continuous 30 minutes of infusion, the rate can be increased to 3 mg/min if well tolerated. If well tolerated after a continuous 30 minutes of infusion at 3 mg/min, the rate may be increased to 5 mg/min. Subsequent infusions may be delivered at the tolerated rate. The overall length of infusion will vary depending on dose and patient tolerability; the infusion time will range from approximately 15 to 60 minutes. Following infusion, the IV line should be flushed with normal saline as needed to ensure delivery of the full dose.

Patients will be carefully observed during each infusion and vital signs taken as outlined in the Schedule of Events (Appendix A, Appendix B, Appendix C).

5.7.4.2. Rituximab

Rituximab will be administered at a dose of 375 mg/m^2 at Day 1 of each 21-day cycle , after administration of Debio 1562 (no minimum time-interval is required between finishing Debio 1562 and starting rituximab), throughout the study as follows:

- Dose 1 (Cycle 1, Day 1): infusion will be initiated at a rate of 50 mg/h and if tolerated, the rate will be increased in increments of 50 mg/h every 30 minutes up to a maximum of 400 mg/h.
- For subsequent doses, the infusion will begin at a rate of 100 mg/h and, if tolerated, the rate will be increased in increments of 100 mg/h every 30 minutes up to 400 mg/h.

Rituximab will be infused over approximately four hours.

5.7.4.3. Post-infusion monitoring period

Patients will remain in the clinic under monitoring for four hours after completion of the rituximab infusion for the first cycle. Post-administration safety monitoring could potentially be shortened (i.e. < 4 hours but at least 1 hour) following subsequent administration of rituximab, based on the judgement of the investigator. Patients receiving Debio 1562 only, i.e., on Day 8 and Day 15 for the QW dosing schedule or due to rituximab intolerability, will also remain in the clinic under monitoring for one hour for all cycles.

5.7.4.4. Clinic Visit Duration

The length of time that patients will be expected to remain in clinic for protocol procedures will vary. The two longest clinic visits (approximately nine hours) are expected to occur on:

- Day 1 in Cycles 1 and 3 during safety run-in (Part 1)
- Day 1 in Cycles 1 and 2 in cohorts A and B (Part 2 and Part 3)

5.7.5. Management of Potential Infusion-related Reactions

Despite pre-infusion prophylaxis, some patients receiving Debio 1562 or rituximab have experienced infusion-related reactions.

Mild to moderate infusion-related reactions consisting of chills and rigors have been experienced by some patients receiving Debio 1562.

Severe infusion reactions have been reported by some patients receiving rituximab. Infusion reactions consisting of fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension may typically occur within 30 to 120 minutes of beginning the first rituximab infusion and resolve with slowing or interruption of the infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion reactions is highest during the first infusion and decreased with each subsequent infusion. As such, all patients will receive pre-infusion prophylaxis. Additionally, patients will be provided oral steroids to be taken on Days 2 and 3 of each cycle.

Some patients treated with IV infusions of therapeutic drugs have experienced concurrent infusion-related reactions (refer to CTCAE Version 4.03). The signs and symptoms may vary and include for example, headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, lightheadedness, hypotension, palpitations, and somnolence. Anaphylaxis might occur at any time during an infusion. Before any infusion is started, appropriate medical personnel, medication (e.g. epinephrine, inhaled beta agonists, antihistamines, and corticosteroids), and other required resources to treat anaphylaxis must be readily available. In general, Investigators should manage acute allergic or hypersensitivity reactions according to Institutional practices. General, suggested guidelines for the management of acute infusion-related reactions and for subsequent retreatment are provided in Table 4. Delayed infusion-related reactions may occur; therefore patients should be advised to seek immediate medical treatment if symptoms newly develop and/or recur after discharge from clinic.

Patients who experience a $\geq$ Grade 2 infusion-related reaction during or immediately following administration of Debio 1562 should have blood drawn within three hours of the onset of the reaction and one week later for determination of drug concentration (PK) and antibodies to Debio 1562 (ADA) (Sections 6.1.1 and 6.2.1).

Table 4: Management Guidelines for Potential Infusion-related Reactions

Infusion Reaction CTCAE v4.03 Severity Grade	Management
Grade 1: Mild, transient reaction	• Maintain infusion rate unless progression of symptoms to ≥ Grade 2; if symptoms worsen, refer to guidelines below • Promethazine 150 mg by mouth (PO) per day (every 4 hours [Q4h]) as needed (prn) for nausea (or equivalent) • Diphenhydramine 25-50 mg PO or IV prn (or equivalent) • Methylprednisolone 125 mg (or equivalent) IV prn
Grade 2: Moderate	• Interrupt infusion and disconnect infusion tubing from patient • Promethazine 150 mg PO per day (Q4h) prn for nausea (or equivalent) • Diphenhydramine 25-50 mg PO or IV prn (or equivalent) • Acetaminophen 650 mg PO prn (or equivalent) • Methylprednisolone 125 mg (or equivalent) IV prn • After recovery from symptoms, resume the infusion at 50% of the previous rate and if no further symptoms appear, gradually increase rate of infusion (do not surpass maximum infusion rate allowed per protocol) until infusion is completed. • For subsequent dosing in future cycles, patients should be pre-medicated with Dexamethasone 8 mg PO twice daily (BID) (or equivalent) the day prior to drug administration and Acetaminophen 650 mg PO (or equivalent) and Diphenhydramine 25-50 mg PO 30-60 minutes (or equivalent) prior to dosing.
Grade 3: Severe, prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	• Stop infusion and disconnect infusion tubing from patient • Administer Diphenhydramine (25-50 mg) IV (or equivalent) • Administer normal saline, epinephrine (0.2-0.5 mL of a 1:1000 dilution [0.2-0.5 mg] subcutaneously [SC] or intramuscularly [IM]) (or equivalent) and bronchodilators (nebulized albuterol, 2.5-5 mg in 3 mL of saline) as medically indicated • Consider IV steroids (methylprednisolone (or equivalent) up to 0.5 mg/kg every 6 hours [Q6h]) to prevent recurrent or ongoing reactions • Advise patient to seek emergency treatment and notify investigator/clinic if the infusion-related symptoms recur after discharge from clinic. • Report as an SAE • Investigators should confer with the sponsor regarding retreatment of the patient. If the investigator and sponsor agree that the patient could be re-challenged, then prophylaxis for an infusion-related reaction should occur in all subsequent cycles. For this, patients should be pre-medicated with Dexamethasone 8 mg PO BID the day prior drug administration and Acetaminophen 650 mg PO and Diphenhydramine 25-50 mg PO 30-60 minutes prior to dosing.
Grade 4: Life-threatening consequences, urgent intervention indicated	• Immediately stop infusion and disconnect infusion tubing from patient • Permanently discontinue study medication treatment • Administer Diphenhydramine 50 mg IV (or equivalent) • Administer normal saline, epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg) SC or IM (or equivalent) • Administer bronchodilators (nebulized albuterol, 2.5-5 mg in 3 mL of saline) as medically indicated • Administer IV steroids (methylprednisolone up to 0.5 mg/kg Q 6h) (or equivalent) to prevent recurrent or ongoing reactions • Report as a serious adverse event • Remove patient from study.

5.8. Toxicity Management Guidelines

Dose modifications should occur based on the emerging safety profile of Debio 1562 and the known safety risks of rituximab.

Frequent AEs observed in patients receiving single agent Debio 1562 included Grade 3/4 neutropenia, febrile neutropenia, thrombocytopenia, fever and infusion reaction. The complete safety risk profile of Debio 1562is detailed in the Debio 1562 IB.

For details on the most commonly-reported toxicities associated with rituximab please refer to the rituximab label.

Table 5 should be used as a guide to help investigators assess study treatment related toxicities. Potential overlapping toxicities include fever, infusion-related reaction, and delayed-onset neutropenia. Investigators should reduce or discontinue Debio 1562 for Grade 3-4 non-hematologic toxicities based on clinical judgment, and should manage rituximab induced toxicity per label (Section 5.9).

Table 5: Debio 1562 and Rituximab Toxicities

AE	Debio 1562 (≥ 10% of patients in monotherapy)	Rituximab (per label)
Fever	●	●
Infusion related reaction	●	●
Neutropenia	●	
Delayed onset Neutropenia		●
Anemia	●	
Asthenia	●	
AST/ALT increase	●	
Decreased appetite	●	
Diarrhea	●	
Dyspnoea	●	
Fatigue	●	
Febrile neutropenia	●	
Hypokalaemia	●	
Muscle weakness	●	
Nausea	●	
Oedema – peripheral	●	
Thrombocytopenia	●	
Bowel obstruction and perforation		●
Cardiac arrhythmias		●

AE	Debio 1562 (≥ 10% of patients in monotherapy)	Rituximab (per label)
Chills		•
Infection		•
Interstitial pneumonitis		•
Lymphopenia		•
Mucocutaneous reactions		•
Progressive multifocal leukoencephalopathy		•
Reactivation of hepatitis B		•
Renal toxicity		•
Severe infusion related reaction		•
Tumor Lysis Syndrome		•

5.8.1. Monitoring and Management of Tumor Lysis Syndrome (TLS)

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, can occur within 12 - 24 hours after the first infusion with rituximab and may be fatal. Signs of TLS have also been observed in patients receiving Debio 1562. Patients with high tumor burden and/or high circulating lymphocyte counts ($> 25 \times 10^9$/L) are at greater risk for TLS and should be adequately hydrated beginning 12 - 24 hours prior to the infusion of Debio 1562 (e.g. 2 L within 12 - 24 hours prior to infusion – roughly 170 cc every two hours).

Any patient experiencing TLS or at risk for TLS should be managed according to institutional practice.

5.8.2. Monitoring and Management of Cytopenias

Cytopenias (neutropenia and thrombocytopenia) have been observed in patients treated with rituximab as well as Debio 1562. In patients receiving rituximab monotherapy at 375 mg/m^2 IV weekly for relapsed or refractory low-grade or follicular NHL, Grade 3-4 neutropenia occurred in 6% and grade 3-4 thrombocytopenia occurred in 2% (Rituxan® (rituximab) Package Insert 2014). In NHL patients who received Debio 1562 monotherapy at the dose of 0.7 mg/kg, Grade 3 neutropenia was the highest grade reported.

Patients experiencing severe cytopenia should follow the recommendations of dose-modification and additional corrective/preventive measures (such as granulocyte colony-stimulating factor [G-CSF]) present in this protocol (Section 5.9). The type of G-CSF support will be determined by the study physician, as well as the clinical judgement to decide the duration of such treatment.

If a patient develops Grade 4 thrombocytopenia lasting >7 days, study treatment should be terminated and the toxicity should be followed until resolution or stabilization (Section 5.9.2).

5.8.3. Monitoring and Management of Rituximab-associated Bowel Obstruction and Bowel Perforation

Patients receiving rituximab should be continually monitored for signs or symptoms of bowel obstruction and bowel perforation. Perforations have been shown to occur at higher frequency in patients who have received radiation therapy. Signs and symptoms of bowel obstruction include intermittent abdominal pain, nausea, vomiting, diarrhea, constipation, and abdominal distension. Signs and symptoms of bowel perforation include fever, nausea, vomiting, hematemesis, chills, and severe stomach pain. Patients are advised to notify their treating physician immediately if they experience any of the signs or symptoms described above. If a positive diagnosis of gastrointestinal perforation is made, rituximab should be immediately discontinued and the patient should be treated as per institutional guidelines.

5.8.4. Monitoring and Management of Rituximab-induced Progressive Multifocal Leukoencephalopathy (PML)

John Cunningham virus infection resulting in PML and death can occur in patients receiving rituximab and it has been shown to occur more frequently in patients who received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab. Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. If a positive diagnosis of PML is made, rituximab should be discontinued.

5.8.5. Monitoring and Management of Rituximab-induced Renal Toxicity

Severe, including fatal, renal toxicity has been shown to occur after rituximab administration in patients with NHL. Renal toxicity has occurred in patients who experience TLS. Patients should be monitored closely for signs of renal failure, including but not limited to weakness, shortness of breath, confusion, metallic taste in mouth, fluid retention, nausea, flank pain, seizures, and decreased urine output. Rituximab should be discontinued in patients experiencing rising serum creatinine or oliguria. Patients experiencing renal failure should be managed according to institutional guidelines.

5.8.6. Monitoring of Rituximab-induced Cardiovascular Toxicity

Cardiac toxicity has been reported in patients receiving rituximab. Cardiac monitoring should be performed during and after all infusions of rituximab for patients who develop clinically significant arrhythmias. Rituximab should be discontinued in patients experiencing serious or life-threatening cardiac arrhythmias. Patients experiencing cardiac toxicity should be managed according to institutional guidelines.

5.8.7. Monitoring of Rituximab-induced Serious Infections

Serious, sometimes fatal bacterial, fungal, or viral (new or reactivated) infections have been shown to occur in patients receiving rituximab, during therapy and up to one year following the completion of rituximab-based therapy. Reported new or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus,

and hepatitis B virus (HBV) and hepatitis C virus. Patients should be monitored for signs and symptoms of infections. Rituximab should be discontinued in patients experiencing serious infections; patients should receive anti-infective therapy as per institutional guidelines.

5.8.7.1. Monitoring and Management of Rituximab-induced HBV Reactivation

HBV reactivation with fulminant hepatitis, hepatic failure, and death has been shown to occur in patients with hematologic malignancies who received rituximab. The median time to diagnosis of hepatitis was approximately four months following the first dose of rituximab and approximately one month after the last dose. Known HBV carriers can participate in this study provided they are HBsAg PCR negative and are receiving antiviral therapy. Rituximab should be discontinued in patients who develop viral hepatitis; patients should receive appropriate treatment including antiviral therapy as per institutional guidelines.

5.8.8. Monitoring of Rituximab-induced Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, have been shown to occur in patients treated with rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has varied from 1 to 13 weeks following rituximab exposure. Rituximab should be discontinued in patients experiencing severe mucocutaneous reactions.

5.9. Debio 1562 and Rituximab Dose Modifications

5.9.1. Delay or Skip Dosing of Study Treatment

In order for a patient to receive any study treatment (Debio 1562 alone or Debio 1562 and rituximab), the following re-treatment criteria must be met.

- ANC must be $\geq 1.0 \times 10^9$/L ($1000/mm^3$)
- Platelet count must be $\geq 50 \times 10^9$/L ($50{,}000/mm^3$)
- All non-hematologic toxicities must be $\leq$ Grade 2 (except alopecia) or returned to baseline

Cohort A and B: If the retreatment criteria are not met on Day 1 of a given cycle, the patient should be re-evaluated within 48-72 hours, and dosing should be delayed until the criteria are met.

If the retreatment criteria are met within 14 days, study treatment should resume at planned or reduced dose (see Section 5.9.2), and the study physician may opt for the routine administration of secondary prophylaxis with G-CSF during following cycles.

If the retreatment criteria are met within 14-21 days, study treatment should resume at planned or reduced dose (see Section 5.9.2), and secondary prophylaxis with G-CSF should be administered if the delay was due to unmet hematological parameters.

If dosing is delayed for > 21 days due to unmet retreatment criteria, both study treatments should be discontinued (see Section 5.9.2).

Cohort B: If the retreatment criteria are not met on Day 8 or Day 15 of a given cycle, dosing of Debio 1562 should be skipped on that visit, secondary prophylaxis with G-CSF will be indicated

and the retreatment criteria will be re-evaluated at the next visit when infusion is planned to occur. If the retreatment criteria are not met on Day 1 of the next cycle, the rules described above for the delay on Day1 of any given cycle will apply.

5.9.2. Dose Modifying Events (DME)

Dose Modifying Events (DMEs) are defined as any adverse events that require dose reduction or discontinuation of the study treatment.

5.9.2.1 Adverse Events Requiring Permanent Study Treatment Discontinuation

Both Debio 1562 and rituximab should be permanently discontinued in the case of the following treatment-related events:

- ≥ Grade 3 cardiac event
- ≥ Grade 3 cutaneous reactions related to rituximab treatment
- Other non-hematologic events of Grade 4 severity
- Grade 4 thrombocytopenia lasting >7 days
- ≥ Grade 3 neuropathy
- Dose delay > 21 days due to unmet retreatment criteria

Rituximab should be permanently discontinued in patients experiencing the AEs listed in Table 6.

Table 6: Adverse Events Requiring Permanent Discontinuation of Rituximab

Severity Grade (CTCAE v4.03 Grade)	Adverse Event
Any Grade	Bowel Perforation
Grade ≥ 3	Cardiac Arrhythmias
Any Grade	Hypersensitivity and/or Allergic Reactions to rituximab
Grade ≥ 3	Infections
Grade ≥ 3	Mucocutaneous Reactions
Any Grade	Progressive Multifocal Leukoencephalopathy (PML)
Grade ≥ 3	Renal Failure
Any Grade	Viral Hepatitis

5.9.2.2 Adverse Events Requiring Dose Reduction

Rituximab dose reductions are not allowed. If patients do not tolerate treatment with rituximab, they may continue on Debio 1562 alone.

For **Cohort A**, dose reduction of Debio 1562 will occur as follows:

- 0.7 mg/kg → 0.4 mg/kg

For **Cohort B**, dose reduction of Debio 1562 will occur as follows:

- 0.4 mg/kg → 0.2 mg/kg
- 0.2 mg/kg → 0.1 mg/kg

Dose of Debio 1562 should be reduced in patients experiencing the AEs below:

Second occurrence of hematologic events:

- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 thrombocytopenia associated with bleeding that requires transfusion
- Grade 4 thrombocytopenia lasting < 7 days
- ≥ Grade 3 febrile neutropenia

Non-hematologic events:

- Grade 3 nausea, vomiting or diarrhea, lasting more than 48 hours, despite the use of optimal supportive care
- Other non-hematologic toxicities ≥ Grade 3 except for the following:
    - AEs related to underlying disease
    - Isolated, asymptomatic Grade 3 laboratory biochemistry abnormalities that last for ≤ 7 days or have not been optimally managed

Other events:

- Two dose delays (on the first day of two consecutive cycles) due to unmet retreatment criteria

Dose of Debio 1562 can be reduced for only once for a given patient, and it cannot be re-escalated. If a patient cannot tolerate treatment with Debio 1562, both Debio 1562 and rituximab should be discontinued.

5.10. Removal of Patients from the Study

The patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Patients may be discontinued from study treatment, and continue to be followed per protocol, or they may be removed from the study altogether.

5.10.1. Discontinuation from Study Treatment

Patients may be withdrawn from study treatment at any time at their own request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety or non-compliance to the protocol.

Reasons for permanent discontinuation of both study drugs may include the following:

- Radiological PD
- Clinical progression
- Withdrawal of consent to study treatment, but agrees to the protocol-defined follow up

- AE
- Investigator decision
- Study terminated by Sponsor
- Major protocol deviation or non-compliance
- Patient becomes pregnant
- Death
- Other

Depending on the disease state and the tumor response, patients who permanently discontinue study treatment will enter into the response and survival follow-up portion of the study: patients who had discontinued study treatment due to PD will be followed-up for survival every 12 weeks (± 4 weeks) for up to one year from the last patient's first dose (Cycle 1 Day 1); Patients who discontinued the treatment for reasons other than PD (including treatment completion) will be followed by radiographic assessment every 12 weeks (± 4 weeks) from the time of the patient's last on-study tumor assessment until documentation of PD or beginning of subsequent anti-cancer therapy (regimen and start date to be recorded in the EDC). After the response follow-up, patients will enter into the survival follow-up. Patients will not be required to visit the clinic for survival follow-up.

5.10.2. Discontinuation from the Study

Reasons for patient discontinuation from the study are as follows:

- Withdrawal of consent to study treatment and follow up
    - If a patient withdraws from the study, and also withdraws consent for disclosure of future information, no further study-specific evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before each withdrawal of consent.
- Lost to Follow-up
    - If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. Every effort should be made to document patient outcome.
- The study was terminated by the Sponsor
- Investigator Decision
- Death
- Other

5.11. Period of Observation

For purposes of this study, the period of safety observation extends from the time the patient signs the study consent until the final safety follow-up visit.

5.12. Concomitant Medications and Procedures

All concomitant medications and supportive therapy taken within four weeks before Cycle 1, Day 1 until the end of the period of safety observation must be recorded on the appropriate eCRF. The identity of all medications, dosage, and route of administration, frequency, duration of administration, and indication for use will be recorded in the appropriate sections of the eCRF.

5.12.1. Antineoplastic Therapy

Other chemotherapy, investigational agents, or biologic therapy will not be permitted during the study treatment.

Palliative radiotherapy for local peripheral metastases not being used on target lesions is allowed. However, the need for such therapy may be an indication of disease progression and should be discussed with the Sponsor prior to implementation. Radiotherapy for central metastases (e.g. vertebral, mediastinal) will not be allowed; the need for such radiotherapy while on therapy will be seen as an indication of disease progression and the patient should be withdrawn from therapy.

5.12.2. Hematopoietic Growth Factors

Patients receiving recombinant erythropoietin or darbepoietin alfa prior to study start may continue to receive pre-treatment doses. The use of erythropoietic growth factors may be implemented at the discretion of the treating physician or Investigator. The use of granulocyte growth factors may be implemented as specified in Section 5.8.2.

5.12.3. Bisphosphonates

Bisphosphonates are permitted if a patient was receiving ongoing bisphosphonate therapy at time of screening and will continue on a stable regimen throughout protocol therapy. The need to start bisphosphonates while on therapy will be seen as an indication of disease progression and the patient should be withdrawn from therapy.

5.12.4. Anticoagulants

Therapeutic doses of anticoagulation therapy are permitted, as long as platelets $\geq 100 \times 10^9$/L ($100{,}000/mm^3$) at baseline and the patient does not have a history of $\geq$ Grade 2 bleeding while taking anticoagulation therapy and the patient has not been transfused within previous 10 days.

Prophylactic use of low dose anticoagulants for maintenance of line patency is also allowed.

5.12.5. Antivirals

While being treated with rituximab, patients are to receive antiviral prophylaxis throughout the study per institutional guidelines. Type and dosing of such will be implemented at the discretion of the treating physician or investigator.

5.12.6. Immunizations

Vaccination with live viruses (e.g., measles, mumps, rubella, or polio) is prohibited. Vaccinations with non-live organisms (e.g., flu or tetanus) may not be effective while receiving rituximab.

5.12.7. Other Concomitant Medications

Medications for the treatment of AEs or cancer symptoms, e.g. packed red blood cells and pain medications, are allowed. Prophylactic use of steroids and/or antihistamines are required for primary prophylaxis against infusion reaction. Similarly, the use of prophylactic antibiotics are permitted if needed to mitigate risk of infection. Additional medications (not addressed above) used to treat underlying medical conditions at study entry including anti-emetics and anti-diarrheals will be allowed to continue. Antibody-maytansine conjugates with noncleavable thioether-linked DM1 as the cytotoxic agent such as Debio 1562 are not expected to have a potential for drug-drug interaction with any of the major human CYPs (see IB for additional information).

5.13. Overdose and Medication Error

Overdose – There is no known treatment/antidote available for Debio 1562 or rituximab. Supportive measures should be instituted if an instance arises in which a patient suffers an overdose of study drug.

Medication Error – Any mistake made in prescribing, dispensing, administering and/or use of Debio 1562 or rituximab must be reported to the sponsor immediately and recorded on the eCRF.

6. PHARMACOKINETIC [redacted]

6.1. PK Assessments

Blood samples for PK measurements will be collected from all patients (Appendix D, Appendix E, Appendix F). Details of sample preparation and shipping are provided in the Laboratory Manual.

Debio 1562 PK – Patient plasma samples will be analyzed to measure conjugate, total antibody and/or naked antibody, free DM1 and bound DM1; additional metabolites may be evaluated.

Rituximab PK - total rituximab will be measured.

Blood samples for Debio 1562 and rituximab PK measurements in Part 1 and Part 2 of the study will be collected as described in Appendix D, Appendix E, Appendix F.

In part 3 of the study, if the Q3W regimen is continued, the PK sampling schedule will be the same to that in the Cohort A of Part 2; if the QW regimen is continued, the PK sampling schedule will be the same to that in the Cohort B of Part 2. However, the IDMC may recommend some changes in the sampling scheme following review of trial data.

At the end of treatment (EOT) and 30-day safety follow-up visit, blood draws will be taken for PK assessment and for anti-drug antibodies (ADA).

In patients who exceptionally continue the study treatment beyond Cycle 6, the last PK sample will be taken at C7D1 at pre-dose blood draw instead of at the EOT visit. For patients already beyond C7D1 after amendment #5, the last PK sample will be taken at D1 of the next possible subsequent cycle at pre-dose blood draw instead of at the EOT visit. No additional samples will be taken at 30-day follow-up visit.

6.1.1. Unscheduled Visits

Any patient who experiences a ≥ Grade 2 infusion-related reaction during the administration of Debio 1562 will have blood drawn within three hours of the onset of the reaction and one week later for determination of drug concentration to Debio 1562.

PK samples may also be obtained at any time during the treatment period for assessment of treatment-related AEs, if deemed appropriate by the Investigator and Sponsor.

6.2. Immunogenicity Assessments

The potential immunogenicity against Debio 1562 or DM1 or rituximab will be assessed in pre-dose plasma samples at Day1 and at any time point for the other days of PK evaluation in all cycles as outlined in Section 6.1, and at any time point for samples taken at the EOT and 30-day safety follow-up visit (Appendix D, Appendix E, and Appendix F).

In patients who exceptionally continue the study treatment beyond Cycle 6, the last sample for ADAs will be taken at C7D1 at pre-dose blood draw, instead of at the EOT visit. For patients already beyond C7D1 after amendment#5, the last ADA sample will be taken at D1 of the next possible subsequent cycle at pre-dose blood draw instead of at the EOT visit. No additional samples will be taken at the 30-day follow-up visit.

The study will evaluate the potential impact of immunogenicity on PK, safety, and anti-tumor activity of Debio 1562 and total K7153A antibody. In case of non-per protocol rituximab exposure or safety findings, the potential impact of immunogenicity on rituximab PK could be assessed.

Details of sample preparation and shipping are provided in the Laboratory Manual.

6.2.1. Unscheduled Visits

Any patient who experiences a ≥ Grade 2 infusion-related reaction during the administration of Debio 1562 will have blood drawn within three hours of the onset of the reaction and one week later for determination of ADA formation.

[redacted]

7. TRANSLATIONAL RESEARCH STUDIES

[redacted]

The exploratory evaluations will be reported separately.

8. STUDY PROCEDURES

The schedule of clinical [redacted] study assessments and procedures is detailed in the Schedules of Events (Appendix A, Appendix B, and Appendix C) and the schedule of PK and immunogenicity assessments are detailed in Appendix D, Appendix E, and Appendix F.

8.1. Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

8.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be assessed during screening and again on Cycle 1 Day 1 prior to dosing.

8.3. Confirmation of Disease Diagnosis

At screening, disease diagnosis, the stage at original diagnosis, and current disease status will be confirmed in accordance with the Ann Arbor staging criteria (Appendix K, Armitage 2005).

8.4. Demographic/Medical History

The age, race, and gender of the patient are to be recorded during screening.

During the Screening period, a complete medical history for all medically relevant conditions will be compiled for each patient.

8.5. Prior anti-cancer treatment for Lymphoma

All prior anti-cancer therapies for the treatment of lymphoma must be recorded in the EDC: grouping if possible the individual agents belonging to the same treatment regimen (e.g. R-CHOP, R-ICE, R-Gemox, etc), the maintenance therapy if any, with indication of the starting and end-dates, the best response achieved, and the primary reason for discontinuation if applicable. The end-date of the last treatment regimen and the date of the subsequent disease progression must be available. If applicable, the high-dose therapy and the bone marrow transplantation should be described as part of the same regiment. Reason for patients' ineligibility for HA-ASCT should be recorded as well.

8.6. Vital Signs

Vital signs including blood pressure, heart rate, temperature, and respiratory rate will be measured at the times specified in the Schedule of Events (Appendix A, Appendix B and Appendix C).

8.7. Physical Examination, Weight and Height

Physical examination, height (screening only) and weight must be performed as indicated in the Schedule of Events (Appendix A, Appendix B and Appendix C). A complete physical examination including assessments of general appearance, skin, head (eyes, ears, nose, and throat), neck, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological system will be

completed at screening and EOT. Directed physical examinations will be completed at additional time points as specified in the Schedule of Events.

8.8. Assessment of Health-related Quality of Life

In Part 2 and Part 3 of the study, HRQoL will be assessed at Day 1 of each cycle (before Debio 1562 infusion), at the EOT visit and at the 30-day safety follow-up visit (Appendix B and Appendix C). The FACT-Lym instrument will be used and will be self-administered via pen and paper. The FACT-Lym is a standardized measure of HRQoL specific to patients with NHL. It is comprised of the Functional Assessment of Cancer Therapy-General version 4 (27 items), scored in four domains (Physical well-being: 7 items; Social/Family well-being: 7 items; Emotional well-being: 6 items; Functional well-being: 7 items), and the FACT-Lymphoma Subscale, reflecting Lymphoma specific concerns (15 items).

In patients who exceptionally continue the study treatment beyond Cycle 6, the last HRQoL assessment will be performed at C7D1 before infusion instead of at EOT visit, and no additional HRQoL assessment will be completed at the 30-day follow-up visit.

8.9. Electrocardiogram (ECG)

A standard 12-lead ECG will be performed as outlined in the Schedules of Events (Appendix A, Appendix B and Appendix C).

8.10. Laboratory Assessments

Laboratory assessments will be performed as outlined in the Schedules of Events (Appendix A, Appendix B and Appendix C) and as clinically indicated.

Note that prior to each administration of Debio 1562, laboratory results must be reviewed to evaluate for potential toxicity.

Clinical laboratory tests will include the following:

8.10.1. Hematology

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Platelet count
- Red blood cell (RBC) count
- WBC count with differential

8.10.2. Serum Chemistry

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- ALT; SGPT
- AST; SGOT
- Lactate dehydrogenase (LDH)
- Magnesium
- Phosphorus
- Potassium (K)

- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Chloride (Cl)
- Creatinine
- Glucose
- Sodium (Na)
- Total bilirubin
- Total protein
- Uric acid
- Immunoglobulin levels (IgG, IgA, IgM)

8.10.3. Urinalysis

- Appearance, specific gravity and pH
- Semi-quantitative dipstick evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood
- Microscopic examination of sediment to be performed if urinalysis is positive for WBC, proteins or blood

8.10.4. Coagulation

- Prothrombin time (PT) or INR
- Activated partial thromboplastin time (aPTT)

8.10.5. Viral Serology

Patients will be tested during screening for HBsAg.

8.11. Pregnancy Screen

All female patients of child-bearing potential will complete a serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy test (as Institutional or Country requirements dictate) during screening and at time points specified in the Schedules of Events (Appendix A, Appendix B and Appendix C). The Sponsor will notify investigators where country-specific pregnancy testing requirements are requested by the National Health Authority. If the test is performed within three days prior to start of study treatment, it need not be repeated on Day 1 of Cycle 1. The pregnancy test result must be negative for the patient to be enrolled and to receive the study drug.

If a female patient becomes pregnant while participating in this study, the Investigator and Sponsor must be informed immediately and the patient will be withdrawn from study treatment if the pregnancy is confirmed (Section 9.2.2).

Female patients who are not of childbearing potential are defined those meeting at least one of the following criteria:

1. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
2. Have medically-confirmed ovarian failure;
3. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause;

status may be confirmed by having a serum follicle stimulating hormone level within the laboratory's reference range for postmenopausal women.

8.12. B-symptom assessment

B-symptoms (unexplained fevers [body temperature of > 38° Celsius], drenching night sweats and/or weight loss greater than 10% of body weight) will be documented at time points specified in the Schedule of Events (Appendix A, Appendix B and Appendix C).

8.13. Eastern Cooperative Oncology Group Performance Status

ECOG performance status (Appendix H) will be assessed during screening and at other times specified in the Schedule of Events (Appendix A, Appendix B and Appendix C). An assessment is not necessary on Day 1 of Cycle 1 if the screening assessment was obtained within three days prior to Day 1.

8.14. Radiologic Imaging and Tumor Response Assessment

Tumor response assessment will be based on the 5-point scale per the Lugano classification of response assessments of Hodgkin and NHL (Cheson 2014).

Radiographic tumor evaluation by computed tomography (CT) or positron-emission tomography (PET)-CT scan of chest, neck, abdomen, and pelvis will be performed within 28 days prior to first dose of study treatment. The anatomical regions to be assessed radiographically post baseline will be determined individually by extent of disease. Though less preferred, a MRI is acceptable. Patients with FDG-avid disease will be followed by [^{18}F]-FDG-PET scan. Repeat assessments will be performed every 6 weeks ± 1 week, beginning at Cycle 1, Day 1 and will not shift as a result of delays in study treatment.

Whenever possible, the same radiographic scan assessment used at screening (e.g., PET-CT) should be used at all subsequent radiographic evaluations.

Response Follow-up: Patients who have discontinued study treatment for reasons other than PD will be followed by radiographic assessment every 12 weeks (± 4 weeks), beginning from the time of the patient's last on-study tumor assessment, until documentation of PD, or beginning subsequent anti-cancer therapy or death.

For patients who are exceptionally granted continued study treatment after completion of 6 cycles, repeat radiographic tumor response assessments can be performed as per local institutional care practice. Ideally, repeat assessments should continue at 6-week (± 1 week) intervals and should not be longer than 12-weeks (± 4 weeks). Periodic tumor assessment will be conducted using the same imaging modality of prior cycles of treatment until PD, start of any new anti-cancer therapy, or death.

8.15. Bone Marrow Assessment

If applicable, a bone marrow assessment will be performed within three months prior to the first dose. A repeat bone marrow biopsy or aspirate will be required for patients with bone marrow infiltration at baseline who have a CR by imaging and physical examination and will, in case possible and deemed acceptable by the Investigator, be performed every 6 weeks as clinically

indicated. In order to better understand the effect of Debio 1562 on WBCs, bone marrow biopsies/aspirates may also be requested for those patients who experience Grade 4 cytopenias.

8.16. Tumor Biopsy

Patients must provide a fresh or archived tumor biopsy sample reflecting their DLBCL disease. If the tissue biopsy is older than 18 months and a fresh one cannot be available, patient should provide FNA samples as described in the lab manual. De-identified pathology reports should be included with sample shipment to the Sponsor or designee. Addendums to pathology reports should be shared with the Sponsor or designee as soon as they are available. If a patient has a tumor biopsy obtained any time while on study, slides may be requested to be sent to the Sponsor for further [redacted] testing or testing for the presence of Debio 1562 or DM-1 in the sample; the pathology report for such a sample should also be shared with the Sponsor. If there is no medical urgency, the timing of the biopsy or surgical operation relative to the administration of Debio 1562 and the nature of the sample to be given to the Sponsor should be coordinated with the Sponsor, in order to enable observation of the drug and/or its components in the tumor. Pathology reports performed on older biopsies of the patient should be shared with the Sponsor or designee when available.

Details of sample preparation and shipping of tumor biopsies are described in the Laboratory Manual.

[redacted]

9. ASSESSMENT OF SAFETY

9.1. Recording Adverse Events and Serious Adverse Events

AEs (including SAEs) will be documented on the AE eCRF and monitored continuously throughout the study from the time informed consent is obtained until 30 days after the patient's last study treatment or until the event has resolved or stabilized or an outcome has been reached, whichever comes first.

For patients who discontinue study treatment due to a study-related AE, the reporting time-period may be extended. These patients must be followed at least once a week for four weeks, and subsequently at 4-week intervals until resolution or stabilization of the AE or laboratory abnormality, whichever comes first (Section 5.10.1).

If the Investigator considers it necessary to report an AE considered study drug related in a patient occurring after the end of study, he or she should contact the Sponsor to determine how the AE should be documented and reported.

9.1.1. Definition of Adverse Events

9.1.1.1. Adverse Event (AE)

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. AEs include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight

Note that PD should not be reported as an AE.

Throughout the study, the Investigator must record all AEs which occur in a patient from the time that informed consent is obtained until 30 days after last study treatment on the AE CRF, regardless of the severity or relationship to study drug. The Investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. AEs may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

In addition, AEs may also include laboratory values that become significantly out of range. Such abnormal laboratory values or test results constitute AEs if they induce clinical signs or symptoms, i.e., are considered clinically significant (e.g., a clinically significant AE resulting in study

discontinuation constitutes in and of itself an SAE), or require therapy (e.g., any hematologic abnormality that requires transfusion or granulocyte growth factor treatment); and should be recorded on the AE eCRF under the signs, symptoms or diagnosis associated with them. For abnormal laboratory values that qualify as a DME, patients must have an evaluation within 48-72 hours, and then followed until return to baseline or stabilization, whichever comes first.

An AE will be considered to be a TEAE if it begins or worsens on or after the first dose of Debio 1562 or rituximab, whichever occurs first, and before the 30-day following the last dose of Debio 1562 or rituximab, whichever occurs last.

9.1.1.2. Serious Adverse Event (SAE)

A SAE is any AE occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Note that hospitalization is defined as admission to treat a clinical AE. The following events would not be considered hospitalizations for SAE reporting purposes: 23-hour hold for observation, admission to a hospice facility or nursing home, respite care, outpatient surgery, social admission (e.g. a patient who has nowhere to sleep) or admission not associated with a precipitating clinical AE (e.g. elective or pre-planned surgery, or in-patient administration of subsequent chemotherapy, etc.).

All AEs will be evaluated according to version 4.03 of NCI CTCAE. If the AE is not listed in the CTCAE version 4.03, it should be graded for severity based on the description given in Table 7.

Table 7: Adverse Event Severity

Severity	Definition
Grade 1 (Mild)	No limitation of usual activities.
Grade 2 (Moderate)	Some limitation of usual activities.
Grade 3 (Severe)	Inability to carry out usual activities.
Grade 4 (Life-threatening or disabling)	Immediate risk of death.
Grade 5 (Fatal)	Resulting in death

Relationship of an AE or SAE to study medication is to be determined by the Investigator based on the definitions in Table 8. Relationship should be attributed not only to the combination regimen, but also to each drug within the combination regimen.

Table 8: Adverse Event Relatedness

Relationship to Product(s)	Definition
Not Related	No relationship between the event, including laboratory test abnormality and the administration of study drug. There is no temporal relationship and there is unambiguous evidence supporting another cause.
Unlikely Related	A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration which makes a causal relationship improbable, and in which other drugs/chemicals or underlying disease provide plausible explanations.
Possibly Related	A clinical event, including laboratory test abnormality with a reasonable time sequence to administration of study drug, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of study drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition. The association of the clinical event/laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely Related	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to administration of study drug, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs (effective September 16, 2013): http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf	

9.2. Recording Adverse Events

9.2.1. Reporting Serious Adverse Events

Any SAE, regardless of relationship to study medication, which occurs in a patient from the time informed consent is obtained until 30 days after the last study treatment, should be recorded by the clinical site on an SAE Report form. This reporting requirement also includes SAEs that are attributed to a study procedure performed during the screening period (from the time of consent until the time of first dose of study treatment). The SAE must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the study treatment (Debio 1562 and rituximab). The Investigator will promptly supply all information identified and requested by the Sponsor (or Contract Research Organization [CRO]) regarding the SAE.

The Investigator must report the SAE to the Sponsor's Medical Director or designee. The SAE Report form must be completed and submitted within 24 hours of the Investigator's learning of the event to the contact persons listed in the Study Manual provided to each site and maintained in the Investigator study files. Any follow-up information must also be completed on an SAE Report form and submitted to the same contacts.

When reporting SAEs, the following additional points should be noted:

- The underlying diagnosis or syndrome should be reported as the primary SAE term, rather than the signs or symptoms (signs and symptoms may be described in the narrative).
- Progression of disease should not be reported as an SAE; any serious medical event/condition that results from progression of underlying disease should be reported as the SAE.
- Death should not be reported as an SAE, but rather as an outcome of a specific SAE, unless the event preceding the death is unknown. In these exceptional cases, death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.

It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any Council for International Organizations of Medical Sciences (CIOMS) or MedWatch report that has been submitted to the appropriate national regulatory agencies as notification of a suspected unexpected serious adverse reaction (SUSAR). The Investigator (or Sponsor or Sponsor's representative if so designated) must promptly report all SUSARs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for review in accordance with national regulations. IRB/IEC notification of the SUSAR may take the form of a submission of a copy of the CIOMS/MedWatch report or other format accepted by the IRB/IEC. A copy of the CIOMS/MedWatch report and notification to IRB/IEC should be retained in the site's study files.

In addition to CIOMS/MedWatch reports, the Sponsor will also notify the Investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication, through annual updates to the Debio 1562 IB.

Disease progression and/or progression of the disease under study are anticipated occurrences in oncology drug development, and as such, are considered expected as per the current IB for the

compound. If a patient expires from progression of disease and/or from the disease under study during the period of obligation to report SAEs, disease progression and/or progression of the disease under study with a fatal outcome do not need to be reported as SAEs. The applicable protocol eCRF page(s) pertaining to death should be appropriately completed however, as disease progression.

9.2.2. Reporting a Pregnancy

Pregnancy and lactation are exclusion criteria. The Sponsor must be notified in the event of a pregnancy, reported by a patient or patient's partner, during the course of the study and through 30 days after the patient's last dose of Debio 1562. Pregnancy is not to be reported as an AE. However, SAEs associated with or resulting from the pregnancy should be recorded, and the pregnancy reporting form should be used to report the pregnancy. The pregnancy will be followed through delivery or final outcome.

10. STATISTICS

All statistical analyses will be performed using the most recently released and available SAS statistical software, unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be calculated. For continuous variables, the sample size (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated. There will be a summary of patient disposition, patient demographics, and baseline characteristics. PK parameters will be computed and presented in tables and listings. Plasma concentrations will be presented in graphs for each patient and by cohorts. Latest version of SAS or WinNonlin will be used for the PK analyses.

A SAP will fully describe the planned analyses for this study, including sensitivity analysis related to patients who might switch dose regimen during the COVID-19 pandemic. Analyses will be performed the safety population, the efficacy evaluable population or the PK population. All analyses for anti-tumor activity will use the first dose date as the start time.

The primary endpoints of this study are:

- TEAEs, clinically-significant changes in clinical laboratory test results, ECG, and vital sign measurements;
- ORR defined as the proportion of subjects with a best overall response of PR or CR as assessed by the 2014 Lugano classification of response assessments of NHL.

The primary analysis will be conducted after all enrolled patients have reached their 3rd on-treatment scheduled response assessment or have discontinued from treatment. The final analysis will be triggered one year after the last accrued patient's first dose date. In the exceptional case that after the final analysis a patient(s) might continue to receive study treatment under the protocol, any subsequent data generated from this patient(s) will be summarized in an addendum report to be issued after the last treatment of the last patient.

As the recruitment continued between completion of the safety run-in part of the implementation of the protocol amendment #3 (when cohort B of QW was introduced), a number of NHL patients have received Debio 1562 0.7mg/kg Q3W in combination with rituximab. Patients presenting with relapsed DLBCL as per current inclusion criteria will be analyzed together with the patients enrolled in cohort A. All other patients (i.e. refractory DLBCL, or other forms of NHL) enrolled in this period will be analyzed separately.

[redacted]

[redacted]

10.2. Analysis Populations

The following analysis populations will be considered:

- **Screened Population:**

  All subjects screened will be part of the screened population.

- **Safety Population:**

  All subjects who receive at least one dose Debio 1562 will be part of the safety population. Reporting in the safety population will be done against the actual treatment received.

- **Efficacy Evaluable Population:**

  All subjects who received at least one dose of Debio 1562 and rituximab, and had both baseline and post-baseline evaluable disease will be part of the efficacy evaluable population. Reporting in the efficacy evaluable population will be done against the assigned treatment.

- **PK Population:**

  All subjects who receive one dose of study drug and have at least one PK concentration result available (Debio 1562 or rituximab concentration, including value below limit of quantification). Reporting in the PK population will be done against the actual treatment received.

10.3. Pharmacokinetic (PK) Analyses

PK parameters that will be evaluated include, but are not limited to: C_{max}, T_{max}, Terminal half-life ($t_{1/2}$), V_{ss}, CL, AUC_{0-t}, AUC_{inf}. These will be derived from plasma concentrations of Debio 1562, total and/or naked humanized CD37 mAb (K7153A), DM1 (free and bound), as well as potential catabolites, and total rituximab, using the actual sampling times. Concentration data and all PK parameters will be listed per patient and summarized descriptively per dose. If appropriate, non-compartmental (Model independent) methods will be used to compute the PK parameters using the latest version of SAS or Phoenix WinNonlin software.

The PK disposition of Debio 1562 (and rituximab, if deemed appropriate) will also be described through a population PK approach using NONMEM (ICON Solutions). This evaluation will be reported separately.

Individual plasma concentration versus actual time profiles for each patient and treatment, as well as the mean (+/- standard deviation) plasma concentration versus scheduled time profiles for each dose level, will be presented graphically on normal and semi-log scale.

10.4. Safety Analyses

AEs, concomitant medication, and results from physical examination will be listed.

AEs will also be coded with the Medical Dictionary for Regulatory Activities (MedDRA; version 19.0 or later) and summarized per System Organ Class (SOC) and preferred term.

Concomitant medications will be coded using the WHO Drug Dictionary (WHO-DD; June 1, 2012 or later version). A dictionary listing of all unique concomitant medications used in the study will be provided.

All hematology, blood chemistry, vital signs, and ECG results will be listed per patient for each assessment and descriptive statistics will be tabulated for select criteria. Changes from baseline in hematology, blood chemistry, vital signs, and ECG results will be summarized by treatment. Shifts in hematology and blood chemistry from Baseline values will be summarized. Plasma will also be evaluated for the presence of humoral responses against the humanized anti CD37 antibody component or against the DM1 component (ADA).

10.5. Anti-Tumor Activity

ORR – The best overall response will be determined by the Investigator for each evaluable patient as CR, PR, stable disease (SD), or relapsed disease/PD. The ORR will be tabulated by dose cohort assigned as well as the dose at which the response occurred along with the 80% and the 95% confidence interval (CI). To meet the definition of response-evaluable, patients must have undergone radiographic assessment at baseline, received at least one dose of Debio 1562 and rituximab, and must have had at least one post-dose tumor assessment.

OS – Overall survival will be analyzed using the Kaplan-Meier method. Median OS and 95% CI (if feasible) will be presented. The OS rate at one year along with the 95% CI will be estimated and presented.

DoR – The DoR will be estimated for all evaluable patients who achieve an objective response (PR or CR). Median duration and associated 95% CIs will be presented.

PFS – PFS will be analyzed using the Kaplan-Meier method. Median PFS and 95% CI (if feasible) and the rate of PFS at six months and at 1 year and their 95% CI will be estimated and presented.

10.6. Analysis and Stopping Rules

10.6.1. Futility Analyses

No formal interim analysis for efficacy will be performed; however, futility analyses will be conducted after 10 patients and, if deemed necessary, 15 patients in cohort A are evaluable for efficacy (i.e., patients should have performed at least one post baseline objective response assessment- *unless there is earlier clear evidence of PD*), as well as cumulative after enrollment of every 10 evaluable patients for efficacy (if deemed necessary) in study Part 3. At each analysis, futility will be evaluated using a Bayesian approach with a non-informative conjugate prior.

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10.6.3. Stopping Rules for Safety

There are no formal interim analyses for safety planned for this study. However, safety will be reviewed regularly during the study by the SRC and IDMC (Section 4.1.3).

The SRC and IDMC can recommend to terminate or modify any dosing regimen to guard patient's safety. The SRC and IDMC will monitor all safety aspects with special focus on neutropenia, febrile neutropenia, hepatic damage, pneumonitis and neuropathy.

10.7. Statistical Analysis of FACT-Lym

Health-related quality of life will be evaluated based on the FACT-Lym. Please refer to scoring manual (www.facit.org) for instruction for computing overall score and subscale scores.

Overall score and subscale score will be presented by visits, for each cohort and overall (index score and change from baseline). In addition, count and percentage of subjects with/without clinically meaningful minimally important differences from baseline will be reported by visits, for each cohort and overall.

11. ADMINISTRATIVE CONSIDERATIONS

11.1. Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572. Study medications may be administered only under the supervision of the Investigators listed on this form. Curriculum vitae must be provided for the Investigators and sub-investigators listed on Form FDA 1572.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

Designated responsibilities are to be recorded on a Delegation of Responsibility Log (or equivalent document) that is signed by the Principal Investigator and designees. It is the Principal Investigator's responsibility to ensure that the Log is maintained and remains current throughout the study.

11.2. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC approval of the protocol and the Informed Consent Form (ICF). This approval must refer to the ICF and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC at least once per year or as per institutional guidelines. The IRB/IEC must be notified of completion of the study and a final report must be provided to the IRB/IEC. A copy of these reports will be sent to the study clinical monitor or designee. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. AEs which are reported to the US FDA or other Regulatory agencies (Expedited Safety Reports) must be submitted promptly to the IRB/IEC as per institutional guidelines.

11.3. Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by GCP as described in the 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

11.4. Patient Information and Consent

Before enrolling in the clinical study, the patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An ICF that includes information about the study will be prepared and given to the

patient, or the patient's legally authorized representative(s). This document will contain all relevant regulatory authority and ICH-required elements. The ICF must be in a language understandable to the patient or the patient's legally authorized representative(s) and must specify who informed the patient or the patient's legally authorized representative.

After reading the informed consent document, the patient or the patient's legally authorized representative(s) must give consent in writing. If the patient or the patient's legally authorized representative(s) is unable to read, oral presentation and explanation of the written ICF and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient or by the patient's legally authorized representative(s). The witness and the person conducting the informed consent discussions must also sign and personally date the ICF. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated ICF(s) must be given to the patient or the patient's legally authorized representative(s). The original signed and dated ICF will be retained by the Investigator. Patient confidentiality will be maintained as outlined in Section 11.5.

The Investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

A model of the ICF to be used in this study will be provided to the sites separately from this protocol.

11.5. Patient Confidentiality

Patient names will not be supplied to the Sponsor. If the patient name appears on any documents, it must be obliterated before a copy of the document is supplied to the Sponsor. If a patient's name or other patient details were hidden in a physical manner before a document was scanned, it should be verified that the name and all other details are invisible in the electronic document before it is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. Patient scans, blood, and tissue samples sent to outside laboratories and/or CROs (e.g., tissue analysis laboratory) are identified by study patient number only to ensure maintenance of confidentiality. The patient ICF will state that publications resulting from this study will not refer to patient name or include any other information that might disclose the identity of the patient. The patients will be told that the Sponsor, representatives of the Sponsor, the IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) that will only be kept at site to enable records to be identified.

11.6. Study Monitoring

Monitoring procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. On-site monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the eCRFs and source

documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (e.g. letter, telephone, email, and facsimile).

During the COVID-19 pandemic, remote data monitoring might be implemented, if feasible at the site level and allowed by local regulations.

11.7. Case Report Forms and Study Reports

eCRFs are provided for each patient. All forms must be filled out by authorized study personnel. All corrections to the original eCRF entry must indicate the reason for change. The Investigator is required to e-sign the eCRF after all data have been captured for each patient. If corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by re-signing the eCRF.

11.8. Protocol Deviations

The Investigator will conduct the study in compliance with the protocol.

Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will be reviewed by the sponsor and may be required to be submitted to the IRB/IEC as per institutional guidelines.

11.9. Protocol Amendments

Any change to the protocol will be recorded in a written amendment. The signed amendment will be attached to this Protocol. Amendment to the protocol may require regulatory submissions (e.g. IRB/IEC) in accordance with local regulations. If this study is a regulatory commitment, changes to the protocol will be implemented with approval from the applicable regulatory authorities. In some cases, an amendment may require a change to the ICF.

11.10. End of Study

The End of Study will be defined as the latter of the completion of the Safety follow-up visit for the last patient remaining on treatment or one year from the last accrued patient's first visit.

11.11. Study Termination

11.11.1. Study Termination

If the Sponsor, an Investigator, or Study Clinical Monitor discovers conditions arising during the study that indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study must be terminated after appropriate consultation between the Sponsor and the Investigators. In addition, a decision on the part of the Sponsor to suspend or discontinue development of the test material may be made at any time.

Within 15 days of premature closure, the Sponsor must notify the competent authorities and IRB/IEC of any member state where the study is being conducted, providing the reasons for study closure.

11.11.2. Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site
- Failure of the Investigator to enter patients at an acceptable rate
- Insufficient adherence by the Investigator to protocol requirements
- Insufficient, incomplete, and/or unevaluable data

11.12. Source Documentation

Source data are defined as the original documents, data, and records. This includes, but is not limited to the following: hospital records, clinic and office charts, study-specific source document worksheets, phone logs, lab requisitions and reports, images, local laboratory reports (if applicable), electronic data/information sources and any other documentation regarding the patients.

11.13. Quality Control and Assurance

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents. Data will be captured using validated systems. Training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals (e.g., laboratory manuals and pharmacy manuals) will be provided to aid consistency in data collection and reporting across sites.

All required data will be entered into a database in accordance with CFR 21 Part 11 compliance. The database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be given restricted access based on their role in the study through a password protected environment. All missing data will be explained.

Data entered in the system must be verifiable against source documents and will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications. During the COVID-19 pandemic, remote data monitoring might be implemented, if feasible at the site level and allowed by local regulations.

11.14. Sponsor Audits and Inspections by Regulatory Agencies

For the purpose of ensuring compliance with the clinical trial protocol, GCP and other applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel will not disclose any personal identity or personal medical information. The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection. The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

11.15. Record Retention

The Investigator must maintain confidential study documentation and prevent accidental or premature destruction of those documents. Study documents should be retained for at least 10 years after the completion or discontinuation of a clinical trial. However, applicable regulatory requirements will be taken into account in the event that a longer period is required.

The Investigator must notify the sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

11.16. Publication and Disclosure Policy

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. All information concerning the product as well as any matter concerning the operation of the Sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.

Information obtained during the conduct of this study will be used by the Sponsor in connection with the development of Debio 1562. The study Investigator is obliged to provide the Sponsor with complete test results and all data developed in this study. The Sponsor has full ownership of the original eCRFs completed as part of the study. This information may be disclosed to other physicians who are conducting similar studies and to the FDA as deemed necessary by the Sponsor. Patient-specific information may be provided to other appropriate medical personnel related to the care of that patient only with patient's prior consent.

The Investigator and any other personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with the Sponsor, provided the Sponsor a copy of the draft document intended for publication, and obtained the Sponsor's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential. The Sponsor will use the information for registration purposes and for the general development of the drug.

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13. APPENDICES

APPENDIX A. SCHEDULE OF EVENTS OF SAFETY RUN-IN FOR Q3W DOSING (STUDY PART 1)

Activity	Screening	Cycles 1 and 3					Cycle 2			Cycles ≥ 4	EOT[j]	30-day Follow-up[f, n]
	≤28 days prior to 1st dose	Day 1[k]	Day 2	Day 3	Day8 ±1 day	Day15 ±1 day	Day 1[k]	Day 8 ±1 day	Day 15 ±1 day	Day 1[k]		(30-42 Days)
Informed Consent	•											
Demography	•											
Confirm disease diagnosis, stage at diagnosis and current stage	•											
Medical History	•											
Review and Document Inclusion/Exclusion Criteria	•											
Confirm patient continues to satisfy I/E Criteria		C1 only										
Physical examination[a]	•	•					•			•	•	•
Vital Signs[b]	•	•			•	•	•	•	•	•	•	•
Weight	•	•					•			•	•	•
Height	•											
B-symptoms	•	•					•			•	•	•
ECOG performance status	•	•					•			•	•	•
Pregnancy test (urine or serum)	•	•					•			•	•	•
Hematology and Chemistry[c]	•	•	•	•	•	•	•	•	•	•	•	•

Activity	Screening	Cycles 1 and 3					Cycle 2			Cycles ≥ 4	EOT[j]	30-day Follow-up[f, n]
	≤28 days prior to 1st dose	Day 1[k]	Day 2	Day 3	Day 8 ±1 day	Day 15 ±1 day	Day 1[k]	Day 8 ±1 day	Day 15 ±1 day	Day 1[k]		(30-42 Days)
Coagulation[c]	•	•					•			•	•	•
Urinalysis[c]	•	•					•			•	•	•
Viral Serology (HBsAg)	•											
Radiologic tumor assessments[d]	•		Every 6 weeks (±1 week) from Cycle 1 Day 1 (no schedule shift due to dose delays)[e]delays)[e]								•[f]	•[f]
Biopsy tumor tissue[g]	•											
Bone Marrow Assessment[h]	•		Every 6 weeks (±1 week) from Cycle 1, Day 1 as Clinically Indicated									
[redacted]												
ECG (12-lead)[i]	•	•	•				On Day 1 of Cycles 2 and 4 to coincide with PK draws (± 1 hour)				•	•
Pharmacokinetic and Immunogenicity Assessments	See Appendix D											
AE and SAE evaluation[l]	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant Medication[m]	•	•	•	•	•	•	•	•	•	•	•	•
Debio 1562 Infusion		•					•			•		
Rituximab Infusion		•					•			•		

a) Directed physical examination is acceptable while on study treatment and at the 30-day safety Follow-up Visit. Complete examination is required at screening and EOT. Physical examinations may be performed up to 3 days prior to study drug administration on Day 1 of all Cycles.

b) **Debio 1562 -** vital signs (blood pressure, heart rate, temperature, and respiratory rate) will be measured immediately before each administration, every 30 min ± 5 min during the infusion (if applicable), and immediately after infusion. **Rituximab** - vital signs will be measured immediately before each administration, every 60 min ± 5 min during the infusion and immediately after infusion. For all cycles, patients must remain in the clinic for safety observation for one hour following completion of their rituximab infusion.

c) Laboratory assessments may be performed up to 3 days prior to study **drug** administration **in all cycles.** All draws on Day 1 of treatment should be pre-dose. In the event of severe toxicity, repeat laboratory tests should be performed within 48 hours, and then followed at least twice weekly until re-treatment criteria are met.
Serum Chemistry- ALB, ALK-P, ALT, AST, BUN, Ca, Cl, Creatinine, Glucose, LDH, Magnesium, Phosphorus, K, Na, Total bilirubin, Total protein, Uric acid, Immunoglobulin levels (IgG, IgA, IgM).

Hematology- Hct, Hgb, Platelet count, RBC count, WBC count with differential.
Urinalysis - Appearance, specific gravity and pH, Semi-quantitative dipstick evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood, Microscopic examination of sediment to be performed if urinalysis is positive for WBC, proteins or blood.
Coagulation tests: T/INR and aPTT

d) Radiographic tumor evaluation by CT or PET-CT scan of chest, neck, abdomen and pelvis will be performed within 28 days prior to first dose of study treatment. The anatomical regions to be assessed radiographically post baseline will be determined by individual patients' extent of disease. Whenever possible, the same radiographic scan assessment used at screening (e.g., PET-CT) should be used at all subsequent radiographic evaluations.
e) Post-baseline disease assessments will be performed every 6 weeks from Cycle 1, Day 1 and will not shift due to dose delays. For patients who are exceptionally granted continued study treatment after completion of 6 cycles, repeat radiographic tumor response assessments can be performed as per local institutional care practice. Ideally, repeat assessments should continue at 6-week (± 1 week) intervals and should not be longer than 12-weeks (± 4 weeks). Periodic tumor assessment will be conducted using the same imaging modality of prior cycles of treatment until PD, start of any new anti-cancer therapy, or death.
f) Patients discontinuing Debio 1562 for reasons other than PD will have subsequent clinic visits for radiographic assessment every 12 weeks (± 4 weeks) from the time of their last on-study tumor assessment until PD or starting a subsequent anti-cancer therapy. For patients who discontinue for PD, no radiographic scans will be required at the EOT visit or the follow-up visits. All patients will be followed for survival every 12 weeks (± 4 weeks) from the time of the 30-day safety Follow-up visit, for up to one year from the last patient's first dose (Cycle 1 Day 1). Patients will not be required to visit the clinic for survival follow-up.
g) Patients must have available a pathology-informed tumor biopsy sample representative of the current disease, [redacted].
h) If applicable, a bone marrow biopsy or aspirate will be performed within 3 months prior to first dose. A repeat bone marrow biopsy or aspirate will be required for patients with bone marrow infiltration at baseline who have a CR by imaging and physical examination, and will, in case possible and deemed acceptable by the Investigator, be performed every 6 weeks as clinically indicated. In order to better understand the effect of Debio 1562 on WBCs, bone marrow biopsies/aspirates may also be requested for those patients who experience grade 4 cytopenias.
i) The screening ECG will be performed within 14 days prior to first treatment. In Cycles 1 and 3, ECGs will be performed within three hours prior to dose, at the end of the Debio 1562 infusion (to coincide with Cmax and PK blood draw) and 24 ± 4 hours after infusion. An ECG will be performed on Day 1 of Cycles 2 and 4 (inclusive) to coincide with the pre-dose PK blood draw. An ECG at the 30-day Follow-up visit is not required unless clinically indicated or if the EOT assessment was missed.
j) EOT visit should occur within 7 days of the decision to discontinue study treatment.
k) Cycle 1 Day 1 assessments (ECOG, weight, B Symptoms and pregnancy test) do not need to be repeated if they are collected within 3 days of study drug administration. For all other cycles, the Day 1 window is ±3 days.
l) The period of safety observation extends from the time of consent until 30 days after the patient's last study treatment or until the AEs has resolved or stabilized or an outcome has been reached, whichever comes first.
m) Concomitant medications should be collected beginning from 4 weeks prior to Cycle 1, Day 1 until the end of the period of safety observation.
n) In the event that a patient is unable to return to the clinic for a follow-up visit, telephone contact with the patient to assess AEs, concomitant medications, anti-cancer treatments will be conducted.

APPENDIX B. SCHEDULE OF EVENTS OF COHORT A FOR Q3W DOSING (STUDY PART 2 AND 3)

Activity	Screening	Cycles 1 and 2					Cycles 3-6 [q]	EOT [l]	30-day Follow-up [g, p]
	≤28 days prior to 1st dose	Day 1[m]	Day 2	Day 3	Day8 ±1 day	Day15 ±1 day	Day 1[m]		(30-42 Days)
Informed Consent	•								
Demography	•								
Confirm disease diagnosis, stage at diagnosis and current stage	•								
Medical History	•								
Review and Document Inclusion/Exclusion Criteria	•								
Confirm patient continues to satisfy I/E Criteria		C1 only							
Physical examination [a]	•	•					•	•	•
Vital Signs [b]	•	•			•	•	•	•	•
Health-related Quality of Life [c]		•					•	•	•
Weight	•	•					•	•	•
Height	•								
B-symptoms	•	•					•	•	•
ECOG performance status	•	•					•	•	•
Pregnancy test (urine or serum)	•	•					•	•	•
Hematology and Chemistry [d]	•	•	•	•	•	•	•	•	•

Activity	Screening	Cycles 1 and 2					Cycles 3-6 [q]	EOT [l]	30-day Follow-up [g, p]
	≤28 days prior to 1st dose	Day 1[m]	Day 2	Day 3	Day 8 ±1 day	Day 15 ±1 day	Day 1[m]		(30-42 Days)
Coagulation [d]	●	●					●	●	●
Urinalysis [d]	●	●					●	●	●
Viral Serology (HBsAg)	●								
Radiologic tumor Assessments [e]	●		Every 6 weeks (± 1 week) from Cycle 1, Day 1 (no schedule shift due to dose delays) [f]					●[g]	●[g]
Biopsy tumor tissue [h]	●								
Bone Marrow Assessment [i]	●		Every 6 weeks (± 1 week) from Cycle 1, Day 1 as Clinically Indicated						
[redacted]									
ECG (12-lead) [k]	●	●	●				●	●	●
Pharmacokinetic and Immunogenicity Assessments	See Appendix E								
[redacted]									
AE and SAE evaluation [n]	●	●	●	●	●	●	●	●	●
Concomitant Medication [o]	●	●	●	●	●	●	●	●	●
Debio 1562 Infusion		●					●		
Rituximab Infusion		●					●		

a) Directed physical examination is acceptable while on study treatment and at the 30-day safety Follow-up Visit. Complete examination is required at screening and EOT. Physical examinations may be performed up to 3 days prior to study drug administration on Day 1 of all Cycles.

b) **Debio 1562** - vital signs (blood pressure, heart rate, temperature, and respiratory rate) will be measured immediately before each administration, every 30 min ± 5 min during the infusion (if applicable), and immediately after infusion. **Rituximab** - vital signs will be measured immediately before each administration, every 60 min ± 5 min during the infusion and immediately after infusion. Patients will remain in the clinic under monitoring for four hours after completion of the rituximab infusion for the first cycle. Post-administration safety monitoring could potentially be shortened (i.e. < 4 hours but at least 1 hour) following subsequent administration of rituximab, based on the judgement of the investigator. Patients receiving Debio 1562 only will also remain in the clinic under monitoring for one hour.

c) HRQoL assessment at Day 1 of each cycle will be performed prior to Debio 1562 infusion. In patients who exceptionally continue the study treatment beyond C6, the last HRQoL assessment will be performed at C7D1 before the infusion and no additional HRQoL assessment will be completed at 30-day follow up

visit.

d) Laboratory assessments may be performed up to 3 days prior to study **drug** administration **in all cycles.** If the screening laboratory assessments are performed within 3 days prior drug administration on Day 1 of Cycle 1, no assessments need to be repeated on Day 1 of Cycle 1. All draws on days of treatment should be pre-dose. In the event of severe toxicity, repeat laboratory tests should be performed within 48 hours, and then followed at least twice weekly until retreatment criteria are met.
Serum Chemistry- ALB, ALK-P, ALT, AST, BUN, Ca, Cl, Creatinine, Glucose, LDH, Magnesium, Phosphorus, K, Na, Total bilirubin, Total protein, Uric acid, Immunoglobulin levels (IgG, IgA, IgM).
Hematology- Hct, Hgb, Platelet count, RBC count, WBC count with differential.
Urinalysis - Appearance, specific gravity and pH, Semi-quantitative dipstick evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood, Microscopic examination of sediment to be performed if urinalysis is positive for WBC, proteins or blood.
Coagulation tests: T/INR and aPTT.
If deemed necessary by the Investigator an additional hematological assessment can be performed on Day 15 of Cycles 3-6.

e) Radiographic tumor evaluation by CT or PET-CT scan of chest, neck, abdomen and pelvis will be performed within 28 days prior to first dose of study treatment. The anatomical regions to be assessed radiographically post baseline will be determined by individual patients' extent of disease. Whenever possible, the same radiographic scan assessment used at screening (e.g., PET-CT) should be used at all subsequent radiographic evaluations.

f) Post-baseline disease assessments will be performed every 6 weeks from Cycle 1, Day 1 and will not shift due to dose delays. For patients who are exceptionally granted continued study treatment after completion of 6 cycles, repeat radiographic tumor response assessments can be performed as per local institutional care practice. Ideally, repeat assessments should continue at 6-week (± 1 week) intervals and should not be longer than 12-weeks (± 4 weeks). Periodic tumor assessment will be conducted using the same imaging modality of prior cycles of treatment until PD, start of any new anti-cancer therapy, or death.

g) Patients discontinuing Debio 1562 for reasons other than PD will have subsequent clinic visits for radiographic assessment every 12 weeks (± 4 weeks) from the time of their last on-study tumor assessment until PD or starting a subsequent anti-cancer therapy. For patients who discontinue for PD, no radiographic scans will be required at the EOT visit or the follow-up visits. All patients will be followed for survival every 12 weeks (± 4 weeks) from the time of the 30-day safety Follow-up visit, for up to one year from the last patient's first dose (Cycle 1 Day 1). Patients will not be required to visit the clinic for survival follow-up.

h) Patients must have available a pathology-informed tumor biopsy sample representative of the current disease, [redacted].

i) If applicable, a bone marrow biopsy or aspirate will be performed within 3 months prior to first dose. A repeat bone marrow biopsy or aspirate will be required for patients with bone marrow infiltration at baseline who have a CR by imaging and physical examination, and will, in case possible and deemed acceptable by the Investigator, be performed every 6 weeks as clinically indicated. In order to better understand the effect of Debio 1562 on WBCs, bone marrow biopsies/aspirates may also be requested for those patients who experience grade 4 cytopenias.

[redacted]

k) The screening ECG will be performed within 14 days prior to first treatment. In Cycles 1 and 2, ECGs will be performed within three hours prior to dose, at the end of the Debio 1562 infusion (to coincide with Cmax and PK blood draw) and 24 ± 4 hours after infusion. An ECG will be performed on Day 1 of Cycles 3-6 to coincide with the pre-dose PK blood draw. An ECG at the 30-day Follow-up visit is not required unless clinically indicated or if the EOT assessment was missed.

l) EOT visit should occur within 7 days of the decision to discontinue study treatment.

m) Cycle 1 Day 1 assessments (ECOG, weight, B Symptoms and pregnancy test) do not need to be repeated if they are collected within 3 days of study drug administration. For all other cycles, the Day 1 window is ±3 days.

n) The period of safety observation extends from the time of consent until 30 days after the patient's last study treatment or until the AEs has resolved or stabilized or an outcome has been reached, whichever comes first.

o) Concomitant medications should be collected beginning from 4 weeks prior to Cycle 1, Day 1 until the end of the period of safety observation.
p) In the event that a patient is unable to return to the clinic for a follow-up visit, telephone contact with the patient to assess AEs, concomitant medications, and anti-cancer treatments will be conducted.
q) Permission to prolong the study treatment could be exceptionally granted by Study Sponsor if patients are deriving benefit from the study treatment and after complete presentation of the individual case by the Study Investigator, particularly the medical justification for extending the treatment and the re-assessment of the risk/benefit balance. The Sponsor's decision will consider the availability of IMP at the time of request. A report of the discussions with the Sponsor must be filed in the source documentation.

APPENDIX C. SCHEDULE OF EVENTS OF COHORT B FOR QW DOSING (STUDY PART 2 AND 3)

Activity	Screening	Cycles 1 and 2					Cycles 3-6 [q]			EOT [l]	30-day Follow-up [g, p]
	≤28 days prior to 1st dose	Day 1 [m]	Day 2	Day 3	Day8 (-1 to +3 days)	Day15 (-1 to +3 days)	Day 1 [m]	Day 8 (-1 to +3 days)	Day 15 (-1 to +3 days)		(30-42 Days)
Informed Consent	•										
Demography	•										
Confirm disease diagnosis, stage at diagnosis and current stage	•										
Medical History	•										
Review and Document Inclusion/Exclusion Criteria	•										
Confirm patient continues to satisfy I/E Criteria		C1 only									
Physical examination [a]	•	•			•	•	•	•	•	•	•
Vital Signs [b]	•	•			•	•	•	•	•	•	•
Health-related Quality of Life [c]		•					•			•	•
Weight	•	•			•	•	•	•	•	•	•
Height	•										
B-symptoms	•	•			•	•	•	•	•	•	•
ECOG performance status	•	•			•	•	•	•	•	•	•
Pregnancy test (urine or serum)	•	•					•			•	•
Hematology and Chemistry [d]	•	•	•	•	•	•	•	•	•	•	•

Activity	Screening	Cycles 1 and 2					Cycles 3-6 [q]			EOT [l]	30-day Follow-up [g, p]
	≤28 days prior to 1st dose	Day 1 [m]	Day 2	Day 3	Day8 (-1 to +3 days)	Day15 (-1 to +3 days)	Day 1 [m]	Day 8 (-1 to +3 days)	Day 15 (-1 to +3 days)		(30-42 Days)
Coagulation [d]	●	●			●	●	●	●	●	●	●
Urinalysis [d]	●	●			●	●	●	●	●	●	●
Viral Serology (HBsAg)	●										
Radiologic tumor assessments [e]	●		Every 6 weeks (± 1 week) from Cycle 1, Day 1 (no schedule shift due to dose delays) [f]							●[g]	●[g]
Biopsy tumor tissue [h]	●										
Bone Marrow Assessment [i]	●		Every 6 weeks (± 1 week) from Cycle 1, Day 1 as Clinically Indicated								
[redacted]											
ECG (12-lead) [k]	●	●	●		●	●	●	●	●	●	●
Pharmacokinetic and Immunogenicity Assessments	See Appendix F										
[redacted]											
AE and SAE evaluation [n]	●	●	●	●	●	●	●	●	●	●	●
Concomitant Medication [o]	●	●	●	●	●	●	●	●	●	●	●
Debio 1562 Infusion		●			●	●	●	●	●		
Rituximab Infusion		●					●				

a) Directed physical examination is acceptable while on study treatment and at the 30-day safety Follow-up Visit. Complete examination is required at screening and EOT. Physical examinations may be performed up to 3 days prior to study drug administration on Day 1 of all Cycles.

b) **Debio 1562** - vital signs (blood pressure, heart rate, temperature, and respiratory rate) will be measured immediately before each administration, every 30 min ± 5 min during the infusion (if applicable), and immediately after infusion. **Rituximab** - vital signs will be measured immediately before each administration, every 60 min ± 5 min during the infusion and immediately after infusion. Patients will remain in the clinic under monitoring for four hours after completion of the rituximab infusion for the first cycle. Post-administration safety monitoring could potentially be shortened (i.e. < 4 hours but at least 1 hour) following subsequent administration of rituximab, based on the judgement of the investigator. Patients receiving Debio 1562 only, i.e., on Day 8 and Day 15 of each cycle or due to rituximab intolerability, will also remain in the clinic under monitoring for one hour.

c) HRQoL assessment at Day 1 of each cycle will be performed prior to Debio 1562 infusion. In patients who exceptionally continue the study treatment beyond C6, the last HRQoL assessment will be performed at C7D1 before the infusion, and no additional HRQoL assessment will be completed at the 30-day follow-

up visit.

d) Laboratory assessments may be performed up to 3 days prior to study **drug** administration **in all cycles.** If the screening laboratory assessments are performed within 3 days prior drug administration on Day 1 of Cycle 1, no assessments need to be repeated on Day 1 of Cycle 1. All draws on Day 1 of treatment should be pre-dose. In the event of severe toxicity, repeat laboratory tests should be performed within 48 hours, and then followed at least twice weekly until retreatment criteria are met.
Serum Chemistry- ALB, ALK-P, ALT, AST, BUN, Ca, Cl, Creatinine, Glucose, LDH, Magnesium, Phosphorus, K, Na, Total bilirubin, Total protein, Uric acid, Immunoglobulin levels (IgG, IgA, IgM).
Hematology- Hct, Hgb, Platelet count, RBC count, WBC count with differential.
Urinalysis - Appearance, specific gravity and pH, Semi-quantitative dipstick evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood, Microscopic examination of sediment to be performed if urinalysis is positive for WBC, proteins or blood.
Coagulation tests: T/INR and aPTT

e) Radiographic tumor evaluation by CT or PET-CT scan of chest, neck, abdomen and pelvis will be performed within 28 days prior to first dose of study treatment. The anatomical regions to be assessed radiographically post baseline will be determined by individual patients' extent of disease. Whenever possible, the same radiographic scan assessment used at screening (e.g., PET-CT) should be used at all subsequent radiographic evaluations.

f) Post-baseline disease assessments will be performed every 6 weeks from Cycle 1, Day 1 and will not shift due to dose delays. For patients who are exceptionally granted continued study treatment after completion of 6 cycles, repeat radiographic tumor response assessments can be performed as per local institutional care practice. Ideally, repeat assessments should continue at 6-week (± 1 week) intervals and should not be longer than 12-weeks (± 4 weeks). Periodic tumor assessment will be conducted using the same imaging modality of prior cycles of treatment until PD, start of any new anti-cancer therapy, or death.

g) Patients discontinuing Debio 1562 for reasons other than PD will have subsequent clinic visits for radiographic assessment every 12 weeks (± 4 weeks) from the time of their last on-study tumor assessment until PD, or starting a subsequent anti-cancer therapy. For patients who discontinue for PD, no radiographic scans will be required at the EOT or follow-up visits. All patients will be followed for survival every 12 weeks (± 4 weeks) from the time of the 30-day safety follow-up visit, for up to one year from the last patient's first dose (Cycle 1 Day 1). Patients will not be required to visit the clinic for survival follow-up.

h) Patients must have available a pathology-informed tumor biopsy sample representative of the current disease, [redacted].

i) If applicable a bone marrow biopsy or aspirate will be performed within 3 months prior to first dose. A repeat bone marrow biopsy or aspirate will be required for patients with bone marrow infiltration at baseline who have a CR by imaging and physical examination, and will, in case possible and deemed acceptable by the Investigator, be performed every 6 weeks as clinically indicated. In order to better understand the effect of Debio 1562 on WBCs, bone marrow biopsies/aspirates may also be requested for those patients who experience grade 4 cytopenias.

[redacted]

k) The screening ECG will be performed within 14 days prior to first treatment. On Day 1 of Cycles 1 and 2, ECGs will be performed within three hours prior to dose, at the end of the Debio 1562 infusion (to coincide with C_{max} and PK blood draw) and 24 ± 4 hours after infusion. On Day 8 and 15 of Cycles 1 and 2, ECGs will be performed within three hours prior to dose and at the end of the Debio 1562 infusion (to coincide with C_{max} and PK blood draw). An ECG will be performed on Day 1 of Cycles 3-6 to coincide with the pre-dose PK blood draw. An ECG at the 30-day Follow-up visit is not required unless clinically indicated or if the EOT assessment was missed.

l) EOT visit should occur within 7 days of the decision to discontinue study treatment.

m) Cycle 1 Day 1 assessments (ECOG, weight, B Symptoms and pregnancy test) do not need to be repeated if they are collected within 3 days of study drug administration. For all other cycles, the Day 1 window is ±3 days.

n) The period of safety observation extends from the time of consent until 30 days after the patient's last study treatment or until the AE(s) has resolved or stabilized or an outcome has been reached, whichever comes first.
o) Concomitant medications should be collected beginning from 4 weeks prior to Cycle 1, Day 1 until the end of the period of safety observation.
p) In the event that a patient is unable to return to the clinic for a follow-up visit, telephone contact with the patient to assess AEs, concomitant medications, and anti-cancer treatments will be conducted.
q) Permission to prolong the study treatment could be exceptionally granted by Study Sponsor if patients are deriving benefit from the study treatment and after complete presentation of the individual case by the Study Investigator, particularly the medical justification for extending the treatment and the re-assessment of the risk/benefit balance. The Sponsor's decision will consider the availability of IMP at the time of request. A report of the discussions with the Sponsor must be filed in the source documentation.

APPENDIX D. PHARMACOKINETIC AND IMMUNOGENICITY ASSESSMENT OF SAFETY RUN-IN FOR Q3W DOSING (STUDY PART 1)

Activity	Cycles 1 and 3					Cycles 2 and 4-8	EOT	30-Day Follow-up
	Day 1	Day 2	Day 3	Day 8	Day 15	Day1		
Blood samples for PK	• Pre-dose • 5' after EOI D1562 • 5' after EOI RTX	• 24±4h after EOI D1562	• 48±4h after EOI D1562	●	●	• Pre-dose • 5' after EOI RTX*	●	●
Blood samples for immunogenicity (ADA) assessment	• Pre-dose					• Pre-dose	●	●
Unscheduled PK and immunogenicity (ADA) samples	As clinically indicated during active study treatment[a]							

D1562: Debio 1562; **EOI:** End Of Infusion; **EOOP:** End Of Observational Period; **RTX:** Rituximab. ●: Any time during the visit

* In the event that rituximab is discontinued, a post-dose blood draw will be taken following completion of the Debio 1562 infusion.

a) Patients who experience a ≥ Grade 2 infusion reaction during or immediately following administration of Debio 1562 will have blood drawn for determination of drug concentration and antibodies to Debio 1562 (ADA). Two samples should be obtained: (1) within three hours of the onset of the reaction; and (2) one week later.

APPENDIX E. PHARMACOKINETIC AND IMMUNOGENICITY ASSESSMENT OF COHORT A FOR Q3W DOSING (STUDY PART 2 AND 3)

Activity	Cycles 1 and 2					Cycles 3-6 [b]		EOT [b]	30-Day Follow-up [b]
	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1			
Blood samples for Debio 1562	• Pre-dose • 5' after EOI D1562 • 2h after SOI RTX • 5' after EOI RTX • EOOP	• 24±4h after EOI D1562	• 48±4h after EOI D1562	●	●	• Pre-dose • 5' after EOI D1562 • 5' after EOI RTX			
Blood samples for rituximab	• Pre-dose • EOI RTX	• 24±4h after EOI D1562	• 48±4h after EOI D1562	●	●	• Pre-dose • 5' after EOI RTX		●	●
Blood samples for immunogenicity (ADA) assessment	• Pre-dose					• Pre-dose		●	●
Unscheduled PK and immunogenicity (ADA) samples	As clinically indicated during active study treatment[a]								

D1562: Debio 1562; **EOI:** End Of Infusion; **EOOP:** End Of Observational Period; **RTX:** Rituximab; **SOI:** Start Of Infusion, ●: Any time during the visit

a) Patients who experience a ≥ Grade 2 infusion reaction during or immediately following administration of Debio 1562 will have blood drawn for determination of drug concentration and antibodies to Debio 1562 (ADA). Two samples should be obtained: (1) within three hours of the onset of the reaction; and (2) one week later.

b) In patients who exceptionally continue the study treatment beyond C6, the last PK sample and the sample for immunogenicity (ADA) assessment will be taken at C7D1 at pre-dose blood draw instead of at the EOT visit. For patients already beyond C7D1 after Amendment 5, the last PK sample will be taken at D1 of the next possible subsequent cycle at pre-dose blood draw instead of at the EOT visit. No additional samples will be taken at the 30-day follow-up visit.

APPENDIX F. PHARMACOKINETIC AND IMMUNOGENICITY ASSESSMENTS OF COHORT B FOR QW DOSING (STUDY PART 2 AND 3)

Activity	Cycles 1 and 2					Cycle 3			Cycles 4-6 [b]			EOT [b]	30-Day Follow-up [b]
	Day 1	Day 2	Day 3	Day 8	Day 15	Day1	Day 8	Day 15	Day1	Day 8	Day 15		
Blood samples for Debio 1562	• Pre-dose • 5' after EOI D1562 • 2h after SOI RTX • 5' after EOI RTX • EOOP	• 24±4h after EOI D1562	• 48±4h after EOI D1562	• Pre-dose • 5' after EOI D1562 • EOOP	• Pre-dose • 5' after EOI D1562 • EOOP	• Pre-dose • 5' after EOI D1562 • 5' after EOI RTX	• Pre-dose • 5' after EOI D1562	• Pre-dose • 5' after EOI D1562	• Pre-dose • 5' after EOI D1562	• Pre-dose • 5' after EOI D1562	• Pre-dose • 5' after EOI D1562		
Blood samples for rituximab	• Pre-dose • EOI RTX	• 24±4h after EOI D1562	• 48±4h after EOI D1562	●	●	• Pre-dose • EOI RTX	●	●	• Pre-dose • EOI RTX	●	●	●	●
Blood samples for immunogenicity (ADA) assessment	●					●			●			●	●
Unscheduled PK and immunogenicity (ADA) samples	As clinically indicated during active study treatment[a]												

D1562: Debio 1562; **EOI:** End Of Infusion; **EOOP:** End Of Observational Period; **RTX:** Rituximab; **SOI:** Start Of Infusion, ●: Any time during the visit

a) Patients who experience a ≥ Grade 2 infusion reaction during or immediately following administration of Debio 1562 will have blood drawn for determination of drug concentration and antibodies to Debio 1562 (ADA). Two samples should be obtained: (1) within three hours of the onset of the reaction; and (2) one week later.

b) In patients who exceptionally continue the study treatment beyond C6, the last PK sample and the sample for immunogenicity (ADA) assessment will be taken at C7D1 at pre-dose blood draw instead of at the EOT visit. For patients already beyond C7D1 after Amendment 5, the last PK sample will be taken at D1 of the subsequent cycle at pre-dose blood draw instead of at the EOT visit. N o additional sample will be taken at the 30-day follow-up.

APPENDIX H. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

(Oken 1982)

GRADE	SCALE
0	Fully active, able to carry out all pre-disease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

APPENDIX I. RESPONSE ASSESSMENTS OF HODGKIN AND NON-HODGKIN LYMPHOMA: THE LUGANO CLASSIFICATION (CHESON 2014)

Response and Site	PET-CT Scan	CT-based Response
Complete Response	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS† In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. Complete metabolic response may be inferred if uptake at sites of initial involvement is no great than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesions	N/A	Absent
Organ enlargement	N/A	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, [redacted]
Partial Response	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease.	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites

	At end of treatment, these findings indicate residual disease.	When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, assign 0 X 0 mm For a node > 5mm X 5mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	N/A	Absent/normal, regressed, but no increase
Organ enlargement	N/A	Spleen must have regressed by ≥ 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	N/A
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	N/A	No increase consistent with progression
Organ enlargement	N/A	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	N/A
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**

Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by > 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement
Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; [redacted] LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; N/A: not applicable; PET, positron emission tomography; PPD,		

cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.
*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).
†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X new areas of uptake unlikely to be related to lymphoma.

APPENDIX J. BODY SURFACE AREA CALCULATION

In order to prepare the correct rituximab dose for administration to each patient, the body surface area must be calculated using the following formula or equivalent:

Body Surface Area (m^2) = ([Height {cm} x Weight {kg}] / 3600)½

The value calculated will then be used to determine the quantity of chemotherapeutic drug to be placed into the infusion bag. The weight used for calculation of BSA should be obtained prior to first treatment and thereafter should only be modified for significant (≥ 10%) changes in body weight not influenced by weight gain or loss attributed to fluid retention (exceptions may be made for institutional policies).

APPENDIX K. ANN ARBOR CLASSIFICATION AND THE COTSWOLD MODIFICATIONS

Stage	Features
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E
For all stages: A B	 No symptoms Fever (>38°C), drenching sweats, weight loss (10% body weight over 6 months)
For Stages I to III E	 Involvement of a single, extranodal site contiguous or proximal to known nodal site
Cotswold modifications	• Massive mediastinal disease has been defined by the Cotswold meeting as a thoracic ratio of maximum transverse mass diameter greater than or equal to 33% of the internal transverse thoracic diameter measured at the T5/6 intervertebral disc level on chest radiography. • The number of anatomic regions involved should be indicated by a subscript (e.g., II3) • Stage III may be subdivided into: III1, with or without splenic, hilar, celiac, or portal nodes; III2, with para-aortic, iliac, mesenteric nodes • Staging should be identified as clinical stage (CS) or pathologic stage (PS) • A new category of response to therapy, unconfirmed/uncertain complete remission (CR) can be introduced because of the persistent radiologic abnormalities of uncertain significance
Armitage 2005	

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