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

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Statistical Analysis Plan

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

Investigational Product: Debio 1562

Study Number: Debio 1562-201

SPONSOR:

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Version 3.1 dated 2021-05-07

TRIAL SUMMARY

Study Number:	Debio 1562-201
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 Phase:	2
Design:	The clinical trial consists of three parts: a safety run-in (part 1), initial assessment of safety and efficacy of every three-week (Q3W) and every week (QW) dosing regimens of Debio 1562 (part 2) and an expansion (part 3). Please refer to Section 4.1 for the full description of the study design.
Protocol Version and Date:	Amendment 6, dated of 2020-04-24
Statistical Analysis Plan Version and Date:	Version 3.1, dated of 2021-05-07

Sponsor (Debiopharm International S.A., Lausanne, Switzerland)

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Study Biostatistician

(Electronically signed)

REVISION HISTORY

Version	Date	Changes
1.3	2017-05-12	Statistical analysis plan compliant with protocol amendment 1. First and only version signed by Immunogen and provided by PPD Biostatistics department.
2.0	2018-10-13	Implementation of changes to be compliant with protocol amendment 2 and amendment 3: - Change of clinical trial sponsor (Immunogen to Debiopharm International S.A.); - Change in investigational product name from IMGN529 to Debio 1562; - Use of Debiopharm International S.A. statistical analysis plan template; - Timing of statistical analysis; - Updates in sample size calculation; - Clarifications of PFS definition and sensitivity analyses; - Section on futility boundaries as part of the adaptive design; - Adding analysis of Health-related Quality of Life; - Adding additional exploratory endpoints analysis; - Revision of the section on pharmacokinetics; - Re-structuring the sections of the document.
3.0	2021-03-10	Implementation of changes to be compliant with protocol amendment 6: - Revision of the section on sample size calculation; - Revision of the section on pharmacokinetics; - Update of the schedule of assessments (appendices); - Addition of sensitivity analyses on efficacy endpoints to take into account the possibility for a subject to switch from QW regimen to a Q3W regimen due to the COVID-19 pandemic. - [redacted] - Addition of the per protocol population
3.1	2021-05-07	Minor Formating changes: update TOC, and few hyperlink.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse events
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastic time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BASO	Basophils
BILI	Total bilirubin
BOR	Best overall response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA	Calcium
CI	Confidence interval
CL	Chloride
C_{max}	Maximum concentration
CMR	Complete metabolic response
COVID	Coronavirus disease
CR	Complete response
CREAT	Creatinine
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DLBCL	Diffuse large B-cell lymphoma
DM1	emtansine
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
[redacted]	[redacted]
FDA	Food and Drug Administration

Abbreviation	Definition
GLUC	Glucose
FL	Follicular lymphoma
[redacted]	[redacted]
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HGB	Hemoglobin
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
[redacted]	[redacted]
INR	International normalized ratio
ITT	Intent-to-treat
IV	Intravenous
K	Potassium
LDH	Lactate dehydrogenase
LYM	Lymphocyte
MALT	Mucosa-associated lymphoid tissue
MedDRA	Medical dictionary for regulatory activities
MCL	Mantle cell lymphoma
MG	Magnesium
MONO	Monocyte
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
NCI	National cancer institute
NA	Not available
NE	Not evaluable
NEUT	Neutrophil
NHL	Non-Hodgkin's lymphoma
NMR	No metabolic response
ORR	Objective response rate
OS	Overall survival
PCST	Prior Cancer Systemic Therapy
PD	Progressive disease
PET	Positron-emission tomography

Abbreviation	Definition
PFS	Progression-free survival
PHOS	Phosphorous
PK	Pharmacokinetic
PLAT	Platelet count
PMD	Progressive metabolic disease
PMR	Partial metabolic response
PP	Per Potocol
PPD	Product of perpendicular diameters
PROT	Total protein
PR	Partial response
PT	Preferred term
QT	QT interval
QTc	Corrected QT interval
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QW	Once every week
Q3W	Once every three weeks
RBC	Red blood cells
R-CHOP	Rituximab - Cyclophosphamide Hydroxydaunomycin Oncovin Prednisone
R/R	Relapsed/refractory
RR	RR interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SMCC	Succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate
SOC	System organ class
SP	Safety population
SPD	Sum of products of diameters
SRC	Safety review committee
$t_{1/2}$	Terminal half-life
TBL	Total bilirubin
TAb	Total Antibody
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
T_{max}	Time to reach maximum concentration
TTR	Time to response

Abbreviation	Definition
ULN	Upper limit of normal
URATE	Uric acid
UREAN	Blood urea nitrogen
V_{ss}	Volume of distribution at steady state
WBC	White blood cells
WHO-DD	World Health Organization – data dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analyses for the clinical trial Debio 1562-201 entitled "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". This SAP is compliant with protocol amendment 6, dated of 2020-04-24. It will be finalized prior to the database lock for the primary analysis. Production version of the eCRF dated from 2019-03-12 was used.

In this Phase 2 study, the safety and anti-tumor activity of Debio 1562 in combination with rituximab will be investigated for the treatment of subjects with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and other forms of non-Hodgkin's lymphoma (NHL) in study part 1, and in relapsed DLBCL only in study parts 2 and 3.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objectives of this study are to:

- 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.

2.2 Secondary Objectives

The secondary objectives of this study are to:

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

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

- Correlate the extent of CD37 and CD20 antigen expression in tumor samples with anti-tumor activity of Debio 1562 and rituximab combination;
- [redacted]
- [redacted]
- [redacted]
- Assess health-related quality of life (HRQoL).

3 STUDY ENDPOINTS

3.1 Primary Endpoint(s)

The primary endpoints of this study are:

- Incidence of treatment-emergent adverse events (TEAEs), clinically significant changes in clinical laboratory test results, electrocardiogram (ECG), and vital sign measurements;
- Objective response rate (ORR) defined as the proportion of subjects with a best overall response of partial response (PR) or complete response (CR) as assessed by the 2014 Lugano classification of response assessments of NHL (Cheson, 2014).

3.2 Secondary Endpoints

The secondary endpoints of this study are:

- PK parameters for both Debio 1562 and rituximab (evaluated but not limited to): maximum concentration (C_{max}), area under the curve ($AUC_{0\ t}$, AUC_{inf}), terminal half-life ($t_{1/2}$), clearance, volume of distribution at steady state (V_{ss}), and time to reach maximum concentration (T_{max});
- Efficacy time-to-event endpoints:
  - Progression-free survival (PFS) defined as the duration between the first dose date of Debio 1562 and the date of progressive disease (PD) or death due to any cause, whichever occurs first. As this study has randomized and non-randomized parts, starting date for the calculation of PFS is set to the first dose date of Debio 1562;
  - Time to response defined as the duration between the first dose date of Debio 1562 and the date of first objective response (PR or CR). This will be computed for responders only. As this study has randomized and non-randomized parts, starting date for the calculation of TTR is set to the first dose date of Debio 1562;
  - Duration of response (DoR) defined as the duration between the date of first objective response (PR or CR) and the date of PD or death due to any cause, whichever occurs first. This will be computed for responders only;
  - Overall survival (OS) defined as the duration between the first dose date of Debio 1562 and the date of death due to any cause. As this study has randomized and non-randomized parts, starting date for the calculation of OS is set to the first dose date of Debio 1562;
- Immunogenicity of Debio 1562: Presence of human anti-drug antibody.

Unless otherwise specified in subsequent sections, pharmacokinetics, [redacted] and immunogenicity analyses are beyond the scope of this document. They will be covered by dedicated analysis plans.

3.3 Exploratory Endpoints

The exploratory endpoints of this study are:

- Expression levels of CD37, CD20 by immunohistochemistry (IHC, protein) and/or mRNA detection and correlation of these measures to clinical response criteria;
- [redacted]
- Health-related quality of life (HRQoL) will be evaluated based on the functional assessment of cancer therapy-lymphoma (FACT-Lym). It is comprised of:
  - The functional assessment of cancer therapy-general (FACT-G) 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);
  - The FACT-Lymphoma Subscale, LymS, reflecting Lymphoma specific concerns (15 items).

The exploratory analyses including HRQoL analyses are beyond the scope of this document. They will be covered by dedicated analysis plans.

[redacted]

4 STUDY DESIGN AND TREATMENT

4.1 Study Design

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

The clinical trial includes a screening period, a treatment period, an end of treatment visit, a 30-day safety follow-up visit, a response follow-up period if relevant, and a survival follow-up period if relevant.

The clinical trial consists of three parts: a safety run-in with its expansion Phase 2[1] (part 1), initial assessment of safety and efficacy of Q3W and QW dosing regimens of Debio 1562 (part 2) and an expansion (part 3).

4.1.1 Part 1: Safety run-in and Phase 2

[1] Phase 2 is described in protocol versions 1, 2, and 3, and includes Cohort 1 (R/R DLBCL) and Cohort 2 (other NHL)

Subjects with DLBCL, follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma/mucosa associated lymphoid tissue (MZL/MALT) or other NHL subtypes (with Sponsor's approval) are eligible for enrollment in the safety run-in part.

During the safety run-in, subjects are given Debio 1562 and rituximab IV on day 1 of each 21 days cycle. Debio 1562 is given at a dose of 0.7 mg/kg, followed by 375 mg/m^2 of rituximab.

Safety run-in continued with a Phase 2: Cohort 1 (R/R DLBCL) and Cohort 2 (other R/R NHL subtypes; see protocol versions 1, 2, and 3).

The Safety Review Committee (SRC) is comprised of the Sponsor's Medical Director and Investigators from participating sites, and is responsible for safety data review during the course of the trial.

Treatment emergent adverse events (TEAEs) occurring in patients enrolled into the safety run-in phase will be reviewed by the SRC. Once the Phase 2 dose is determined by the SRC, Cohorts 1 and 2 will open and enroll simultaneously, with rituximab and Debio 1562 being administered at the same schedule used in the safety run-in phase.

4.1.2 Part 2: Initial assessment of safety and efficacy of Q3W and QW dosing regimens of Debio 1562

Subjects with pathologically and clinically confirmed diagnosis of relapsed DLBCL are eligible for enrollment into two parallel cohorts.

In cohort A, subjects are given Debio 1562 IV and rituximab IV on day 1 of each 21 days cycle. Debio 1562 is given at a dose of 0.7 mg/kg, followed by 375 mg/m^2 of rituximab (same dose and schedule as in part 1).

In cohort B, subjects are given Debio 1562 IV once every week (QW) and rituximab IV Q3W. Debio 1562 is given at a dose of 0.4, 0.2 and 0.2 mg/kg on day 1, 8 and 15 of each 21 days cycle. Rituximab is given at a dose of 375 mg/m^2 on day 1 of each 21 days cycle.

Subjects in both cohorts will be treated for a maximum of six 21-day cycles. Subjects may exceptionally be granted treatment extension.

An independent data monitoring committee (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.

Assignment of subjects to cohort A and cohort B will be done through a central allocation system (IWRS). One-to-one randomization will be done when both cohorts are open for recruitment and automatic allocation of subjects to cohort A during IDMC review of cohort B.

4.1.3 Part 3: Expansion

Part 3 of the study will enroll additional subjects with pathologically and clinically confirmed diagnosis of relapsed DLBCL to further assess the safety, proof of activity and PK of the dosing schedule recommended following the evaluation of Part 2 by the IDMC.

IDMC will perform regular reviews of cumulative safety, proof of activity and PK data available.

Patients of the planned Part 3 were recruited under Part 2/3, no specific distinction was made between cohort 2 and 3.

4.2 Safety Review Committee and Independent Data Monitoring Committee

4.2.1 Safety Review Committee

The safety review committee (SRC), comprised of the Sponsor's medical director and investigators from participating sites, is responsible for safety data review during the course of part 1 (safety run-in). Please refer to Section 4.1.3.1 of the protocol for additional information on the SRC. The SRC determines 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.

4.2.2 Independent Data Monitoring Committee

The IDMC, comprised of independent experts in the field of hematology, oncology PK and biostatistics, will be responsible for the review of safety, proof of activity and PK data during the course of part 2 and part 3 of the clinical trial.

Available cumulative safety, PK and anti-tumor activity data will be provided for review by the IDMC:

- **For part 2, cohort A:**
  1. Once the 10th subject is 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 the 15th subject is 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 part 2, cohort B:**
  1. Once the 3rd subject has completed one cycle of treatment. Enrollment in this cohort will continue during the IDMC safety review;
  2. Once the 6th subject has completed two cycles of treatment. Enrollment in this cohort will be paused during the IDMC safety review;
  3. Once the 12th subject has completed two cycles of treatment. Enrollment in this cohort will be paused during the IDMC safety review;

  At IDMC review 2 or 3, PK evaluation might be available to support potential IDMC recommendation to explore new QW dosing schedule. At the maximum, only one potential new dosing will be explored. In such a case, the same IDMC reviews (1-3) as described above will be repeated for evaluation of this new schedule.
- **For part 3:**

After every 10 subjects 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).

Please refer to Section 4.1.3.2 of the protocol and to the IDMC charter for additional information on the IDMC.

4.3 Study Treatments

The investigational study drug, Debio 1562, will be provided by Debiopharm International S.A. in 20 mL glass vials each containing 5 mL of a protein concentration of 8.0 mg/mL Debio 1562 in aqueous buffered solution of pH 5.0 ± 0.3.

Rituximab will be supplied as a commercially available formulation.

4.4 Overall End-of-Study

The Overall End-of-Study is 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.

4.5 Study Procedures

Please refer to Appendix A, Appendix B and Appendix C for the description of the schedule of events. Study procedures are listed in Section 8 of the protocol.

5 RANDOMIZATION AND BLINDING

This is an open label clinical trial. Table 1 is providing a description of the randomization characteristics and constraints during each study part.

Table 1 - Study Parts and Randomization

Study Part	Randomization	Comments
Part 1	No	Subjects are given Debio 1562 (0.7 mg/kg) and rituximab IV (375 mg/m^2) on day 1 of each 21 days cycle.
Part 2	Yes	One-to-one block randomization will be done when both cohort A and cohort B are open for recruitment. Please refer to Section 4.1 for the automatic allocation to the open cohort during IDMC review
Part 3	Yes	Open for enrolment if and only if at least one cohort is eligible for part 3: - One-to-one block randomization if both cohort A and cohort B are eligible to part 3; - If cohort A (resp. cohort B) is not eligible for part 3, subjects will be assigned to cohort B (resp. cohort A).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7 ANALYSIS POPULATIONS

7.1 Screened Population

All subjects screened will be part of the screened population.

7.2 All treated / Safety Population

The All treated/safety population will include all patients from the screened population who received at least one dose of Debio 1562. Reporting in the All treated population will be done per the actual cohort as defined in the protocol.

7.3 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 assessment (including clinical progressive disease) will be part of the efficacy evaluable population. Reporting in the efficacy evaluable population will be done per the assigned treatment and cohort as per protocol (version 7, Section 10.2).

7.4 Per protocol population

The per-protocol (PP) population will include all patients from the Efficacy evaluable population who do not have any protocol deviation that could confound the interpretation of efficacy analyses. Patients who died from disease progression before end of first cycle will also be part of the per-protocol population.

The protocol deviations that could confound the interpretation of efficacy analyses include violation of key eligibility criteria (inclusion and/or exclusion) designed to ensure a specific subject population. It also includes the failing to collect data necessary to interpret the primary efficacy endpoints.

A detailed description of the protocol deviations which will exclude patients from the PP population is given in Appendix K.

7.5 PK Population

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

8 DATA HANDLING

8.1 Missing Data

Imputation rules for missing or partial dates are specified in Appendix J. No other imputation of missing data will be implemented.

8.2 Coding

Adverse events, medical history, concomitant procedures, prior cancer related surgery and prior radiotherapy will be coded using the last available version of the medical dictionary for regulatory activities (MedDRA). Prior medications, prior cancer systemic therapy and concomitant medications will be coded using the last available world health organization drug dictionary (WHO-DD).

8.3 Handling of Values Below (or Above) a Threshold

For statistical and graphical summaries of the safety laboratory tests, values below or above the limit of detection (e.g. '< 3' or '>500') are substituted with the lower/upper limit of detection (e.g. '< 3' is substituted by 3, '> 500' is substituted by 500). In data listings, the values will be shown as collected, e.g. including the < or > sign.

8.4 Handling of Unscheduled Assessments or Retests

Unscheduled assessments will not be used in the summary statistics, but will be used in the derivation of endpoints that are not related to a specific timepoint. All values collected will be displayed in listings.

9 GENERAL STATISTICAL CONSIDERATIONS

9.1 General Conventions

All output will be generated in Rich Text Format (RTF) from Microsoft Word and pdf file formats and labeled according to the International Conference on Harmonization (ICH) recommendations (ICH E3).

Unless otherwise specified, subjects enrolled in this study will be classified into the following reporting cohorts:

- Safety run-in
- R/R DLBCL Q3W (Cohort 1 of the Part 1 run in expansion)
- Other R/R NHL subtypes (Cohort 2 of the Part 1 run in expansion)
- Relapsed DLBCL Q3W (Cohort A of the Part 2/3)
- Relapsed DLBCL QW (Cohort B of the Part 2/3)

Continuous data will be described using descriptive statistics, including but not limited to: number of non-missing values (n), mean, standard deviation (SDev), median, minimum (Min) and maximum (Max). Categorical data will be described using the subject count and percentage in each category with a category for missing data.

For summary statistics of all continuous variables, unless otherwise specified, the minimum and maximum will be displayed to the same level of precision as the reported data. The mean and median will be displayed to one level of precision greater than the collected data. The standard deviation will be displayed to two levels of precision greater than the data collected.

P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001", if a p-value is greater than 0.999 it will be reported as "1.000".

Subjects will be identified in the listings by the investigator site number combined with the subject identification number.

When a count of zero is presented, the percentage (0% per definition) will be shown in the table, to draw attention to the non-zero counts. A row denoted "Missing" will be included in tables where specified in the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment group within the analysis set of interest, unless otherwise specified.

Unless otherwise specified, baseline will be defined as the last non-missing evaluation prior to the first infusion of Debio 1562, whether on the date of the infusion or prior to that date.

Study day will be calculated as follows:

- if date of measurement/observation is on or after the first dose date of Debio 1562: Date of measurement/observation – first dose date of Debio 1562 +1
- if date of measurement/observation is prior to the first dose date of Debio 1562: Date of measurement/observation – first dose date of Debio 1562.

As this clinical trial has randomized and non-randomized parts, study day 1 will be defined as the day of first dose of Debio 1562.

A month length is calculated as 30.4375 days (365.25 days / 12 months).

Partial missing date will be imputed for (see Appendix J):

- Dates for disease progression and death
- Start and end dates of concomitant medication and/or procedure
- Start dates of adverse events.

Expected duration of each cycle is 21 days. The first treatment cycle for each specific subject starts with its first dose of Debio 1562. The last treatment cycle is defined as the cycle for which the last dose of Debio 1562 is started. Unscheduled visits, if included for analysis, will be specified in footnote of tables and figures.

All analyses will be conducted using SAS Version 9.3 or higher.

[redacted]

9.3 Multi-Centre Studies

Given the limited number of subjects expected per center, all centers will be pooled for the statistical analysis.

9.4 Timing of Analyses

The following analyses are planned to be performed:

- SRC/IDMC mandated analyses
- 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 any patients 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 and the safety follow up visit of the last patient.

Due to the COVID-19 epidemy and subsequent delays in data entry and cleaning, the primary analysis will in fact coincide with the final analysis.

10 STATISTICAL ANALYSIS METHODS

10.1 Disposition of Patients, Demographic and Baseline Data

10.1.1 Screen Failures and Eligibility Criteria

A subject is considered enrolled when informed consent is signed, eligibility criteria are met, and eligibility for Debio 1562 administration is confirmed.

Number and percentage of subjects screened, screened but not enrolled, and reasons for not being enrolled will be summarized.

Supportive by-subject listing for all subjects screened, along with whether the subject was a screen failure (as of <28 days prior to first dose of Debio 1562) and if yes, the reason for the screen failure.

Additionally, a second by-subject listing will be provided showing whether the subject continued to meet eligibility criteria on Cycle 1 Day 1 prior to dosing, and if not, which inclusion/exclusion criteria were violated.

10.1.2 Subject Disposition

Subject disposition will be displayed in a listing and summarized in a table by cohort and overall for the safety population.

The number and percentage of subjects completing treatment, treatment discontinuation from Debio 1562, treatment discontinuation from rituximab, study discontinuation, along with reasons for discontinuation, and treatment regimen switching from QW to Q3W due to the Covid-19 pandemic will be presented in a table and a listing by cohort and overall.

The primary reasons for treatment discontinuation from Debio 1562 and/or rituximab may include any of the following: progressive disease, adverse event, subject withdrew consent to treatment, subject withdrew consent to treatment and follow up, death, investigator decision (not related to an AE), study terminated by sponsor, significant protocol deviation, and other (reason will be specified in data listings).

The primary reason for study discontinuation may include any of the following: subject withdrew consent, lost to follow up, significant protocol deviation, sponsor decision, investigator decision, death, study completion, and other (reason will be specified in data listings).

10.1.3 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the Institutional Review Board / Independent Ethics Committee and agreed to by the investigator. A major deviation occurs when there is non-adherence to the protocol by the subject or investigator that results in a risk to the subject, and/or the completeness, accuracy and reliability of the study data. All other deviations are minor. Descriptions of protocol deviations are listed in the Deviation Management Plan.

Protocol deviations will be summarized in a table by cohort and overall and displayed in a supporting listing.

10.1.4 Demographic and Baseline Characteristics

Baseline demographics will be summarized and listed by cohort and overall for all subjects in the safety population and will be repeated for all subjects in the efficacy evaluable population. Baseline demographic data to be evaluated will include age, sex, ethnicity, race, childbearing potential, height, weight, body mass index (body mass in kg divided by the square of the body height in meter) and body surface area. Age will be recorded on the electronic case report form (eCRF). Age will also be displayed in categories of 18-65 and > 65 years of age. No inferential statistics will be generated. Subject pregnancy test results will be included in a separate by-subject listing.

Moreover, baseline demographics will be summarized and listed [redacted].

10.1.5 Medical History

Medical history events will be coded using the medical dictionary for regulatory activities (MedDRA) per preferred term (PT) and system organ class (SOC). Summary of medical history will include number and percentage of subjects with a medical history condition overall, per SOC and per PT within each SOC. Listing will include condition/procedure, start and end dates and grade.

10.1.6 Disease Characteristics and Prior Therapy

10.1.6.1 Current Cancer Diagnosis

The current diagnosis will include the type of lymphoma, grade, [redacted] and method of assessment for DLBCL, Ann Arbor staging system at initial diagnosis and current stage, longest diameter (LDi, for listing only), shorter diameter perpendicular to LDi (SDi, for listing only), product of perpendicular diameters (PPD, for listing only), sum of the products of perpendicular diameters (SPD), results from cytogenetics/FISH/Molecular studies, [redacted], relapsed/refractory status, type of transformation if appropriate, extranodal disease status, Eastern cooperative oncology group (ECOG) performance status (PS). In addition, the International Prognostic Index (IPI) will be provided. The IPI is calculated[2] as the number of times the 5 following factors are met:

- Age above 60 years
- LDH above the upper limit of normal (ULN)
- Ann Arbor Stage III or IV
- ECOG PS ≥2
- Number of extranodal sites[3] >1.

According to the revised IPI categorization (R-IPI), the prognosis is considered very good for IPI=0, good for IPI=1-2, and poor for IPI=3-5 (Sehn 2007).

All the aforementioned data will be summarized and listed by cohort and overall. Moreover, these data will also be summarized and listed [redacted] among the safety population, this will be repeated [redacted] among the efficacy evaluable population and repeated again [redacted] among the Per Protocol evaluable population.

10.1.6.2 Prior Cancer Systemic Treatments

Prior cancer systemic therapy (PCST), radiotherapy and cancer related surgeries will be presented in separate listings. Number and percentage of subjects per number of PCST line (reasons therapy was given, best response, reasons for discontinuing, number of cycles for first and last regimen, time from first dose to recurrence (relapse or progression), time from

[2] If one or more of the 5 factors are unknown, a range of possible IPI will be calculated for the subject. If the range is within one of the groups (IPI=1-2 or IPI=3-5), then the patient will be included in the grouped R-IPI analysis in Table 3.

[3] Number of extranodal sites is different from number of extranodal lesions if there are >1 extranodal lesions per disease site. For example, if there are 2 extranodal lesions but they are both in the liver, this will be considered as 1 extranodal site (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993). For the purpose of IPI calculation, the spleen is considered as an extranodal site (whereas it is considered nodal for the Ann Arbor classification). Bone marrow involvement should also be taken into account: if either the bone marrow biopsy or the bone marrow aspirate have lymphoma involvement, this should be considered as involvement in the organ "Bone". If liver is noted as having "diffuse liver involvement" at screening, that should also count as an organ.

last dose to recurrence), prior radiation (site, best response), and prior surgical procedure (residual disease) will be summarized. If the start and/or end date of PCST or the recurrence date is missing, it will be imputed (see Section 8.1). Moreover, these aforementioned data will also be summarized and listed [redacted] among the safety population and this will be repeated [redacted] among the efficacy evaluable population.

10.1.7 Prior and Concomitant Medications/Procedures

Medications/Procedures will be classified into two categories:

- Prior, defined as medications/procedures with start date before the first dose date;
- Concomitant, defined as medications/procedures administered during treatment period (from first dose date to the end of the period of safety observation).

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD; version MAR2016 or higher). If the start and/or end date of concomitant medications is missing, it will be imputed (see Section 8.1).

Summary of prior and concomitant medication will include number and percentage of subjects with a concomitant medication overall, per ATC level 2 and per ATC level 4 within each ATC level 2. Separate supporting by-subject listings will be provided.

Additionally, the number and percentage who received a transplant will be tabulated under the prior medications summary table.

By-subject listing for concomitant procedures will be provided.

10.1.8 Eastern Cooperative Oncology Group Performance Status

Eastern cooperative oncology group (ECOG) performance status (Appendix I) will be assessed during screening and at other times specified in the schedule of events (Appendix A, Appendix B and Appendix C). All measurements will be displayed in a data listing.

10.1.9 Bone Marrow Assessment

If applicable, a bone marrow biopsy or aspirate assessment will be performed within three months prior to the first dose. A repeat bone marrow biopsy or aspirate may be performed per investigator's discretion for subjects with bone marrow infiltration at baseline who have a CR. In order to better understand the effect of Debio 1562 on white blood cells, bone marrow biopsies or aspirates may also be requested for those subjects who experience grade 4 cytopenias. All measurements will be displayed in a data listing.

10.1.10 Tumor Biopsy

Subjects must provide a fresh or archived tumor biopsy sample at screening; archived tissue obtained within one year of the screening period is acceptable, provided that the subject's tumor(s) had not transformed during that time. Starting from protocol version 5, samples

obtained within 18 months of the screening period are acceptable. If transformation occurred one year (18 months for patients recruited according to protocol version 5 or later) prior to study treatment, the most recent tumor biopsy must be from after the latest transformation; otherwise a fresh biopsy must be collected. Tumor biopsy results from central laboratory [redacted] will be displayed in a data listing.

10.1.11 Transfusion Log

Subjects who received a transfusion during treatment will be presented in a listing including the date, blood product received, and indication.

10.2 Efficacy Analyses

All summaries will present data by cohort and overall for the efficacy evaluable population. The data summaries of Responses, OS, PFS, and DoR will also be presented by Cohorts and overall for the Efficacy evaluable population . Data summaries for OS and PFS analyses will also be presented for the All treated population.

Subject level data will be provided in listings.

10.2.1 Multiple Comparisons/Multiplicity

No formal comparison between cohorts will be performed. Therefore, adjustment for multiple comparisons will not be required.

Hypothesis testing will be done only for the primary efficacy endpoint. Therefore, adjustment for multiplicity will not be required.

10.2.2 Radiologic Tumor Assessment

Tumor response assessment is based on the Lugano classification of response assessment of Hodgkin and non-Hodgkin Lymphoma (Cheson, 2014, see Appendix H).

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 by individual subject's extent of disease. 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. The same radiographic assessment method used at screening should preferably be used at all subsequent evaluations.

The results from the tumor assessments will be listed for target, non-target, and new lesions including: lesion number, date, site, and method. For target lesions their measurements (LDi, SDi and PPD), sum of product of diameters (SPD), and FDG-PET Deauville score will be provided. Non-target lesions will be assessed and listed as present, not present, or unknown and whether worsened or not. An overall response will be determined by the investigators following the recommendations from the 2014 Lugano classification. If a new tumor is

identified, the date of biopsy, site, size, diagnosis of lymphoma per biopsy, grade, [redacted], and method of assessment (if appropriate) will be listed. As per the 2014 Lugano classification, spleen and liver assessments will also be listed as appropriate.

Subject maximum percent change from baseline for the SPD (MCL, DLBCL, MZL, and FL) and the associated best overall response will be plotted (waterfall plot) for the efficacy evaluable population.

Subjects 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 subject's last on-treatment tumor assessment, until documentation of PD, or beginning subsequent anti-cancer therapy. The date of attempted contact, PD status, new anti-cancer therapy status, regimen, and dates will be listed.

10.2.3 Primary Efficacy Analysis

The BOR is the best response recorded from the start of the treatment until disease progression or initiation of new anti-cancer therapy or end of the study period, whichever occurs first. Additionally, best response will be evaluated from first dose date up to first on-treatment scheduled assessment, up to second on treatment scheduled assessment, up to third on-treatment scheduled assessment, and up to End of the treatment period, i.e. up to the date of last cycle day 1 + 21 days..

Response assessment will be determined by the investigator for each subject as:

- Complete (metabolic) response (CMR/CR)
- Partial (metabolic) response (PMR/PR)
- No metabolic response or stable disease (NMR/SD)
- Progressive (metabolic) disease (PMD/PD)
- Not evaluated (NE)
- Not done.

The following rules will be applied to define period:

- From first dose date up to first on-treatment scheduled assessment:
    - From first dose date up to 6 weeks + 7 days from first dose date
- From first dose date up to second on-treatment scheduled assessment:
    - From first dose date up to 6 weeks + 7 days from first on-treatment scheduled scan if first on-treatment scheduled scan is performed
    - From first dose date up to 12 weeks + 14 days from first dose date if first on-treatment scheduled scan is not performed
- From first dose date up to third on-treatment scheduled assessment:
    - From first dose date up to 6 weeks + 7 days from second on-treatment scheduled scan if second on-treatment scheduled scan is performed
    - From first dose date up to 12 weeks + 14 days from first on-treatment scheduled scan if second on-treatment scheduled scan is not performed but first on-treatment scheduled scan is performed
    - From first dose date up to 18 weeks + 21 days from first dose date if first and second on-treatment scheduled scan are not performed.

The ORR is defined as the proportion of subjects with a BOR of PR or CR. The BOR and ORR will be tabulated along with percentages.

Ninety-five and eighty percent two-sided exact confidence intervals (CIs) will be constructed using the Clopper-Pearson method (Clopper, 1934). For the analyses carried out by cohort, the one-sided exact binomial distribution will also be used to test the hypotheses that the ORR is below or on 40% and above or on 60%, respectively.

The following sensitivity analysis will be performed:

- An additional analysis will be done by censoring the Cohort B subjects who have switched to Q3W regimen at their last assessment date while they were still in QW regimen

10.2.4 Secondary Efficacy Analyses

Progression free survival (PFS), OS, and DoR will be analyzed using the Kaplan-Meier method in both summary tables and figures. The number and percentage of subjects censored and those with events will be summarized. Additionally, the median, 25th and 75th percentile estimates and 95% CI (where calculable based on Brookmeyer and Crowley 1982), and minimum and maximum in months will be presented. The PFS rate, DoR rate and OS rate, calculated at 3, 6, 9, 12, 15, 18, 21, 24, and last point of observation months will be presented along with 95% CI (using the log-log transformation) based on Kaplan-Meier product limit estimates. The denominator for event/censored rates will be the number of subjects within each cohort and total. Time to response will be analyzed using descriptive statistics only.

10.2.4.1 Progression Free Survival

PFS is defined as the time (in months) between the date of the first Debio 1562 dose until the earliest of either first occurrence of PD (radiologic or clinical) or death. It is calculated as:

(date of first PD/death - date of first Debio 1562 dose + 1) / 30.4375.

The following censoring rules will be applied:

1. Subjects who do not experience death or PD, nor initiate a new systemic therapy will be right-censored at the date of their last adequate tumor assessment (i.e. a tumor assessment not showing NE);
2. Subjects having initiated a new systemic therapy before experiencing death or PD will be right-censored at the date of their last adequate tumor assessment prior to initiation of a new systemic therapy;
3. Subjects who experienced death or PD after two or more consecutive missing or inadequate tumor assessments (i.e. 2*6*7 + 2*7 = 98 days, based on assessments every 6 +/- 1 week) while assessments are done every 6 +/- 1 week will be right-censored at their latest adequate assessment before death or PD;

4. Subjects who experienced death or PD after one or more consecutive missing or inadequate tumor assessments (i.e. 12*7 + 4*7 = 112 days, based on assessments every 12 +/- 4 week) while assessments are done every 12 +/- 4 week will be right-censored at their latest adequate assessment before death or PD;
5. Subjects without a baseline or post-baseline assessment will be right-censored at the date of first administration of the Debio 1562 unless the subject died within 190 days from the first dose date (5*(21+3)+21+7+42 = 190 days, considered as an event at the date of death).

If multiple event and censoring conditions are met for the same subject, then the condition with the earliest date will be selected.

When an analysis cutoff date is implemented, only data occurring on or prior to the cutoff date will be used for analysis and subjects will be censored at the latest adequate assessment prior to cutoff date.

The following sensitivity analyses will be performed:

1. An additional sensitivity analysis for progression-free survival consists of ignoring the 3rd and 4th censoring rules.
2. For progression-free survival, subjects who do not experience disease progression or death or who initiate anti-cancer therapy other than for a transplant or CAR-T will be right-censored at the date of their last adequate tumor assessment using the same rules as above. Hence, data collected after a transplant therapy or CAR-T until PD, death or last adequate tumor assessment - whichever occurs first will be included in the PFS derivation.
3. An additional analysis will be done by censoring the Cohort B subjects who have switched to Q3W regimen at their last assessment date while they were still in QW regimen
4. An additional analysis will be done by censoring the subjects who died due to Covid-19 at their death date, if they haven't progressed yet.

10.2.4.2 Duration of Response

Duration of Response is defined as the time between the earliest date of CR or PR response and the date of the first occurrence of PD or death and calculated as:

(date of first PD/death - date of first CR/PR + 1) / 30.4375.

Censoring rules for PFS will be applied to DoR. The DoR will be estimated for all evaluable subjects who achieve an objective response of PR or CR.

The sensitivity analyses for PFS will also be reproduced for DoR.

10.2.4.3 Time to Response

Time to response is defined as the time from the date of the first dose until the date of first CR or PR. It is calculated as:

(date of first CR/PR - date of first Debio 1562 dose + 1) / 30.4375.

Time to response will be estimated for all evaluable subjects who achieve an objective response of PR or CR. No subject censoring is involved.

Time to complete response is defined as the time from the date of the first dose until the date of first CR. It is calculated as:

(date of first CR - date of first Debio 1562 dose + 1) / 30.4375.

Time to complete response will be estimated for all evaluable subjects who achieve an objective response of CR. No subject censoring is involved.

10.2.4.4 Overall Survival

Overall Survival is defined as the time between the date of the first dose and the date of death. It is calculated as:

(date of death – date of first Debio 1562 dose + 1) / 30.4375.

Subjects who do not experience the event of death will be right-censored at their last date known to be alive as 'Ongoing' or 'Lost to follow-up'.

The date of attempted contact, survival status and - if new anti-cancer therapy was started - along with the respective regimen will be listed.

The following sensitivity analyses will be performed:

1. An additional analysis will be done by censoring the Cohort B subjects who have switched to Q3W regimen at their last assessment date while they were still in QW regimen
2. An additional analysis will be done by censoring the subjects who died due to Covid-19 at their death date, instead of considering that they died

[redacted]

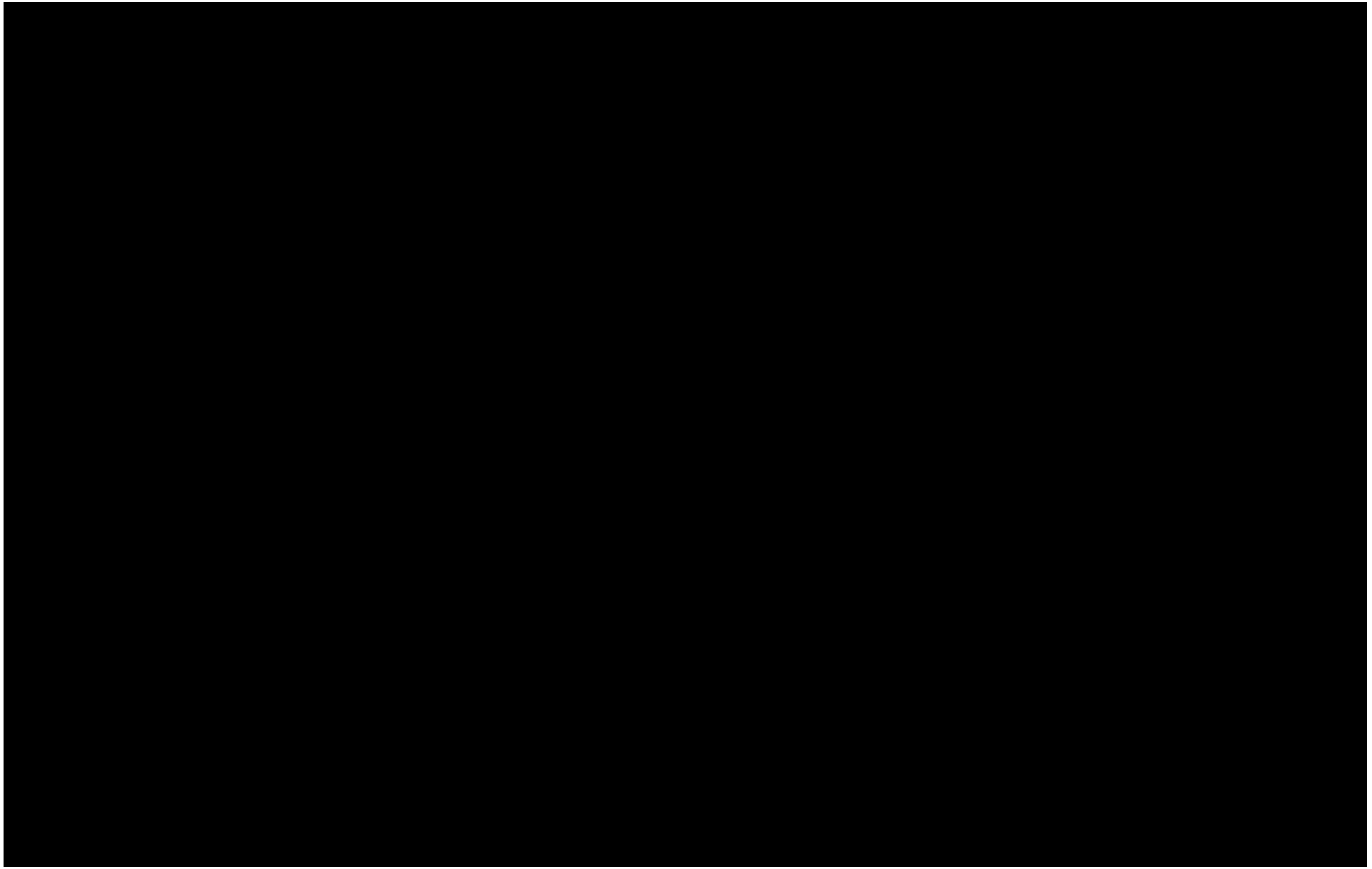
[redacted]

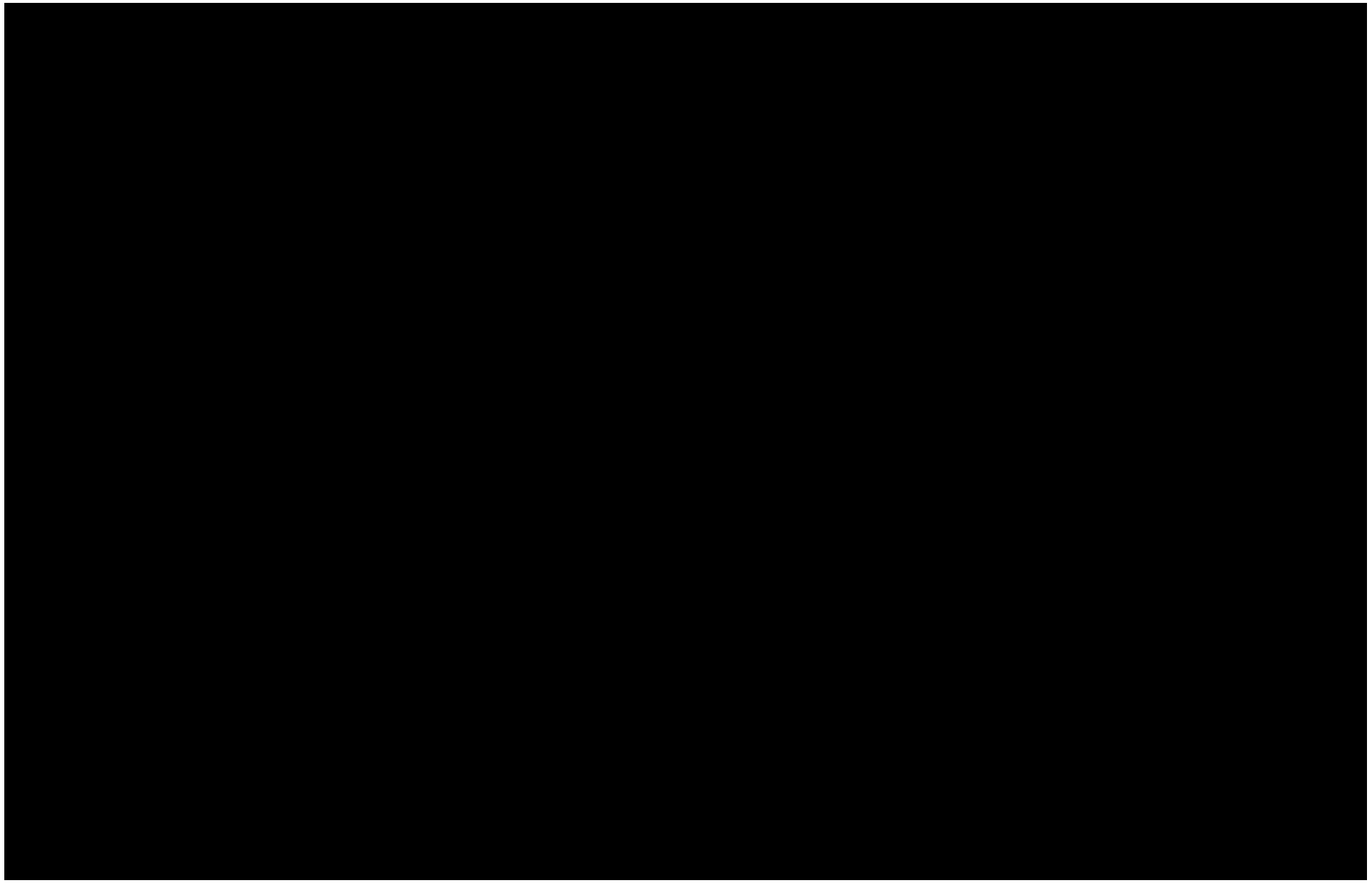
[redacted]

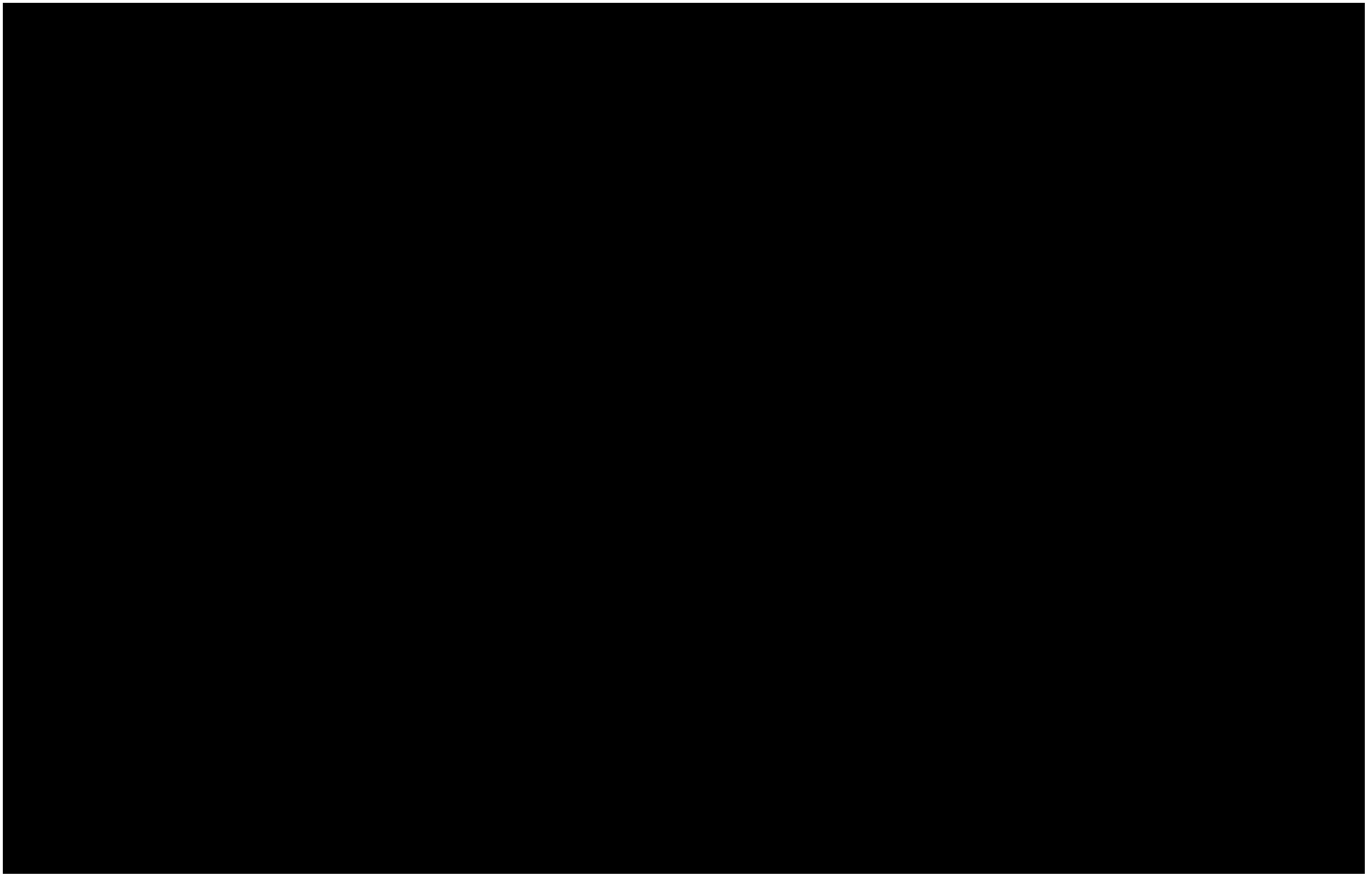
[redacted]

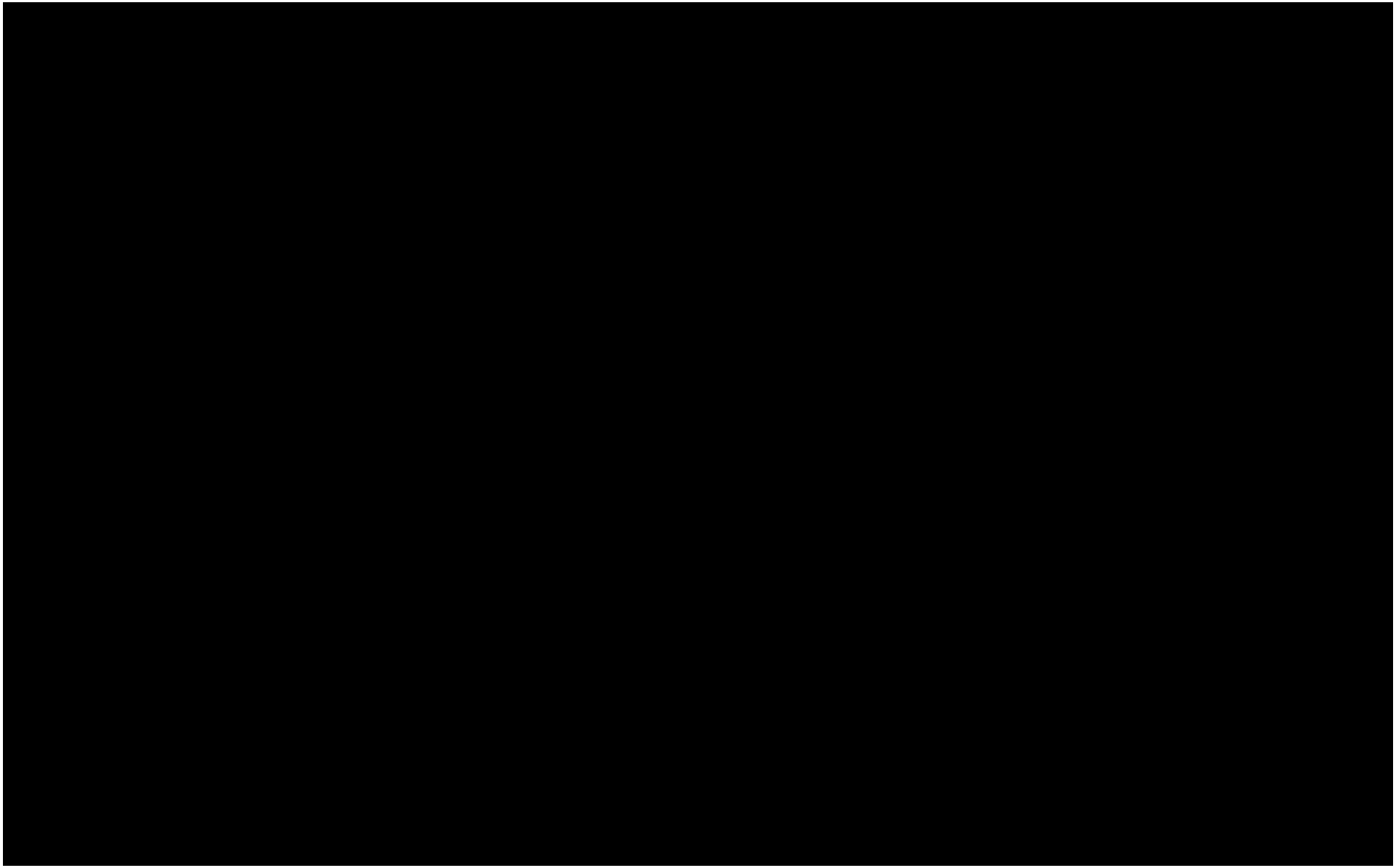
[redacted]

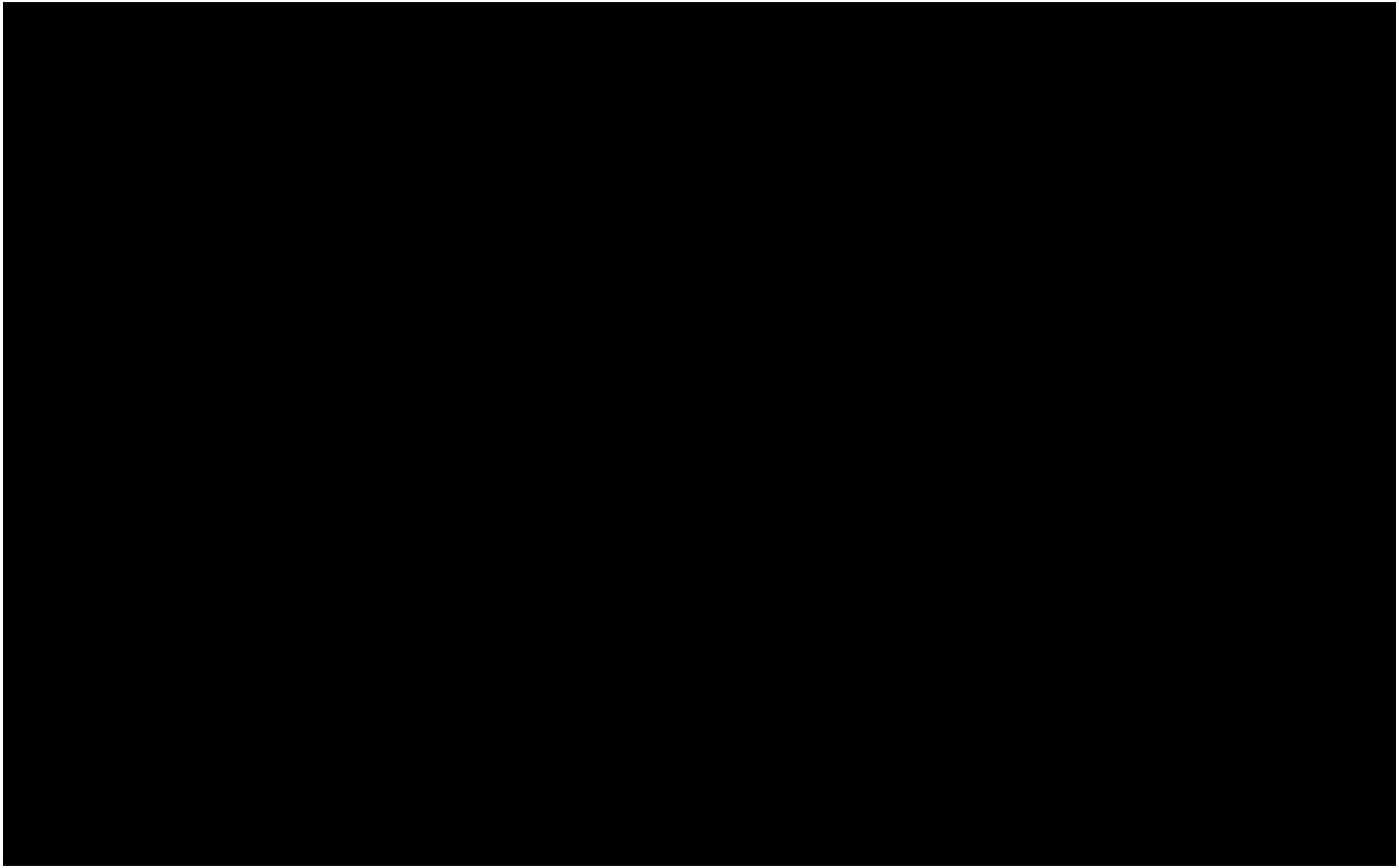
[redacted]

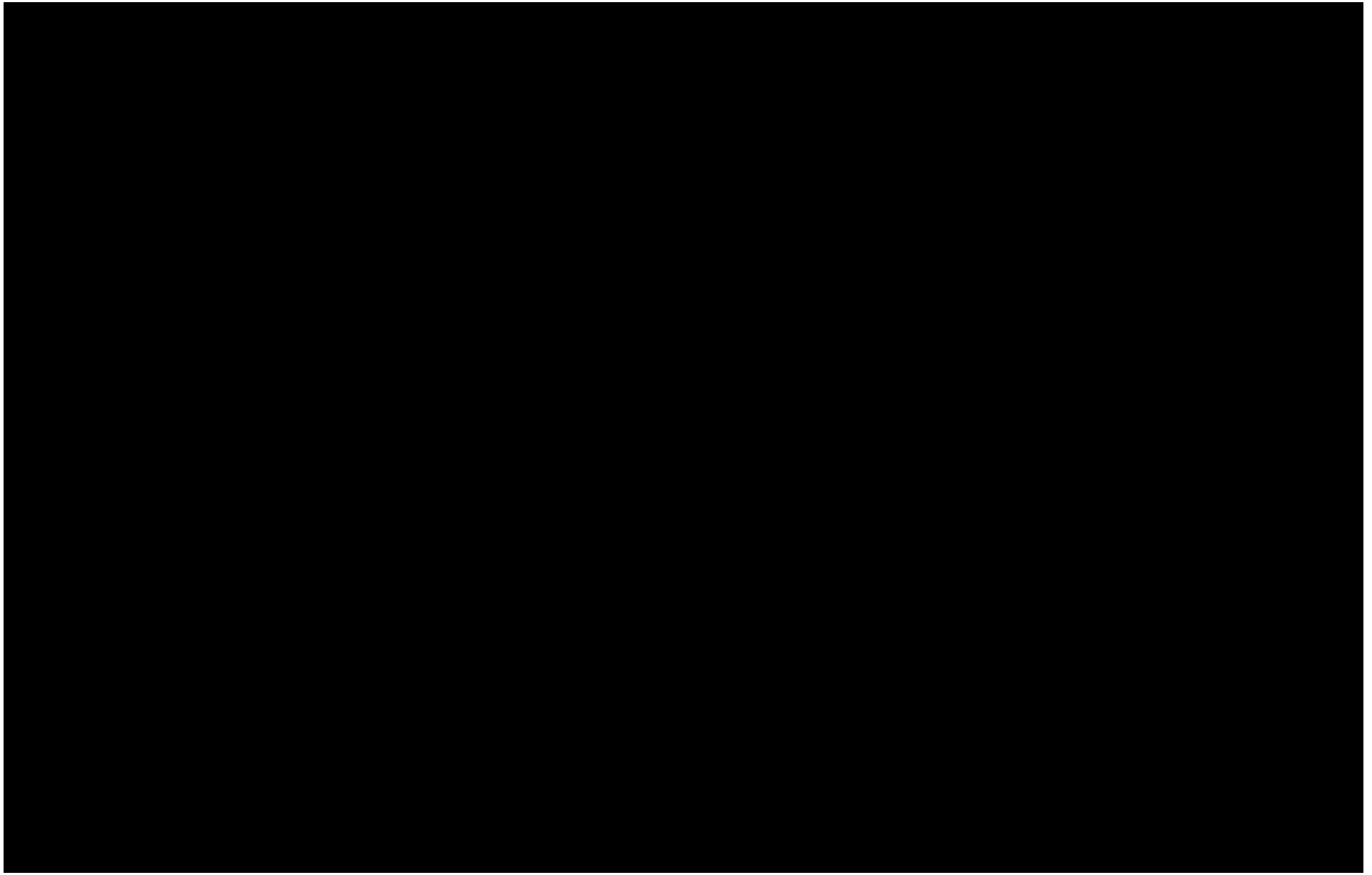












10.3 Safety Analyses

All safety analyses will be conducted on the safety population. All summaries will present data by cohort, unless otherwise specified. Safety evaluations will be based on the incidence and severity of adverse events (AEs), clinically significant changes or abnormalities in the subject's laboratory results, vital signs, physical examination, ECG, and Eastern Cooperative Oncology Group (ECOG) score.

10.3.1 Adverse Events

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.

An AE will be considered to be a treatment-emergent adverse event (TEAE) if it begins or worsens on or after the first dose date of either Debio 1562 or rituximab, whichever occurs first, and before the last dose date of either Debio 1562 or rituximab + 30 days, whichever occurs last.

A serious adverse event (SAE) is defined as any event that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, results in a congenital anomaly/birth defect, or may jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse events will 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 (PT). Severity grade will be defined according to the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) v4.03.

A study drug related AE is an event where the investigator determined that the relationship to study drug (evaluated separately for Debio 1562 and rituximab) was "possibly related", "probably related", or "definitely related".

Only missing AE onset dates will be imputed as shown in Appendix I. Adverse events for which onset date could not be determined after imputation of missing date are considered to be treatment emergent.

Adverse events will be summarized per SOC, PT, and CTCAE grade. For summaries by relationship, adverse events with missing relationship are counted as "Possibly Related". Adverse events with missing CTCAE grade will not have CTCAE grade imputed. In tabulations, however, if the subject has at least one PT with a non-missing CTCAE grade, the non-missing grade will be displayed.

In addition, the following groups of terms will be analyzed in a grouped manner:

- Neutrophil count decreased (PT Code 10029366) and Neutropenia (PT Code 10029354)

- Lymphocyte count decreased (PT Code 10025256) and Lymphopenia (PT Code 10025327)
- White blood cell count decreased (PT Code 10047942) and Leukopenia (PT Code 10024384)
- Platelet count decreased (PT Code 10035528) and Thrombocytopenia (PT Code 10043554)
- Blood magnesium decreased (PT Code 10005654) and Hypomagnesaemia (PT Code 10021027)
- Oxygen saturation decreased (PT Code 10033318) and Hypoxia (PT Code 10021143)
- Pneumonia (PT code 10035664) and lung infection (PT Code 10061229)

[redacted]

Treatment emergent adverse events will be summarized by the total number of events and CTCAE grade. TEAEs will also be summarized by the number of subjects with at least one event and will be grouped by SOC, PT, and CTCAE grade. In all tables, a subject contributes only once to the count for a given AE (SOC or PT) at the worst CTCAE grade. Each subject will contribute only once for the most related occurrence or the most intense occurrence to each of the incidence rates in the descriptive analysis, regardless of the number of episodes, e.g. worst grade per subject per AE (except for total number of events). All summary tables will be grouped by cohorts defined at Section 9.1 and overall.

Besides the overall summary of all TEAEs, the following summaries of TEAEs by system organ class, preferred term, and CTCAE grade will be provided:

- All TEAEs;
- All Grade 3 or higher TEAEs;
- All treatment-related TEAEs (overall and by cohort and study treatment);
- All treatment-related Grade 3 or higher TEAEs (overall and by cohort and study treatment);
- All serious TEAEs;
- All treatment-related serious TEAEs (overall and by cohort and study treatment);
- All TEAEs excluding serious;
- All TEAEs resulting in treatment discontinuation (overall and by cohort and study treatment);
- All TEAEs leading to death;
- All dose-modifying events;

The following summaries of TEAEs by preferred term and CTCAE grade will be provided:

- TEAEs with at least 10% overall incidence (tables and figures)
- Treatment-related TEAEs with at least 10% overall incidence (overall and by cohort and treatment, tables and figures)

-

As a subgroup analysis, the overall summary of all TEAEs will be done for subjects with a treatment duration inferior or equal to 6 cycles versus for subjects with a treatment duration greater than 6 cycles.

Data listings will be provided for all AEs, SAEs, study drug related AEs, AEs resulting in study drug discontinuation, AEs considered as being dose-modifying events and AEs leading to death. Relationship to Debio 1562 or rituximab, and action taken regarding Debio 1562 and/or rituximab administration, respectively will be provided. Non-TEAEs will be flagged in the listings.

10.3.2 Deaths and Other Significant Adverse Events

The primary cause of death will be presented in a table with the following reasons: PD, AE, Other, or Unknown; also whether an autopsy was performed or not. Separate summaries of deaths occurring on-study or within 30 days of last dose of either Debio 1562 or rituximab, and deaths after 30 days of last dose of either Debio 1562 or rituximab will also be provided. All deaths occurring on-study and during follow-up will be presented in a listing; deaths occurring after 30 days of last dose of either Debio 1562 or rituximab will be flagged.

10.3.3 Clinical Laboratory Evaluations

Screening laboratory evaluations (hematology, clinical chemistry, urinalysis, and coagulation) may be performed within 28 days before the first dose. Repeat testing will be performed as outlined in schedule of events (Appendix A, Appendix B and Appendix C) and as clinically indicated. Clinical laboratory results will be classified as Low, Normal, and High, or Normal/Abnormal according to the lab normal ranges, and will be graded according to NCI CTCAE, Version 4.03.

All hematology, serum chemistry, urinalysis, and coagulation will be listed per subject for each assessment and descriptive statistics will be tabulated for selected criteria detailed below by cohort and overall. SI units will be used for listing and reporting. Changes and percent changes from baseline in hematology and serum chemistry will be calculated for each subject and subsequently summarized by cohort and overall. Shifts from baseline in hematology and serum chemistry values will also be summarized by CTCAE grade within cohorts and overall. Only scheduled visits will be included in change from baseline summary tables; however, unscheduled visits will be included in worse post-baseline shift tables, liver function tests summaries, and listings.

10.3.3.1 Hematology

Hematology will include: hematocrit (HCT), hemoglobin (HGB), platelet count (PLAT), red blood cell (RBC) count, white blood cell (WBC) count with differential [i.e. neutrophils count (NEUT), lymphocyte (LYM), monocytes (MONO), eosinophils, and basophils (BASO)].

Shift from baseline to worst post-baseline low and high CTCAE grade for hematology parameters will be presented in a table for: HGB, RBC, NEUT, PLAT, LYM and WBC. In the

shift table based on being lower than a lower normal limit (worst low), a value above the upper normal limit will be considered as grade 0.

10.3.3.2 Serum chemistry

Serum chemistry will include: albumin (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (UREAN), calcium (CA), chloride (CL), creatinine (CREAT), glucose (GLUC), lactate dehydrogenase (LDH), magnesium (MG), phosphorus (PHOS), potassium (K), Sodium, total bilirubin (BILI), total protein (PROT), Uric acid (URATE), and Immunoglobulin levels (i.e., IgG, IgA, and IgM).

Shift from baseline to worst post-baseline CTCAE grade for serum chemistry parameters (i.e. ALB [worst low only], ALP, ALT, AST, CREAT, BILI, and URATE [worst high only], and PHOS, CA, CL, GLUC, MG, K, and SODIUM [both worst low and worst high]) will be presented in separate tables for CTCAE based on being higher or lower than normal limits, where applicable. In the shift table based on being higher than an upper normal limit (worst high) a value below the lower normal limit will be considered as grade 0. Likewise, in the shift table based on being lower than a lower normal limit (worst low), a value above the upper normal limit will be considered as grade 0.

10.3.3.3 Urinalysis and Pregnancy Test

Urinalysis includes: appearance, specific gravity, and pH. Microscopic examination of sediment is to be performed if the specimen is positive for WBCs, proteins, or blood. Semi quantitative evaluations include using dipsticks for glucose, protein, bilirubin, ketones, leukocytes and blood. Urinalysis and pregnancy test laboratory results will be presented in separate listings.

Coagulation

Coagulation tests include: prothrombin time, International Normalized Ratio (INR), and activated partial thromboplastin time (aPTT). Coagulation results will be presented in a data listing.

10.3.3.4 Liver Function Test

Clinically significant values in liver function tests will be summarized by the following categories using the maximum value while on treatment. The denominator for the summaries will be the number of subjects who had at least one non-missing value during treatment. Please note that the categories for each test are not mutually exclusive:

- AST:
  - > 1xULN & ≤ 3xULN;
  - > 3xULN & ≤ 5xULN;
  - > 5xULN & ≤ 10xULN;
  - > 10xULN & ≤ 20xULN;

    - > 20xULN;
- ALT:
    - > 1xULN & ≤ 3xULN;
    - > 3xULN & ≤ 5xULN;
    - > 5xULN & ≤ 10xULN;
    - > 10xULN & ≤ 20xULN;
    - > 20xULN;
- AST or ALT:
    - > 1xULN & ≤ 3xULN;
    - > 3xULN & ≤ 5xULN;
    - > 5xULN & ≤ 10xULN;
    - > 10xULN & ≤ 20xULN;
    - > 20xULN;
- Total bilirubin (TBL):
    - > 1xULN & ≤ 2xULN;
    - > 2xULN;
- Alkaline Phosphatase:
    - > 1.5xULN;
- (AST or ALT) and TBL (all tests must be conducted within 72 hours):
    - AST or ALT > 3xULN and TBL > 1.5xULN & ≤ 2xULN;
    - AST or ALT > 3xULN and TBL > 2xULN;
- (AST or ALT) and ALP and TBL (all tests must be conducted within 72 hours):
    - AST or ALT > 3xULN and ALP < 2xULN and TBL > 2xULN.

10.3.3.5 Vital Signs

Vital sign measurements will include blood pressure, heart rate, temperature, and respiratory rate. Height will only be measured at screening and weight will be measured as indicated in the schedule of events (Appendix A, Appendix B and Appendix C). A change and percent change from baseline summary table, and a listing of measurement values by visit, will be provided for vital signs. Only scheduled visits will be included in change from baseline summary tables. All visits will be included in listings.

10.3.4 Other Safety Measures

10.3.4.1 Physical Examination

A complete physical examination including assessments of general appearance, skin, head (eyes, ears, nose, and throat), lungs, heart, abdomen, back, lymph nodes, extremities, and neurological system will be completed at screening and at end of treatment. Directed physical examinations will be completed at additional time points as specified in the schedule of events. The results of all time points will be displayed in a listing.

10.3.4.2 Electrocardiogram

Please refer to Appendix A, Appendix B and Appendix C for the schedule of events.

ECG results including: Heart Rate, QT Interval, QTc Interval and method, and classification of Within Normal Limits, Abnormal Not Clinically Significant, and Abnormal Clinically Significant with a description for abnormal findings will be presented in data listings.

QTcB based on Bazetts' formula or QTcF based on Fredericia's formula will be listed for all subjects under the method used by the local laboratory. The denominator for the summaries will be the number of subjects who had non-missing values at each visit time point. Only scheduled visits will be included in summary tables. All visits will be included in listings.

Number and percentage of subjects in the following categories will be tabulated by cohort and overall for QTcF and QTcB:

- > 450 ms;
- > 480 ms;
- > 500 ms;
- change from baseline > 30 ms;
- change from baseline > 60 ms;
- > 500 ms and/or change from baseline > 60 ms;

where they can be calculated using the following:

- Bazett's Formula: QTcB = QT / square-root (RR Interval);
- Fredericia's Formula: QTcF = QT / cube-root (RR Interval);
- RR Interval = 60 / Heart Rate.

The categories used in the tabulation are not mutually exclusive. Additionally, for the tabulations, where the local laboratory did not provide both a QTcB and a QTcF value, the values that were missing will be derived using the above formulas.

Shift from baseline to worst post-baseline ECG results will be presented by cohort and overall.

10.3.4.3 B-Symptoms

B-symptoms are defined as at least one of the following:

- unexplained fevers greater than 38°C
- drenching night sweats
- weight loss greater than 10% of normal body weight over a period of 6 months or less.

B-symptoms will be documented at screening, prior to every cycle and at end of treatment. All results will be displayed in a data listing.

10.4 Extent of Exposure

Debio 1562 will be given intravenously:

- On day 1 of each 21-day cycle for subjects assigned to a Debio 1562 Q3W dosing schedule cohort. Planned Debio 1562 dose for the Q3W dosing schedule is 0.7 mg/kg;
- On day 1, day 8 and day 15 of each 21-day cycle for subjects assigned to the Debio 1562 QW dosing schedule cohort. Planned Debio 1562 dose for the QW dosing schedule is 0.4 mg/kg, 0.2 mg/kg and 0.2 mg/kg at day 1, day 8 and day 15 of each cycle.

Rituximab will be given intravenously on day 1 of each 21-day cycle after the infusion of Debio 1562. Planned dose for rituximab is 375 mg/m2.

For Debio 1562, the total dose of drug will be calculated based on each subject's body weight. The weight used for calculation should be obtained prior to first treatment and thereafter should only be modified for relevant (≥10%) changes in baseline body weight (not influenced by weight gain or loss attributed to fluid retention).

The exposure to Debio 1562 and rituximab will be summarized by cohort and overall, with summary statistics including mean, standard deviation, median, minimum, and maximum on:

- **Number of treatment cycles**, defined as the number of cycles in the eCRF where non-zero dose of Debio 1562 was infused;
- **Treatment duration**, expressed in weeks. It is calculated as:

  Ceiling ((date of last cycle day 1 – date of first dose + 21) / 7);

- **Total cumulative dose**, expressed in mg. It is calculated as the sum of the actual dose administered in all cycles while the subject is on study drug;
- **Actual dose level**:
  - Debio 1562 actual dose level, expressed in mg/(kg*cycle). It is calculated as:

    *Total cumulative dose of Debio 1562 (mg) / (average pre-dose weight (kg) * number of cycles)*

  - Rituximab actual dose level, expressed in mg/(m2*cycle). It is calculated as:

    *Total cumulative dose of rituximab (mg) / (average pre-dose Body Surface Area (BSA) (m2) * number of cycles)*

Relative dose intensity per week (over the treatment duration)

- **Relative dose intensity per week**, expressed in %. It is calculated as: *Actual dose intensity / planned dose intensity * 100*
- **Actual dose intensity**, expressed in mg/week. It is calculated as:

  Total cumulative dose (mg) / duration of dosing (weeks).

- **Planned dose intensity**, expressed in mg/week. It is calculated as

  *Total planned cumulative dose in a cycle (mg/kg or mg/m2) * pre-dose weight (kg) or BSA (m2) / 3 (weeks)*

The pre-dose weight used for this calculation should be obtained prior to first treatment, i.e. at Cycle 1 Day 1, and thereafter should only be modified for significant (≥ 10%) changes in body weight.

Relative dose intensity (Listing)

- **Relative dose intensity**, expressed in %. It is calculated as: actual cumulative dose received / planned cumulative dose during the same number of cycles * 100, where:
- **The number of cycles** for this calculation will be taken as the number of initiated cycles up
- to Cycle 6 included, or until PD, or until decision to end the treatment, whichever comes first.
- **The actual cumulative dose received** will be calculated as the sum of doses that have been administered during the above-defined number of cycles.
- **The planned cumulative dose** will be calculated as the planned per protocol dose (for Debio 1562: 0.8 mg/kg for Cohort B, 0.7 mg/kg for all other cohorts; for rituximab: 375 mg/m^2) multiplied by the number of cycles initiated (up to Cycle 6 or until PD, or until decision to end the treatment, whichever comes first).

The number and percentage of subjects who had interrupted, missed, delayed, or decreased dosing, and the reason(s) will be summarized for Debio 1562 and rituximab. For each modification action, each distinct reason will be reported in each specific category.

Supportive by-subject listings of Debio 1562 and rituximab infusions will be presented.

Infusion rate will be obtained from the relevant data in the EDC but also calculated as (mg in infusion)/(time of treatment end – time of treatment start). Both will be presented in listings.

10.5 Pharmacokinetics

Blood samples for pharmacokinetics will be collected as outlined in Appendix D(Safety run-In and Phase II), Appendix E (Cohort A, Part 2 and 3) and Appendix F (Cohort B, Part 2 and 3).

Concentration of Debio 1562, anti-drug antibody (ADA) Debio 1562, Debio 1562 total antibody (TAb), DM1 Free, DM1-SMCC-lysine, DM1-SMCC, Rituximab, and ADA Rituximab will be summarized by cohort and per visit and also by regimen. The following summary statistics will be produced: the number of non-missing values, the arithmetic mean, the standard deviation, the coefficient of variation, the median, the first and third quartiles, the minimum, the maximum, the geometric mean, the geometric standard deviation and the geometric coefficient of variation.

Concentrations that are below the limit of quantification will be handled as follows:

- All pre-dose concentrations observed before cycle 1 day 1 that are below the limit of quantification will be imputed by:

    - Zero for the computation of the mean, the standard deviation, and the coefficient of variation
    - Half the limit of quantification for the computation of the geometric mean, the geometric standard deviation, and the geometric coefficient of variation
- All concentrations observed after the first dose date that are below the limit of quantification will be imputed by half the limit of quantification.

PK parameters, including but not limited to C_{max}, T_{max}, $t_{1/2}$ and AUC, will be summarized similarly as above for Debio 1562, Debio 1562 TAb, DM1 Free, DM1-SMCC-lysine, DM1-SMCC and rituximab.

The overall PK and PK/PD analyses will be described in a separate analysis plan.

[redacted]

[redacted]

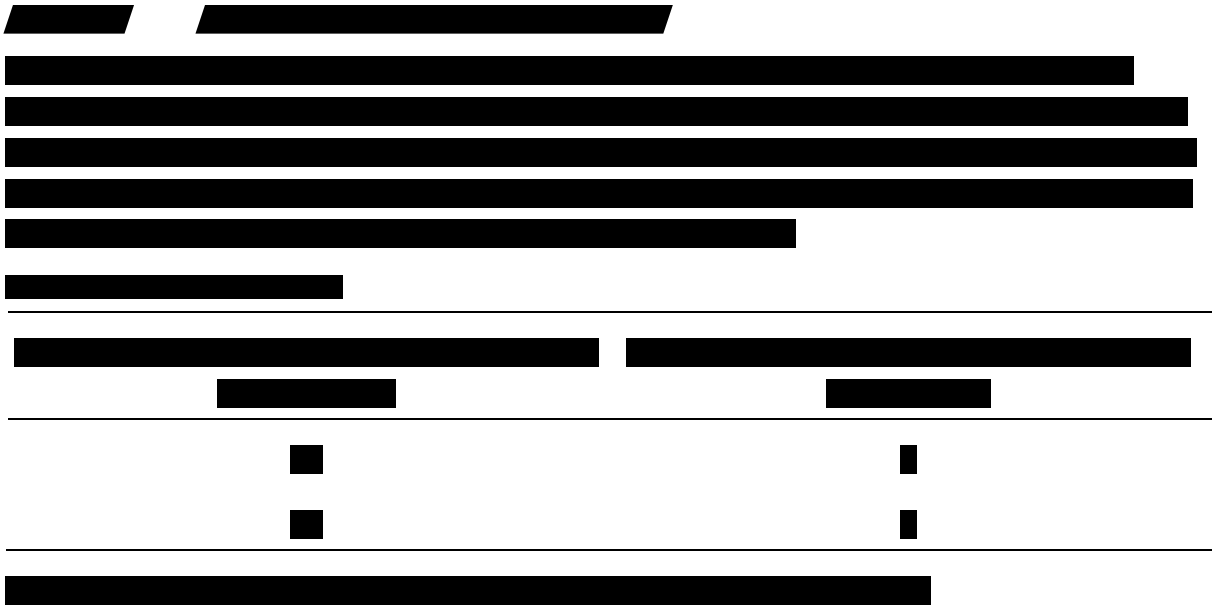
10.7 Other Analyses

10.7.1.1 Health-Related Quality of Life

Health-related quality of life will be evaluated based on the functional assessment of cancer therapy-lymphoma (FACT-Lym). Please refer to scoring manual (www.facit.org) for instruction for computing overall score and subscale scores. Full analysis of the health-related quality of life questionnaire is beyond the scope of this document. It will be described in a separate analysis plan.

10.8 Interim Analyses

No formal interim analysis is planned for this study. However, available safety and PK data will be reviewed by the SRC during the course of study part 1 and by the IDMC during the course of part 2 and part 3 of the study (see Section 4.2).



10.8.1.2 Stopping Rules for Safety

The IDMC will review the safety data regularly and can recommend terminating or modifying any dosing regimen or the study to guard subjects' safety. The IDMC will monitor all safety aspects with special focus on neutropenia, febrile neutropenia, hepatic damage, pneumonitis and neuropathy.

11 SUMMARY OF CHANGES TO THE PROTOCOL

Amendment history to the protocol can be found in Section 1.10 of the protocol.

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13 APPENDICES

Appendix A. **SCHEDULE OF EVENTS OF SAFETY RUN-IN FOR Q3W DOSING (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	Day 8 ±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]								•[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.

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 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 C_{max} and PK blood draw) and 24 $\pm$ 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 within 4 weeks of 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 (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.

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.

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.

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 C_{max} and PK blood draw) and 24 $\pm$ 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 the 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 until 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 (PART 2)**

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.

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.

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. 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 $\pm$ 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 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 D. PHARMACOKINETIC AND IMMUNOGENICITY ASSESSMENT OF SAFETY RUN-IN FOR Q3W DOSING (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.

* 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 (PART 2)

Activity	Cycles 1 and 2					Cycles 3-6 [b]	EOT [b]	30-Day Follow-up
	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 ASSESSMENT OF COHORT B FOR QW DOSING (PART 2)**

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

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. **RESPONSE ASSESSMENT 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 iver. 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. At end of treatment, these findings indicate residual disease.	☐ ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites ☐ 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
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 esions	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 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior ncrease 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 nterval 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 I. 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 J. IMPUTATION ALGORITHM FOR PARTIAL AND MISSING DATES

Adverse Event

- If onset date is completely missing:
  - If AE end date is missing or on/after the date of first dose, then onset date is set to date of first dose
  - If AE end day is missing, but the month and year of the AE end date is larger than the month and year of the first dose date, then the onset date is set to the date of first dose
  - If AE end month is missing, but the year of the AE end date is larger than the year of the first dose date, then the onset date is set to the date of first dose
  - If AE end date is prior to the date of the first dose, then onset date is not imputed
- If (onset year is present and month and day are missing) or (onset year and day are present and month is missing):
  - If year = year of first dose, then set onset month and day to month and day of first dose
  - If year < year of first dose, then set onset month and day to December 31st.
  - If year > year of first dose, then set onset month and day to January 1st.
- If onset month and year are present and day is missing:
  - If year=year of first dose and
    - If month = month of first dose then set day to day of first dose date
    - If month < month of first dose then set day to last day of month
    - If month > month of first dose then set day to 1st day of month
  - If year < year of first dose then set day to last day of month
  - If year > year of first dose then set day to 1st day of month
- For all other cases, set onset date to date of first dose

Concomitant Medications

- If start date is completely missing or year is missing then start date will not be imputed.
- If start year is present and month and day are missing then set start month and start day to January 1.
- If start year and day are present and month is missing then set start month to January.
- If start year and start month are present and start day is missing then set start day to 1st day of month.
- If end date is completely missing or year is missing then end date will not be imputed.
- If end year is present and month and day are missing then set end month and day to December 31.
- If end year and day are present and month is missing then set end month to December.
- If end year and end month are present and end day is missing then set end day to last day of the month.

Death and Disease Progression:

In case of partial missing date the below imputation rules will be used for death date and disease progression date, provided that the imputed dates don't contradict with other information in the database:

- Missing day: 1st day of the month and year of death or progression;
- Missing month: January of the year of death or progression;
- Missing year or missing entire date will not be imputed.

Prior Cancer Systemic Therapy (PCST)

Missing dates will be reviewed during the Data Review meeting to assess the refractoriness status to first or last PCST.

Appendix K. CRITERIA OF PROTOCOL DEVIATIONS THAT CAN LEAD TO EXCLUSION FROM THE PER-PROTOCOL POPULATION

	Affecting efficacy – entails removal from Per Protocol population
Inclusion criteria[5]	
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.	Yes (no need for the diagnosis to be histopathologically confirmed)
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.	PotentiallyPotentially
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.	Yes
4) Patients must be ≥ 18 years.	Potentially
5) Patients must have ECOG Performance Status 0 - 2.	Yes

[5] Inclusion and exclusion criteria were taken from Protocol Version 7. Criteria in previous versions may be slightly different or have different numbering.

	Affecting efficacy – entails removal from Per Protocol population
6) Patients must meet the following laboratory criteria: • Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L (1000/mm3) • 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.	Potentially
7) Patients must have evaluable or measurable disease in accordance with the International Working Group Guidelines for Lymphoma (Cheson 2014).[a]	Yes
8) Patients who are Hepatitis B surface antigen (HBsAg) + (must be polymerase chain reaction [PCR] negative) who are taking antivirals are allowed to enroll.	Potentially
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).	No
10) Patients must be willing to provide informed consent and be willing to comply with the study protocol.	Not affecting, however if no ICF was signed patients will be excluded

	Affecting efficacy – entails removal from Per Protocol population
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.	No
Exclusion Criteria	
1) Patients with a diagnosis of CLL or Small Lymphocytic Lymphoma.	Yes
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).	Potentially
3) For Part 2 and Part 3 of the study, patients that are eligible to undergo first time HD-ASCT.	No
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	Potentially
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.	Yes

	Affecting efficacy – entails removal from Per Protocol population
6) Patients who have had a prior anaphylactic or other severe infusion reaction such that the patient is unable to tolerate antibody administration.	No
7) Patients who have known central nervous system, meningeal, or epidural disease including brain metastases.	Yes
8) Patients who have received or are to receive vaccination with live viruses within 30 days of Cycle 1 Day1.	No
9) Impaired cardiac function or clinically significant cardiac disease such as: • New York Heart Association Class III or IV cardiac disease, including pre-existing clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy; • Unstable angina pectoris ≤ 6 months prior to starting study treatment; • Acute myocardial infraction ≤ 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.	Yes
10) Patients with ≥ Grade 2 peripheral neuropathy.	No
11) Patients with active hepatitis A, B or C infection.	Yes
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.	Yes
13) Known diagnosis of HIV infection.	Yes
14) Patients with a concurrent primary malignancy that requires treatment or that would confound the disease response interpretation for the disease under study.	Potentially
15) Women of child bearing potential who are pregnant or breast feeding.	No

	Affecting efficacy – entails removal from Per Protocol population
16) Patients currently presenting interstitial lung disease, diffuse parenchymal lung disease, or with a past history of severe/Grade 3 parenchymal lung disorders.	Yes
Use of prohibited concomitant medications or procedures	
Concurrent other anti-cancer therapy, or investigational therapy while on study treatment.	Potentially
Tumor assessment not performed per protocol	
Baseline tumor assessment >28 days[b] before Cycle 1 Day 1	Yes

[a] Measurable is defined as: if screening is by CT: measurable in both diameters (i.e. both diameters are >1.0 cm), with LDi>1.5 cm for a lymph node lesion or LDi>1 cm for an extranodal lesion; if screening is by PET-CT: focal uptake in nodal and/or extranodal sites that is in keeping with lymphoma (Deauville score of 4 or 5). If screening by PET-CT but Deauville score <4, the CT criteria apply.

[b] A 7-days windows was considered for baseline tumor assessment leading. A baseline tumor assessment performed less than 35 days prior Cycle 1 day 1 is considered compliant with protocol.