Abbreviated Statistical Analysis Plan

Study Title:	A phase I/II study of lutetium (^{177}Lu)-lilotomab satetraxetan (Betalutin®) antibody radionuclide- conjugate for treatment of relapsed non-Hodgkin lymphoma.
Version:	FINAL 3.0 (21 November 2022)
Nordic Nanovector Study No:	LYMRIT-37-01 Part B/C "PARADIGME"
Veristat Study No:	NOR17001

For Veristat LLC – Lead Statistician

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List of Abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Events
AESI	Adverse Event of Special Interest
ALAT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ASAT	Aspartate Aminotransferase
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
b.w.	Body Weight
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CR	Complete Remission
CRR	Complete Response Rate
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DoCR	Duration of Complete Response
DoR	Duration of Response
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EU	European Union
FACT-Lym	Functional Assessment of Cancer Therapy–Lymphoma
FL	Follicular Lymphoma
γGT	Gamma Glutamyl Transferase

HAMA	Human Anti-Murine Antibody / Human Anti-Mouse Antibody
HLA	Human leucocyte antigen
IRC	Independent Review Committee
ITT	Intent-To-Treat
LDH	Lactate Dehydrogenase
MBq	Mega Becquerel
MedDRA	Medical Dictionary for Regulatory Authorities
N/A	Not Applicable
NAb	Neutralising Antibody
NE	Not Evaluable
iNHL	indolent Non-Hodgkin Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PET	Positron-emission Tomography
PK	Pharmacokinetic
PR	Partial Remission
PT	Preferred Term
QoL	Quality of Life
RoW	Rest of World
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCT	Stem Cell Transplant
SD	Stable Disease
SI	International System of Units

SOC	System Organ Class
SPECT	Single Photon Emission Computed Tomography
SRC	Safety Review Committee
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
WHO	World Health Organization

1 Introduction

This abbreviated statistical analysis plan (SAP) details the proposed analyses to be conducted by Veristat for the LYMRIT-37-01 phase I/II study (Part B) and the phase IIa expansion part (Part C).

Part A, dedicated to assessing the safety of various doses/regimens, was analysed under a separate SAP, Veristat study no: NOR18001.

In July 2022, LYMRIT-37-01 Part B and Part C were both terminated following slow recruitment. An ad hoc efficacy review of 61 patients (July 2022) who had received a dose of "40/15" and also had an Independent Review Committee (IRC) evaluated baseline and 3 month scan and efficacy assessment was conducted. Following this, the decision was taken to terminate the study. Details of this interim analysis are documented separately.

This analysis will be restricted to:

To support the final (close out) CSR, the efficacy and safety will be evaluated at a minimum of 3 months follow-up after the final patient has received the "40/15" regimen in Part B.

Specifically, this means that the following data will be formally analysed:

Table 1: Data to be reported: Analysis datasets and TFL's to be produced

Category	Data	Comments
Demography and baseline information	Demographics	
	Disposition	
	Eligibility	Includes reasons for screening failure
	Med history	diagnosis of NHL (part C patients)
	Med history	diagnosis of FL (part B patients)
	Med history	general med history, listing only, no summaries required
	Prior and con meds	Prior meds, listing only, no summaries required
	Prior and con meds	Previous treatment for FL (part B), iNHL (part C)
Efficacy endpoints to be summarised are: ORR, CRR, DoR, DoCR and PFS from IRC assessment	Tumour visit response	From IRC: ORR, CRR, DoR, DoCR, PFS
Exposure data	Exposure	
Safety (AE and laboratory data) data	AE	
	Biochem	Listings only, no summaries required

	Haematology	Both listings and summaries required

OS variables will not be derived.

For all other data no formal TFL outputs are required. For all data in the table below, SAS datasets of the raw data should be supplied to Nordic Nanovector.

Table 2: Data for which only SAS raw data sets are required

Data table	**Comments**
AE SI	
Dna damage	DNA damage (Date/time) is this available?
ECG	ECG data only collected at baseline
Genomic biomarkers	Sample collection for genomic biomarkers
Imaging	Spect/CT evaluation
Immunological assessment	Protein Electrophoresis
Lab test results	Pregnancy test
Phys exam	Physical exam at baseline and through trial
PK concentrations	PK sampling times
Prior and con meds	Previous treatment for iNHL
Prior and con meds	Further anti-cancer therapies
Prior and con meds	Concomitant medications
Prior and con procedures	
Questionnaire	ECOG
Questionnaire	FACT-Lym
Response	Response following CT and PET assessments
SAE	
Serology sample	Sample collection for serology, hep B hep C HIV
Subject characteristics	Confirms randomisation and dose
Tumour identification	Biopsy tumour tissue - sample date, site, slides
Tumour identification	Target lesions (screening & follow-up)
Tumour identification	Non-measurable lesions (screening & follow-up)
Tumour identification	New lesions
Tumour identification	Bone marrow (screening & follow-up)
Tumour identification	PET (screening & follow-up)
Vital signs	Screening & follow-up
Immunological assessment	ADA (Date/time of sample)

Immunological assessment	HAMA (Date/time of sample)
Immunological assessment	Immunoglobin (Date/time of sample)
Immunological assessment	Lymphocyte (Date/time of sample)

2 Study Design, Objectives and Endpoints

2.1 Study Design

Part B of the LYMRIT-37-01 study started as a randomised phase IIb, open-label, study in participants with relapsed, rituximab/anti-CD20 refractory Follicular Lymphoma (FL), platelet count ≥150×109 /L and having received 2 or more prior chemotherapy or immunotherapy-based regimens.

In Part B, per initial design, up to 130 participants were to be enrolled in a 1:1 randomised fashion to compare the recommended phase II dose of Arms 1 and 4 (40 mg lilotomab + 15 Mega Becquerel (MBq)/kg Betalutin ("40/15") vs 100 mg/m^2 lilotomab + 20 MBq/kg Betalutin, ("100/20"). Following an interim analysis of efficacy and safety data randomisation was stopped and further patients were recruited to "40/15" regimen (as recommended by the SRC).

The eligibility criteria for Part B, were widened (under protocol version 14), to allow enrolment of participants with prior autologous-SCT (that occurred more than 2 years prior to enrolment in the study) and/or with platelet counts ≥100×10^9/L but < 150×10^9/L at study entry. These patients received a reduced dose regimen: "40/12.5" or "40/10".

Part C of the LYMRIT-37-01 study was added in Protocol version 15.1 (EU&RoW) and Protocol version 15.2 and is an open-label phase IIa expansion cohort in participants with relapsed iNHL to enable the collection of samples for Betalutin PK and total lilotomab antibodies PK in receiving the "40/15" dose regime.

Full detail of the study design is provided in the protocol Section 6.

2.1.1 Visit Structure

The visit structure and the schedule of assessments are detailed in Tables 6-7, 6-8 and 6-9 in the study protocol (Section 6).

In the protocol, the Betalutin administration day is referred to as Day 0. However, for statistical analysis and to be in line with CDISC (Clinical Data Interchange Standards Consortium) requirement, the Betalutin administration day will be defined as study Day 1. See Section 3.3 for more details.

The study treatment period starts with the single dose infusion of rituximab (375mg/m^2) 14 days prior to the administration of Betalutin and lasts for 12 weeks after the Betalutin administration for each participant.

The follow-up period starts from 12 weeks (3 months or 92 days) after the first lilotomab/Betalutin administration up to 5 years as follows (see Protocol Section 6.3 Schedule of Assessments for more details):

- Extensive follow-up (hospital visits): for all participants, every 3 months after Betalutin administration for the first year (i.e. Month 3, Month 6, Month 9, and Month 12). In addition, there will be an additional hospital visit at Week 4 and Month 2 after Betalutin administration. Tumour imaging assessments are only required until the participant has disease progression as confirmed by the IRC or further anticancer therapy prior to progression. All other scheduled assessments are performed regardless of disease progression or administration of further therapy.
- After Month 12: follow-up will continue every 6 months up to 5 years after the Betalutin dose.
    - Extensive follow-up (hospital visits) will be performed until the participant has disease progression as assessed by the IRC or further anticancer therapy prior to progression.
    - Survival Follow-up: Thereafter, the participant will continue limited follow up every 6 months for potential long-term toxicity (new onset of Adverse Events of Special Interest (AESIs), Adverse Drug Reactions (ADRs) and study treatment-related Serious Adverse Events (SAEs), Overall Survival, further anticancer treatment and immunogenicity assessment (ADA, if applicable). Unless blood sampling is required for immunogenicity, limited follow-up visits can be performed by telephone.

A visit window of ± 2 days is permitted for the nominal Day 0 visit (the dose of radioactivity will be based on the actual administration date). Weekly assessments should occur within a window of ± 2 days. Visits occurring at 4-week intervals will have a window of ± 3 days. During the treatment and follow-up period, a window of ± 7 days for visits occurring every 3 or 6 months is acceptable.

All samples/assessments for study baseline are to be obtained before rituximab dosing. The associated results will be used for Betalutin treatment baseline except for haematology, which is to be repeated within 72 hours prior to Betalutin administration and will be used as the Betalutin baseline.

2.2 Study Objectives

This abbreviated statistical analysis plan incorporates only the following objectives for which analysis datasets and TFL outputs from Veristat are required:

Objectives of Part B	
Primary Objectives	To evaluate the overall response rate (ORR) of the 40/15 regimen based on the IRC assessment of tumour response rates in adult participants with relapsed rituximab/anti-CD20 refractory FL.
Secondary Objectives	To evaluate the overall response rate (ORR) of the 100/20 regimen based on the IRC assessment of tumour response rates in adult participants with relapsed rituximab/anti-CD20 refractory FL. To evaluate the complete response rate (CRR), duration of response (DOR), Duration of complete response (DoCR) and Progression Free

	Survival (PFS) of the 40/15 and 100/20 regimens based on the IRC assessment of tumour response rates. <u>Safety (Parts B and C)</u> • To characterise the safety profile of Betalutin in terms of Adverse Events and laboratory data.

2.3 Study Endpoints

Primary Endpoints	Part B: Overall Response Rate (ORR) as assessed by IRC assessment based on standard criteria [Cheson 2014]
Secondary Endpoints	<u>Efficacy(Part B)</u> • CRR by IRC assessment • DoR and DCoR by IRC assessment • PFS by IRC assessment <u>Safety endpoints (Part B and C):</u> • Incidence and severity of adverse events (AEs). • Laboratory data

2.4 Sample Size and Power

As described in the Introduction the study was terminated early and so is not powered to meet the original study objectives. Summaries and listings of the data collected will be provided (as detailed in Tables 1 and 2 in Section 1).

3 General Considerations for Data Analyses

3.1 General

Summary statistics for continuous variables will consist of number of non-missing observations (n), mean, standard deviation, minimum, 25th percentile, median, 75th percentile and maximum, unless specified otherwise. The precision (number of decimal places) of these variables is defined in the tables, figures and listings (TFLs) shells document – minimum and maximum will be presented to the same level of precision as the raw data; mean, median, percentiles will be presented to 1 additional decimal place; standard deviation will be presented to 2 additional decimal places.

For categorical variables the number and percentage of participants in each category will be presented, based on the number of non-missing observations apart from disposition of participants, protocol deviations, background and demographic characteristics, prior and concomitant medications/procedures and adverse events where the percentage will be based on the number of participants in the analysis set.

3.2 Analysis Sets

Assignment of participants to analysis sets will be agreed between the study statistician and the client prior to database lock or data extraction for any final formal run and review of outputs, once all study data are available for the respective run.

3.2.1 Screened Set

The screened set includes all participants who provided informed consent.

3.2.2 Efficacy Analysis set

Efficacy Analysis set will be a subset of the Part B participants who received Betalutin and were assigned either "40/15" or "100/20" dose levels.

3.2.3 Safety Analysis Set

The Safety Analysis Set (SAF) will consist of all participants who received at least one dose of study intervention (rituximab, lilotomab or Betalutin). Participants are reported according to the treatment they actually received.

3.3 Derived Data

- *Definition of study day*

Study day is relative to the date of first administration of Betalutin and lilotomab (study Day 1). Therefore, study day for rituximab will be negative.

Note: in the protocol, Betalutin administration day is referred to as Day 0. However, for statistical analysis and to be in line with CDISC requirement, Betalutin administration day will be defined as Day 1, the day before Day 1 is defined as Day -1 and there is no Day 0.

- *Definition of baseline*

Study baseline is defined as the last non-missing value (including scheduled and unscheduled assessments) prior to rituximab dosing. This will usually be the latest value collected at the screening visit.

Betalutin baseline is defined as the last value measured prior to lilotomab and Betalutin dosing. A visit window from day -2 to day 1 (prior to lilotomab and Betalutin dosing) will be used.

- *Incomplete dates*

For calculation purposes, incomplete dates will generally be completed using worst case. For example, the 15th of the month will be used when day is missing and 1st July when day and month are missing.

Further details are given in the relevant sections as required.

- *Non-numeric values*

In the case where a variable is recorded as ">x", "≥x", "<x" or "≤x", then for analysis purposes a value of x will be taken. Where a range of values is quoted the midpoint of the range will be taken.

- *Month windows*

For the laboratory values and change from baseline outputs, to take account of the potential for out of window assessments being conducted due to the COVID-19 pandemic, the following Month labels will be rederived using the table below.

Table 3: LYMRIT-37-01 study, Part B Month Windows

Month	**Days relative to the date of Betalutin administration ***
Week 8	Days 53 to 61

Week 12	Days 81 to 89
Month 3	Days 78 to 122
Within the first 3 Months	Days 1 to 122
Within the first 6 Months	Days 1 to 213

* (Date of assessment – date of Betalutin administration) +1 if date of assessment is on or after date of Betalutin administration. Otherwise (Date of assessment – date of Betalutin administration).

3.4 Data Presentation

The TFLs will present the dose regimens (where relevant) as detailed below:

Table 4: LYMRIT-37-01 study, Part B/C Treatment Group Descriptors

Order	**Descriptor for Dose Regime (where relevant) to be presented in TFLs**	**Meaning of Descriptor**
1 [1]	40 / 12.5	40 mg lilotomab plus 12.5 MBq/kg Betalutin
2	40 / 15	40 mg lilotomab plus 15 MBq/kg Betalutin
3	100 / 20	100 mg/m^2 lilotomab plus 20 MBq/kg Betalutin
4 [1]	Received Rituximab only	Received Rituximab only
5 [1]	Enrolled no treatment	Enrolled but did not receive any trial treatment
6 [1]	Screen failure	Participants in the screened set who failed screening (i.e. are not eligible to join the study per the eligibility eCRF page).

[1] In table summaries, if there is insufficient space to present all treatment groups on a single page, these dose regimes will be presented on the next page.

The data will be summarised in tabular form by Study Part (i.e. B / C) and dose regimen.

Results from scheduled visits will be tabulated. Unscheduled visits will be included in assessments of maximum post-baseline. All assessments will be listed.

Table 5: Populations to be used for output

Type of data	**Listings**	**Summaries**
Disposition	Screened set	Screened set
Demographic characteristics and baseline	SAF	SAF, Efficacy Analysis Set
Efficacy	SAF	Efficacy Analysis set

AE's and lab data	SAF	SAF

Listings will be sorted by Study Part (i.e. B / C) and dose regimen, patient number and date/time of assessment.

Graphical presentations of the data will also be provided where appropriate.

3.5 Participant Disposition

3.5.1 Participant Enrolment

A listing of screen failed participants will be provided which will include the date of informed consent, the date of screening withdrawal, the reason for screen failing and any inclusion/exclusion criteria not met.

A listing of eligibility for participants that were recruited but did not meet all entry criteria will be provided which will include the protocol version number at the time of screening and the inclusion/exclusion criteria not met.

3.5.2 Participant Disposition

A summary of participant disposition will be provided. This summary will present number of participants applicable to each of the following:

- Screened set, including screen-failures with reason.
- SAF.
- Efficacy Analysis Set.
- Gave consent for genomic biomarker analysis of tumour tissue (listing only).
- Gave consent to HLA typing (listing only).
- Gave consent for taking part in PK assessments (listing only).
- Gave consent for taking part in dosimetry assessments (listing only).
- Participants who completed the treatment period. (was in study up to Day 92).
- Participants who discontinued during the study treatment period (up to Day 92) (with summary of reasons for withdrawal from the Completion / Withdrawal eCRF page).
- Participants who discontinued after the study treatment period (from Day 93 onwards) (with summary of reasons for withdrawal from the Completion / Withdrawal eCRF page).

The treatment period is from Day 1 to Day 92 inclusive.

All duration derivations (months) are calculated relative to the date of first Betalutin administration using the following formula:

*Time to data cut off/death/withdrawal (months) = ([date of data cut off/death/withdrawal – date of first Betalutin administration)]+1) *12 /365.25*

For all summaries except the screened summary, the denominator for the percentages of participants in each category will be the number of participants in the SAF. The denominator for the percentages of participants for the screened summaries will be the number in the screened set.

Descriptive statistics for the duration of follow-up (months) will also be included where:

*Duration of follow-up (months) = ([{latest date participant is known to be alive} – date of first Betalutin administration]+1) *12 / 365.25 rounded to 1 decimal place.*

Where latest date known to be alive is obtained using all data available for the participant (i.e. eCRF (including unscheduled), response and survival follow-up data).

Completion and withdrawal data, membership of each of the analysis sets along with reasons for exclusion will be listed.

3.6 Baseline Data

3.6.1 Demographics and Baseline Characteristics

Demographic characteristics (age, sex, ethnic origin and race) and body measurements (height, weight) at screening will be summarised.

Age will be summarised as a numeric variable and by the following categories <65 and >=65. Age will be calculated in years at the date of informed consent as: *(year of informed consent – year of birth).*

Individual participant demographic characteristics and body measurements data will be listed.

3.6.2 Medical History

Medical history events will be coded using the same Medical Dictionary for Regulatory Authorities (MedDRA) dictionary version utilised at the time of the reporting for Part A primary analysis. The version used will be indicated in the data listings. The number and percentage of subjects will be presented for ongoing conditions and previous conditions separately by system organ class (SOC), and preferred term (PT), where SOC and PT will be presented in decreasing frequency of the total number of subjects with medical history events. All events will be listed. No summary tables required for general medical history.

3.6.3 Disease History

Disease history will be reported separately for Parts B and C.

Part B:

All disease history and previous treatments for FL will be listed including any derived variables.

3.6.3.1 Initial diagnosis of Follicular Lymphoma

The following initial diagnosis information will be summarised and listed:

- Time since initial diagnosis (months): calculated as:

12[date of informed consent – date of diagnosis of FL + 1]/365.25, reported to 1 decimal place*

If partial dates are reported for date of diagnosis, the 15th will be used when day is missing and 1st July when day and month are missing.

- Subtype at initial diagnosis: grade I-IIIA or other
- Whether B symptoms were present at initial diagnosis: No, Yes or Unknown
- Transformed lymphoma in disease history (No, Yes or Unknown)

3.6.3.2 Current status of Follicular Lymphoma

The following current status of FL information will be summarised and listed:

- Time since most recent relapse (months), calculated as:

  12[date of informed consent - date of most recent relapse before Betalutin treatment + 1]/365.25, reported to 1 decimal place*

- Current subtype diagnosis: grade I-IIIA or other
- Whether B symptoms present at current visit: No, Yes.

3.6.3.3 Previous treatment for Follicular Lymphoma

The following previous treatment for Follicular Lymphoma information will be summarised and listed:

- Number of prior systemic therapies (derived by excluding radiotherapy and regimen number 99, which corresponds to previous LYMRIT-37-01 PART B exposure to rituximab for any participants re-enrolled, and then counting the distinct regimen numbers. If a regimen contains a mixture of treatments including radiotherapy then radiotherapy and systemic therapy will have the same numbering and the regimen number covering this "composite" regimen should be included).
- Participants with 2 or more prior systemic therapies: No, Yes
- Has the participant exhausted all previous lines of therapy? No, Yes.
- Whether received prior rituximab/anti-CD20 No, Yes determined following clinical review of unique WHO Drug coding *.
- Time from last treatment for FL to first study drug administration (months), calculated as:

  12 [date of first study drug administration (i.e. rituximab) – date of last course of last treatment for FL prior to date of informed consent + 1]/365.25*

  If partial dates are reported for last course of last treatment, the 15th will be used when day is missing and 1st July when day and month are missing.

- Response to last treatment for FL (Complete remission, Partial Remission, Stable disease (No change), Progressive disease, Unknown, Not applicable). Where last treatment for FL is defined as last treatment for FL prior to date of informed consent.
- Last therapy refractory (yes/no).
- Refractory to 2 or more prior therapies for FL (No, Yes).
- Refractory to rituximab/anti-CD20 (No, Yes).

** A clinical review of the unique coded WHO drug terms will be conducted by the sponsor to set the regimes into individual components (rituximab/anti-CD20).*

Part C:

Initial diagnosis, current status and previous treatments for iNHL will be summarised using a similar approach to that for FL.

3.6.4 Prior Medications

Prior medications will be coded according to the World Health Organization Drug dictionary (WHO Drug) (Standard) version utilised for the survival follow-up to date reporting of PART A. The version used will be indicated in the listings. No summaries are required.

Prior medications are those with a start and stop date prior to the first administration of rituximab.

3.6.5 Administration of Study Treatment and Exposure

Administration of Study Treatment and Exposure will be summarised by dose regimen of the actual treatment received.

3.6.5.1 Betalutin

The investigational product, Betalutin, is injected on the nominal Day 0 visit (Study day 1). The weight, actual volume injected (mL) and the total radioactivity injected over all injections (converted to MBq/kg body weight (b.w.) i.e. standardising for body weight) and weight (kg) will be summarised.

Total radioactivity injected over all injections will be derived as follows:

Total radioactivity injected over all injections (MBq/kg b.w.) =∑_(i=1)^n(〖RA〗_i^p- 〖(RA〗_i^a+〖RA〗_(i)^f))/(b.w.)

where,

n = number of injections (1 or 2)

〖RA〗_i^p = radioactivity in injection i prior to administration

〖RA〗_i^a = radioactivity in injection i after administration

〖RA〗_i^f = radioactivity in filter for injection i after administration (if applicable)

b.w. = body weight as recorded on the Betalutin administration eCRF page

Details relating to administration of the investigational product, including whether Betalutin was administered within 4 hours of lilotomab administration and radioactivity in syringe prior to injection, after injection and in the filter after injection MBq will be listed.

Percentage of prescribed dose will be determined programmatically as follows:

[|Total radioactivity injected (MBq/kg.b.w.) – Dose (MBq/kg.b.w.)|/ Dose(MBq/kg.b.w.)] x 100

Differences of +/- 10% of prescribed dose will be flagged, determined programmatically where percentage of prescribed dose > 10% or < -10%.

3.6.5.2 Rituximab

Participants are pre-dosed with 375 mg/m^2 rituximab once on Day -14. The actual rituximab dose administered (mg) and the actual dose standardised by BSA (mg/m^2), as well as weight and BSA at rituximab infusion, will be summarised.

Rituximab dose administered (mg/m^2) = Rituximab dose (mg)/BSA (m^2)

Details relating to administration of rituximab will be listed separately.

3.6.5.3 Lilotomab

Lilotomab will be infused within 4 hours prior to Betalutin administration. The total lilotomab dose (mg) and dose standardised by body weight (kg), as well as body weight (kg) and BSA (mg/m^2) at lilotomab infusion will be summarised.

Standardised lilotomab dose administered (mg/kg b.w.) = Lilotomab dose (mg)/b.w. (kg)

Standardised lilotomab dose administered (mg/ m^2) = Lilotomab dose (mg)/BSA (m^2)

Details relating to administration of lilotomab will also be listed separately.

3.7 Efficacy Analyses

All efficacy analyses will be based on the Efficacy analysis set which includes patients with FL on the following dose regimens: "40/15" and "100/20".

The evaluation of tumour response will be based on the assessment made by the IRC, based on the standard criteria [Cheson 2014]. The disease response (RS) dataset will be transferred from ICON to Veristat according to the data delivery specification and will contain responses per visit per subject per assessor. In cases where more than one independent assessor (e.g. RADIOLOGIST 1, RADIOLOGIST 2) provide independent assessments at the same time point the flag variable RSACPTFL="Y" identifies the record that is considered to be the accepted assessment. Best overall response will be used for the ORR and CRR endpoints. DoR and DoCR will be derived from the visit responses.

All data relating to the efficacy endpoints detailed below, including derived variables, will be listed for all patients who had data from an IRC assessment.

For calculation purposes, incomplete dates will be imputed as 1st of the month when day is missing and 1st January when day and month are missing.

3.7.1 Primary Endpoint: Overall Response Rate (ORR) as assessed by IRC assessment

3.7.1.1 Definition of Overall Response Rate (ORR)

A response of CR, PR, Stable Disease (SD), Progressive Disease (PD) and Not Evaluable (NE) is allowed. The response definitions for each category are based on standard criteria and defined in Section 12.3 of the protocol.

If disease assessments for a participant are not available then the response rate for the relevant timepoint will be set to Not Done (ND).

The Overall Response Rate (ORR) is defined as the proportion of participants who achieve a best response of CR or PR at any time. If all disease assessments for a participant are not available then ORR will be set to NE.

3.7.1.2 Analysis

The following dose regimes will be summarised for ORR: "100 / 20" and "40 / 15".

For ORR (achieved independent of time), the following will be presented:

- The responses of CR, PR, SD, PD, NE and ND for each dosing regimen.
- The number and percentage of responders for each dosing regimen together with the exact 95% CI using the Clopper-Pearson method.

3.7.2 Secondary Endpoint: Complete Response Rate (CRR) by IRC assessment

3.7.2.1 Definition

Complete Response Rate (CRR), defined as the proportion of participants who achieve a CR assessed with the use of standard criteria for lymphoma. The CRR will be calculated based on CR achieved at any timepoint.

3.7.2.2 Analysis

CRR will be analysed in the same manner as ORR.

3.7.3 Secondary Endpoints: Duration of Response and Duration of Complete Response by IRC assessment

3.7.3.1 Definition

DoR is the time from when criteria for response (CR or PR) is first met to the time of relapse or progression, so is therefore only defined for those participants who are responders. Participants who have not relapsed/progressed will be censored at the last adequate tumour assessment.

For those participants with documented disease progression, death or withdrawal after a response was detected during the study, duration of response (months) is defined as:

*([First date of disease relapse – first date of response] + 1)*12/365.25*

Where the first date of disease relapse will be the first documented date of progressive disease or death after the response.

Participants without documented disease progression or death after a CR/PR response: censored at the date of the last CR/PR assessment, where the censoring time will be defined as follows:

*Duration of response (months) = ([Date of last assessment where the participant was assessed as a responder – first date of response] + 1)*12/365.25.*

DoR based on complete remission (DoCR) will also be derived and in an analogous method to DoR but using only CR to determine responders.

3.7.3.2 Analysis

The following dose regimes will be analysed for DoR and DoCR: "100 / 20", "40 / 15".

The following will be presented by dosing regimen.

- The number of participants included in the analysis, those with event and those who are censored.
- The estimate of the median, 25th and 75th percentiles for tumour response durations (months).
- The duration of response rate at 3, 6, 9, 12 and 15 months.

3.7.4 Secondary Endpoint: Progression-free survival (PFS)

3.7.4.1 Definition

PFS is defined as the interval from Betalutin administration and date of:

- Relapse (new or enlarged lesions after CR).
- Progression (new or enlarged lesions after PR or SD).
- Death from any cause.

Documented disease progression is defined as a Relapse (after CR) or progression (after PR or SD) and is indicated at the earliest date when the response assessment is given as progressive disease (PD). Death from any cause includes deaths occurring before the first post-baseline tumour assessment. If death occurs after two or more missed tumour assessments the participant should be censored (see below). PFS for participants meeting the events definition will be derived as follows:

*Progression-free survival time (months) = ([earliest of (First date of documented disease progression or death) – date of Betalutin administration] +1)*12 / 365.25.*

If none of the above events are observed PFS will be censored as follows:

- Incomplete/no baseline tumour IRC assessments: censor at date of Betalutin administration (study day 1).
- No documented disease progression: censor at date of last tumour IRC assessment where progression was not shown.

- Death or progression after two or more missed tumour assessments: censor at date of last tumour assessment where progression was not shown.

PFS for censored participants will be derived as:

*Progression-free survival time (months) = ([Date of censoring – date of Betalutin administration] +1)*12/365.25*

3.7.4.1.1 *Analysis*

The following will be presented by dosing regimen.

- The number of participants included in the analysis, those with event and those who are censored.
- The estimate of the median, 25th and 75th percentiles for progression free survival time
- The progression free survival rate at 3, 6, 9, 12 and 15 months.

The corresponding KM plot of the probability of being progression free against time will also be presented.

3.8 Safety Analyses

3.8.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA dictionary version utilised for Part A. All patients included in Parts B and C of the study will be included in the AE tables.

The start of the AE reporting for a study participant will coincide with signing of informed consent.

Where AE severity is recorded instead of AE Common Terminology Criteria for Adverse Events (CTCAE) grade, this will be mapped to the corresponding CTCAE grade for summary purposes using CTCAE v4.0. AEs recorded as Mild will be mapped to Grade 1, Moderate to Grade 2, Severe to Grade 3, Life-threatening to Grade 4 and Death to Grade 5. AE severity will not be reported.

Although there is an AESI eCRF page, a clinical review of the unique MedDRA coded terms will also be conducted by the sponsor to identify any further applicable AESIs.

3.8.1.1 Treatment-Emergent Adverse Events

The focus of AE summarisation will be on treatment-emergent adverse events (TEAE).

Treatment-emergent adverse events AEs (TEAEs) are defined as those adverse events (AEs) occurring after first administration of rituximab or starting prior to the first administration and worsening during treatment. Adverse events with unknown onset date/time will be considered to be treatment-emergent unless the stop date/time is known to be before first administration of rituximab.

A treatment related TEAE is defined as a TEAE that is possibly or probably or definitively/certainly related to the study treatment (Betalutin, rituximab or lilotomab). If the TEAE has a missing relationship it is assumed to be related to the study treatment for analysis

purposes. This will also be derived separately for Betalutin, rituximab and lilotomab. If the TEAE has a missing relationship it is assumed to be related to all applicable study treatments for analysis purposes.

AEs will be classed as occurring in one of five periods:

- Pre-treatment - any AE that starts after the participant has provided written informed consent and that resolves prior to the first administration of rituximab, or an AE that starts prior to the first administration of rituximab and does not increase in severity after the first administration of rituximab.
- Baseline Period: any AE that starts after the participant has the first administration of rituximab but prior to the first administration of lilotomab or Betalutin (study Day 1).
- Lilotomab/Betalutin Exposure Period: any AE that occurs after the first administration of lilotomab or Betalutin (study Day 1) and upto, and including Day 92, or that is present prior to the first administration of lilotomab or Betalutin and worsens after the first administration of lilotomab or Betalutin.
- Rituximab Exposure Period: relates to the combined Baseline Period and Lilotomab/ Betalutin Exposure Period (i.e. all AEs that start after the first administration of rituximab).
- Post Betalutin follow-up period: any AE which starts more than 92 days after the start of Betalutin.

All pre-treatment AEs will be excluded from the tabulations but will be fully listed.

3.8.1.2 Baseline Period Adverse Events

A table will present the number of events and the number and percentage of participants experiencing TEAEs occurring during the baseline period by SOC and PT.

The table will contain an overall summary and will not be split by actual dose regime. SOC and PT will be presented in descending frequency. If a participant experiences more than one TEAE, the participant will be counted once for each SOC and once for each PT.

3.8.1.3 Lilotomab/Betalutin Exposure Period Adverse Events

The following tables will present the number of events and the number and percentage of participants experiencing TEAEs by SOC and PT for the following break points with separate summaries being produced for each:

- TEAE onset from Day 1 onwards
- TEAE onset from Day 1 to Day 92 (Month 3)

Each table will contain an overall summary. SOC and PT will be presented in descending frequency of the total number of participants with TEAEs. If a participant experiences more than one TEAE, the participant will be counted once for each SOC and once for each PT.

Table 6: LYMRIT-37-01 study, Part B and C Adverse Event Summary Tables

Summary Table	AE onset from Day 1 onwards	AE onset from Day 1 to Day 92 (Month 3)
TEAEs by SOC and PT	X	X
Serious TEAEs	X	X
Study drug related TEAEs (Betalutin, rituximab or lilotomab)		X
Serious study drug related TEAEs (Betalutin, rituximab or lilotomab)		X
TEAEs by CTCAE grading		X
most frequent TEAEs (reported in at least 5% of participants)		X

Adverse event data will be listed in full and will also include a treatment emergent flag (will distinguish pre-treatment, baseline, post treatment (day 93+), an AESI flag, the time of onset and cessation of event relative to first administration of each of rituximab, Lilotomab and Betalutin and duration of AE. Where CTCAE grade changes over time, the worst/most severe will be reported in summary tables.

3.8.2 Deaths

Deaths will be listed from the Death Report form showing date and cause of death.

3.9 Laboratory Evaluations

Conversion factors will be applied where needed to report all laboratory results in International System of Units (SI) units. Global reference ranges will be used to aid interpretation of the laboratory data.

Laboratory parameters will be listed in the following order:

- Haematology: haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophils, lymphocyte subsets.
- Serum biochemistry: sodium, potassium, calcium, creatinine, uric acid, alkaline phosphatase (total ALP), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), LDH, Gamma Glutamyl Transferase (γGT), glucose, bilirubin (total), albumin, immunoglobulin levels.
- Coagulation.

Haematology, biochemistry and coagulation data will be listed separately including global reference ranges, with flags to indicate all out of range values.

Blood urea nitrogen (BUN) and urea will not be listed due to quality concerns. This was due to confusion at sites when collecting the data and it is not possible to correct these issues retrospectively. No concerns were raised regarding renal function during the trial and no signals were seen when reviewing the raw data.

3.9.1 Summaries of Numeric Laboratory Results

- Study baseline and Betalutin baseline values for the following laboratory parameters: Neutrophils, Lymphocytes and Platelets.
- Only data from day 0/1 to day 92 will be included in any summary tables and plots.
- Values at each post-study baseline analysis window (scheduled visit) for all laboratory parameters.
- Change from Betalutin baseline at each post-baseline analysis window (scheduled visit) for all laboratory parameters.

A summary table will be produced for neutrophil, lymphocytes and platelet counts, by dose regimen and overall. This will include the following:

Neutrophil count

- Number (%) participants with neutrophil count < 1 $\times 10^9$/L at any time post-Betalutin baseline (where 1 $\times$ 10^9/L=1 000/mm^3)
- Number (%) participants with neutrophil count < 0.5 $\times 10^9$/L at any time post-Betalutin baseline (where 0.5 $\times$ 10^9/L =500/mm^3)

Platelet count will be presented in an analogous method to neutrophil count but using the following thresholds:

- platelet count < 50 $\times$ 10^9/L (where 50 $\times$ 10^9/L=50 000/mm^3)
- platelet count < 25 $\times$ 10^9/L (where 25 $\times$ 10^9/L=25 000/mm^3)

Lymphocyte counts will be presented in an analogous method to neutrophil count but using the following thresholds:

- Lymphocyte count < 0.2 $\times$ 10^9/L (where 0.2 $\times$ 10^9/L=200/mm^3

Mean haematological data, for each dose regimen, will be plotted for neutrophil count, platelet counts, lymphocytes, and possibly other parameters based on results. Change from baseline plots will not be produced.

3.10 Changes from the Protocol Planned Analysis

There are considerable changes from planned protocol analysis as the study was terminated early and an abbreviated CSR and SAP produced. This SAP covers only the outputs required from Veristat for reporting. The abbreviated CSR will include information from other sources, ie the results of the interim analysis. This will be documented in the CSR.

4 REFERENCES

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