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 5.0 (05 April 2022)

Nordic Nanovector Study No: LYMRIT-37-01 PART A – Phase I & IIa

Syne qua non Study No: NOR18001

For Syne qua non Ltd – Lead Statistician

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List of Abbreviations

AE	Adverse Events
AESI	Adverse Events of Special Interest
ALAT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ASAT	Aspartate Aminotransferase
AUC	Area under plasma drug concentration-time curve
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
b.w.	Body Weight
CDISC	Clinical Data Interchange Standards Consortium
C_{max}	Maximum plasma drug concentration
CI	Confidence Interval
CR	Complete Remission
CRR	Complete Response Rate
CRu	Complete Remission unconfirmed
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
D 5-PS	Deauville 5-Point Score
DLT	Dose Limiting Toxicity
DoCR	Duration of Complete Response
DoR	Duration of Response
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EU	European Union
EWB	Emotional Well-Being (FACT-Lym Quality of Life Questionnaire)
FACT-G	Functional Assessment of Cancer Therapy - General Total Score
FACT-L	Functional Assessment of Cancer Therapy - Lymphoma Total Score
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FWB	Functional Well-Being Score (FACT-Lym Quality of Life Questionnaire)
γGT	Gamma Glutamyl Transferase
HAMA	Human Anti-Murine Antibody / Human Anti-Mouse Antibody

iNHL	indolent Non-Hodgkin Lymphoma
ITT	Intent-To-Treat
LDH	Lactate Dehydrogenase
LYMS	Additional Concerns / Lymphoma Subscale Score (FACT-Lym Quality of Life Questionnaire)
MZL	Marginal Zone Lymphoma
MBq	Mega Becquerel
MedDRA	Medical Dictionary for Regulatory Authorities
MTD	Maximum Tolerated Dose
N/A	Not Applicable
ND	Not Done
NE	Not Evaluable
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron-emission Tomography
PFS	Progression-free Survival
PK	Pharmacokinetic
PPS	Per-Protocol Set
PR	Partial Remission
PT	Preferred Term
PWB	Physical Well-Being Score (FACT-Lym Quality of Life Questionnaire)
QoL	Quality of Life
RoW	Rest of World
RTX	Rituximab
SAF	Safety Analysis Set
SAFB	Safety Analysis Set for Betalutin
SAP	Statistical Analysis Plan
SD	Stable Disease
SI	International System of Units
SOC	System Organ Class
SRC	Safety Review Committee
SUV	Standardized uptake value
SWB	Social / Family Well-Being Score (FACT-Lym Quality of Life Questionnaire)
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures and Listings
TOI	FACT-Lymphoma Trial Outcome Index
US	United States of America
WHO	World Health Organization

Modification History

Version	Change History	Reason	Date
1.0	First Version	N/A	09MAY2019
2.0	• To update the censoring methodology for efficacy analysis from interval censoring to Kaplan-Meier. • To bring text for protocol violations to be in line with the Data Management Plan. • To add major protocol violations applicable to exclusion from the Per Protocol set. • To add derivations for assigned and actual arm/dose and to update the definition of the safety and per-protocol sets to analyse participants according to the arm they actually received. • To add derivation rules for partial dates. • To update the derivations for Betalutin administration for total radioactivity injected, overall radioactivity injected (MBq/kg.b.w) and variance from prescribed dose. • To update the derivation for last therapy refractory for previous treatments for NHL. • To add a missing data rule for the FLIPI score derivation.	Modified following the 2019 DSUR extract and draft TFL production (data and analysis).	25NOV2019

3.0	Part A
	• To clarify in the introduction, the timings of reporting of PART A data.
	• To remove reference to the IB and DSUR and the associated table for combined participant characteristics.
	• To clarify the different study periods: study treatment and follow-up.
	• To update the definition of study day to be relative to the first administration of Betalutin in line with Day as specified in the schedule of events in the protocol.
	• To add visit/month windowing derivations for efficacy, laboratory shift and nadir, FACT-Lym and WHO ECOG analyses.
	• To add a safety analysis set for Betalutin.
	• For the Per-protocol (PPS) analysis set:
	  • To update the definition of major protocol deviations that have a serious impact on efficacy results.
	  • To specify that a clinical review of the unique medical history MedDRA coded terms will be conducted to determine ongoing or recent concomitant cancers at risk of interfering with disease assessment.
	• To update the definition of baseline to define a study baseline and a baseline for Betalutin treatment.
	• To add demographic characteristics summary tables for the SAF and the SAF for Betalutin analysis sets.
	• To update demography and AE listings to use the Enrolled set so that data from screen-failures can be included.
	• For disposition, to further categorise participants ongoing at data cut.
	• For demography, to summarise Weight, BMI and BSA at both study baseline and Betalutin baseline.
	• For current status of NHL, to specify that a clinical review of the unique locations for target lesions at baseline collected on the baseline CT examination eCRF page will be conducted by the sponsor for deriving the number of nodal areas of disease for each participant, for use in the FLIPI score derivation.
	• For prior medications, to remove reference to specific WHO drug terms and to instead specify that a clinical review of the unique coded WHO drug terms will be conducted to set the prior medications into
		Modified to account for protocol amendments V14 and V15.1 relevant to the SAP.	29SEP2021

Version	Change History	Reason	Date

	the individual components of bendamustine, PI3K inhibitor, alkylating agents and rituximab/anti-CD20 and to provide a standardised regimen name for each unique verbatim term.
	• To update various aspects of the statistical methodology for the efficacy analysis.
	  • To define which analyses will use the PPS/ITT analysis sets.
	  • To update summaries and statistical analysis to only include participants in Phase IIa with Follicular Lymphoma (FL). Data for Phase I and other Phase IIa participants will now only be listed.
	  • To remove all efficacy subgroups and associated analyses.
	  • To add efficacy endpoints for Complete Response Rate (CRR) and Durable Response Rate (DRR).
	  • To update the main and alternative censoring schemes for PFS, DoR and DoCR.
	• For AEs:
	  • To define 4 periods: pre-treatment, baseline, lilotomab/Betalutin Exposure and Rituximab Exposure.
	  • To remove AE severity (Mild, Moderate, Severe) in TFLs. AE severity will only be used for mapping AEs to CTCAE grade.
	  • To specify that a clinical review of the unique coded MedDRA terms will be conducted to identify all AESIs.
	  • To remove AE/SAE tables which are surplus to requirements.
	  • To add a summary of DLT AEs.
	• For laboratory data:
	  • To add shift tables for post-study baseline and post-Betalutin baseline.
	  • To adjust the derivation for time to nadir (days).
	• To specify that a clinical review of all causes of death collected on the death report form eCRF page will be conducted to set them into one of three categories: 'Adverse Event' 'Progressive Disease' or 'Other'
	• To update the definition of a DLT and to include a clinical review step of laboratory and related TEAEs to confirm DLTs.
	• To refer to ‘participants’ instead of ‘patients’ in the SAP. The TFLs will continue to use ‘patients’.
	• To add a references section.
	
	PART C:
	• To add a reference to LYMRIT-37-01 Part C in the introduction and study design.		

4.0	PART A • For current status of NHL (section 3.7.3.2), remove reference stating that a clinical review of the unique locations for target lesions at baseline collected on the baseline CT examination eCRF page will be conducted by the sponsor for deriving the number of nodal areas of disease for each participant, for use in the FLIPI score derivation. • For current status of NHL (section 3.7.3.2), remove the calculation and classification of the FLIPI score. • For current status of NHL (section 3.7.3.2), remove number of nodal areas of disease at baseline. • Insert paragraph for the current status of NHL (section 3.7.3.2), to explain why nodal areas of disease and FLIPI score calculations have been removed from the SAP and subsequently from the TFLs.	Modified following the Part A interim analysis dry run (data and TFLs)	20DEC2021

Version	Change History	Reason	Date
	• For the summaries of Neutrophil, lymphocytes and platelet counts only data from Day 1 up to and including Day 92 (i.e. study treatment period) was added (section 3.13.1).		
5.0	• Addition of Demographics, Disease History, Drug administration summaries for subgroup of FL patients. • Addition of PK Sampling times listing. • Update for clarity on DLTs (Phase I patients only). • Addition of Haematological Episodes (Phase IIa patients)	Modified following the Part A interim analysis delivery to add in clarifications and additional subgroup outputs (as required)	05APR2022

1 Introduction

This statistical analysis plan (SAP) describes the analyses to be conducted for the LYMRIT-37-01 phase I/IIa study (Part A). The proposed analysis is based on the contents of the Final Protocol, Version 15.1 (dated 19-FEB-2021; for EU&RoW), Versions 15.2 and 15.4 (dated 06-APR-2021 and 10-AUG-2021; for US) and Version 15.3 (dated 06-AUG-2021; for France). In the event of future amendments to the protocol, this statistical analysis plan (SAP) may be modified to account for changes relevant to the statistical analysis. The LYMRIT-37-01 study comprises 3 parts, each of which will be summarised separately due to differences in study design, dose regimens and participant populations; the phase I/IIa part (Part A) and the phase IIb part (Part B); and the phase IIa expansion part (Part C). This SAP details the proposed analysis of Part A. Part B, which is a randomised, open label study to compare 2 dosing regimens from Part A, will be analysed under a separate SAP, Syne qua non study no: NOR17001. Part C, dedicated to assessing the pharmacokinetics (PK) for Betalutin and total lilotomab antibodies, will be analysed under the cross-part LYMRIT-37-01 SAP.

The PK and biodistribution analyses will be reported separately and are not detailed in this SAP.

The tables, listings, and figures (TFL) shells are supplied in a separate document. All outputs described in this SAP will be produced and reported formally in a Clinical Study Report (CSR), after the last participant has been enrolled and dosed, as follows:

- Survival follow-up to 31 July 2021 (this allows for all participants enrolled and dosed to have a minimum of 3 years of follow-up), which will be the primary analysis and will be reported in a CSR,
- When all participants have completed follow-up (5 years following start of study treatment or until further anticancer therapy is given or have died or are lost to follow-up, whichever occurs first), which will be reported as an addendum to the CSR.

2 Study Design, Objectives and Endpoints

2.1 Study Design

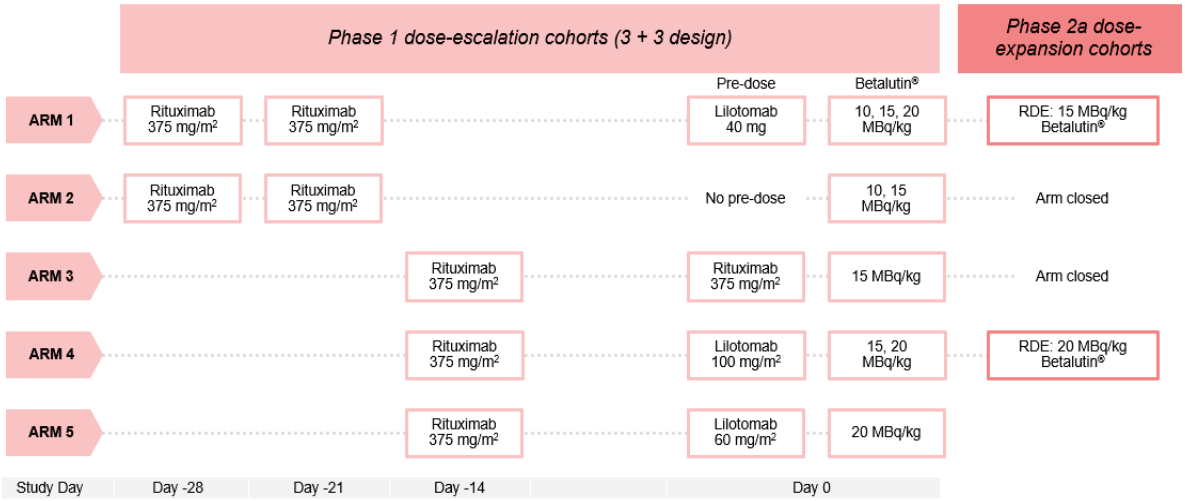

Figure 1: LYMRIT-37-01 study, Part A

The first part of the LYMRIT-37-01 study (Part A) is a phase I/IIa, open-label, dose escalation safety study designed to determine the maximum tolerated dose (MTD) of Betalutin (phase I part) and explore tumour response rate in participants receiving Betalutin (phase IIa part) in participants with relapsed indolent non-Hodgkin lymphoma (iNHL) (Figure 1).

Part B of the LYMRIT-37-01 study is a randomised phase IIb, open-label, study in participants with relapsed, anti-CD20 follicular lymphoma (FL) having received 2 or more prior therapies. The Part B analysis plan will be provided in a separate document with Syne qua non study no: NOR17001.

Part C of the LYMRIT-37-01 study was added in Protocol version 15.1 (EU&RoW) and Protocol version 15.2 (US) 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 dose regime of "40/15". Part C will be analysed under a cross-part LYMRIT-37-01 SAP which will detail analyses in specific populations and dose regimens for the overall study population.

All documentation henceforth will pertain only to Part A. Full detail of the study design is provided in the protocol Section 6.

The Phase I part of the study utilizes a 3+3 dose escalation design with the primary objective of defining the MTD of Betalutin. Secondary objectives are to identify a recommended dose of Betalutin for the Phase IIa part of the study and investigate the safety, biodistribution, pharmacokinetics and efficacy of Betalutin. Participants were enrolled into one of four dose-escalation arms. The Betalutin dose was incrementally increased in a 3+3 design until Dose Limiting Toxicity (DLT) was observed in >20% of treated participants. Betalutin was administered as a single infusion within 4 hours of lilotomab pre-dosing (with the exception of Arm 2 and Arm 3, where no lilotomab pre-dosing was given). From protocol version 5.0, participants received pre-treatment with rituximab (RTX) to deplete B cells on day -28 and day -21 (Arms 1 and 2) or on day -14 (Arms 3, 4, 5). Lilotomab pre-dosing was not mandated in Protocol versions 1.0 – 4.0.

The planned treatment groups were:

- Arm 1: Betalutin + pre-dosing with 40 mg lilotomab
- Arm 2: Betalutin without pre-dosing with lilotomab
- Arm 3: Betalutin + pre-dosing with rituximab
- Arm 4: Betalutin + pre-dosing with 100 mg/m^2 lilotomab

One additional arm (Arm 5) enrolled 3 participants to receive Betalutin 20 MBq/kg following a lilotomab pre-dose of 60 mg/m^2 for PK assessment.

The regimen(s) that completed 6 participants without DLTs enrolled additional participants in Phase IIa. Two phase IIa expansion cohorts (in Arm 1 and Arm 4) enrolled additional participants at the recommended Betalutin doses in conjunction with lilotomab pre-doses of 40 mg (15 MBq/kg Betalutin: Arm 1 expansion) and 100 mg/m^2 (20 MBq/kg Betalutin: Arm 4 expansion) respectively to evaluate tumour response rates, progression free survival, safety and toxicity.

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 6.5, 6.6 and 6.7 in the study protocol.

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) requirements, 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 infusion of rituximab 7 days prior to the administration of Betalutin (protocol versions 1.0 - 4.0) or 28 or 14 days prior to the administration of Betalutin (protocol versions 5.0 onwards) and lasts until 12 weeks (92 days) after Betalutin administration.

The follow-up period starts from 12 weeks (93 days) after Betalutin dosing up to 5 years. See Protocol Section 6.3 Schedule of Assessments for more details.

From protocol versions 1.0 – 9.0, weekly assessments should occur within a window of ± 2 days. Visits occurring at 3 week intervals will have a window of ± 3 days. During the follow-up period, a window of ± 30 days for visits is acceptable. For radiologic evaluation, a window of ± 30 days is acceptable for both treatment and follow-up periods.

From protocol version 10.0 onwards, a visit window of ± 2 days is permitted for the nominal Day 0 visit (study day 1) where 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 3-week intervals will have a window of ± 3 days. During the treatment and follow-up period, a window of ± 2 weeks for visits is acceptable. For positron-emission tomography (PET)/ computed tomography (CT) and CT evaluation a window of ± 2 weeks is acceptable for treatment and follow-up periods. From Week 52 to 5 years, a visit window of ± 3 weeks is acceptable.

Some data collected at unscheduled visits will be slotted to the closest planned visit/month. See Section 3.3 for more details.

The investigator may perform more frequent examinations than indicated if clinically needed. Data from such additional examinations will also be recorded in the electronic case report form (eCRF).

All safety samples/assessments at baseline are to be obtained before dosing. Blood samples for haematology must be taken, analysed and evaluated within 24 hours prior to study drug administration.

The details of schedule of assessments are covered in Section 6.3 and Tables 6-5 to 6-7 of the protocol.

2.2 Study Objectives

The statistical analysis plan incorporates the following objectives as stated in the protocol.

Objectives of Phase 1, Part A	
Primary Objectives	To define the MTD of Betalutin.
Secondary Objectives	• To establish a recommended dose of Betalutin for Phase II. • To investigate safety and toxicity of Betalutin. • To investigate biodistribution and PK of Betalutin. • To explore the efficacy of Betalutin.
Objectives of Phase IIa, Part A	
Primary Objectives	• To explore tumour response rates in participants receiving Betalutin.
Secondary Objectives	• To confirm the recommended dose of Betalutin. • To investigate safety and toxicity. • To estimate progression free survival (PFS). • To estimate overall survival (OS). • To investigate quality of life (QoL).

2.3 Study Endpoints

Safety Endpoints	• Incidence and severity * of adverse events and serious adverse events graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE version 4). • Changes from baseline in laboratory variables: haematology and serum biochemistry. • Changes from baseline in body temperature and vital signs (systolic/diastolic blood pressure and heart rate) during the treatment period. • Changes from baseline in physical examination during the treatment period. • Incidence of potential late toxicity, such as new primary cancers and bone marrow changes (acute myelogenous leukaemia, myelodysplastic syndrome, and aplastic anaemia).
Biodistribution/Pharmacokinetics endpoints	**Biodistribution** Evaluation of biodistribution includes whole-body radioactivity assessment, the counts in region-of-interest (ROIs) from anterior and posterior whole-body images, and measurement of total radioactivity in blood (Betalutin pharmacokinetics). This will enable the following: • Estimation of whole-body retention of radioactivity at each imaging time post-injection. • Estimation of the individual organ uptake/retention of radioactivity at each imaging time-point after injection. • Estimate retention of administered radioactivity in blood. • Calculation of estimated absorbed radiation dose to target organs.

	Pharmacokinetics (this SAP does not cover reporting of these endpoints) • Volume of distribution • Clearance • Mean activity-adjusted area under plasma drug concentration-time curve (AUC) • Activity adjusted total radioactivity in blood • Activity adjusted maximum plasma drug concentration (Cmax) • Effective half-life • Biological half-life
Efficacy Endpoints	• Tumour response rate (Response Rate (RR), Overall Response Rate (ORR) and Complete Response Rate (CRR)) • Tumour response duration (Duration of Response (DoR) and Duration of Complete Response (DoCR)). • PFS. • OS. • Durable response rate (DRR) **
Clinical benefit Endpoints	• Performance status defined as improvement or worsening, respectively, by 1-point or more on the Eastern Cooperative Oncology Group (ECOG) scale from the baseline value. • Quality of life (QoL) assessed using Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) questionnaire. The QoL forms will be used in those countries where the forms are translated and validated.

** Severity as assessed by CTCAE grade.*

*** This endpoint is not included in the protocol. The data for this analysis is collected per protocol procedures.*

2.4 Sample Size and Power

The phase I design utilised a 3 + 3 design, where MTD is defined as highest dose where ≤ 1 of 6 participants experience DLT. The number of participants will depend on the number of dose levels explored and was expected to be up to approximately 40 participants, depending on occurrence of DLTs. The participant will be substituted if the data are insufficient.

2.5 Interim Analysis, data reviews and publications

An interim analysis of safety and efficacy was performed after 6 participants in Phase I and 9 participants in Phase IIa had been treated with 15 MBq/kg Betalutin. The decision to continue the dose was made by the Safety Review Committee (SRC). Thirty more participants were planned in Phase IIa for a total of 36 participants at that dose level.

Following a review of the Arm 4 Phase I participant safety data by the SRC, approximately 10 to 15 additional participants were enrolled into a Phase IIa expansion arm to be treated with 20 MBq/kg Betalutin and 100 mg/m^2 lilotomab.

A data snapshot will be taken when all participants are enrolled and dosed and have a minimum of 3 years of follow-up (up to 31 July 2021), for reporting in a CSR (primary analysis). The final analysis will occur when all participants have completed follow-up (5 years following start of study treatment, until further anticancer therapy is given), for reporting in an addendum

to the CSR. Details of the outputs produced for each of these reporting efforts are documented separately.

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 of these variables (number of decimal places) is fully defined in the TFL 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 Populations

3.2.1 Enrolled Set

The enrolled set includes all participants who provided informed consent. Participants will be analysed according to the arm and dose they are assigned to (where relevant), irrespective of what they actually received.

3.2.2 Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set includes all participants who have received Betalutin. Participants will be analysed according to the arm and dose they are assigned to, irrespective of what they actually received.

The ITT analysis set will be used as a supplementary analysis set to the Per-Protocol in all efficacy statistical analyses.

3.2.3 Per-Protocol Set

The per-protocol set (PPS) includes all participants in the ITT analysis set who have an adequate tumour assessment at baseline, a follow-up tumour assessment ≥12 weeks after starting treatment (unless disease progression is observed before that time), and no major protocol violations considered to have a serious impact on efficacy results. Participants will be analysed according to the arm they are assigned to, irrespective of the treatment that they actually received.

An adequate tumour assessment at baseline is defined as the presence of at least one measurable target lesion and ≥ 12 weeks is defined as ≥ 78 days to take account of the protocol allowing a window of ± 7 days for PET and CT evaluations.

Major protocol violations considered as having a serious impact on the efficacy results include but are not limited to not having:

1. Histological confirmed relapsed non-Hodgkin B-cell lymphoma of following sub-types: follicular grade I-IIIA, marginal zone, small lymphocytic, lymphoplasmacytic and mantle cell lymphoma.
2. Measurable disease by radiological assessment.
3. Baseline disease assessment within 8 weeks (56 days) prior to first dose of any study treatment.
4. Betalutin dose given within +/- 10% of the intended dose.
5. Ongoing or recent concomitant cancer at risk of interfering with disease assessment.

The major protocol violations listed above will be determined programmatically from the study data. Violation type 1 and 2 will be determined from the inclusion/exclusion criteria, type 3 will be determined from the date of screening CT examination and first rituximab treatment, type 4 will be determined from the Betalutin dose data (see Section 3.7.10.1 for more details) and type 5 will be determined from a clinical review by the sponsor of the unique Medical Dictionary for Regulatory Authorities (MedDRA) coded terms of all ongoing medical history.

Protocol violations classed as key severity may also be identified as having a serious impact on the efficacy results and leading to exclusion from the PPS (see Section 3.6 for more details).

The PPS analysis set will be the primary analysis set used in all efficacy statistical analyses.

3.2.4 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).

The SAF for Betalutin (SAFB) will consist of all participants who received at least one dose of Betalutin.

Participants will be analysed according to the arm, regimen and dose they actually received.

3.2.5 Review and Agreement of Analysis Sets

The list of participants included in the enrolled set, ITT, PPS, SAF and SAF for Betalutin will be agreed prior to database lock, once all study data are available. The definitions for enrolled set, ITT and SAF and SAF for Betalutin are sufficient to determine the participant included within these analysis sets and so do not require listing and agreeing prior to database lock.

The Analysis Set Planning form indicates which analysis sets require individual subject assignments to be listed for review and agreement prior to final analysis, as well as the timing of the reviews.

3.2.6 Assigned and Actual Arm and Dose

Assigned Arm and Dose will be determined from the list of planned arm and dose of all participants that were eligible and gave consent to take part in the study, this will be received as an Excel spreadsheet from the sponsor.

Actual Arm and Dose will be determined from the rituximab, lilotomab and Betalutin administration pages on the CRF.

Actual arm will be based on the pre-dose on the nominal Day 0 (Study Day 1) as follows:

- *Arm 1 (with lilotomab 40 mg)*: >0 and ≤80 mg lilotomab administered (total dose) on Study Day 1
- *Arm 2 (without pre-dose)*: No pre-dose on Study Day 1
- *Arm 3 (with rituximab)*: Rituximab administered on Study Day 1 (any dose)
- *Arm 4 (with lilotomab 100 mg/m^2)*: >80 and ≤120 mg/m^2 lilotomab administered (total dose) on Study Day 1
- *Arm 5 (with lilotomab 60 mg/m^2)*: >40 and ≤80 mg/m^2 lilotomab administered (total dose) on Study Day 1

Any participants receiving a dose of lilotomab on Study Day 1 not covered by the above ranges will be presented as a separate arm.

Actual dose will be assigned based on the overall radioactivity injected (MBq/kg.b.w) rounded to the nearest 5 MBq/kg.b.w.

Where *overall radioactivity injected (MBq/kg.b.w) =*

$$\sum_{i=1}^{n} \frac{\text{radioactivity in syringe before injection i (MBq)} - \text{radioactivity in syringe after injection i (MBq)}}{\text{weight (kg)}}$$

and n is the total number of Betalutin injections.

3.3 Derived Data

- Definition of study day

Study day is relative to the date of first administration of Betalutin (study Day 1). Therefore, study day(s) 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 Betalutin dosing. A visit window from day -2 to day 1 inclusive (prior to Betalutin dosing) will be used.

Note: for Arms 2 and 3 no lilotomab pre-dosing was given.

- Incomplete dates

For calculation purposes, incomplete dates will 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 detailed 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.

- Visit Windows

In order to summarise the FACT-Lym and World Health Organisation (WHO) ECOG data over time, all assessments (including unscheduled) will be visit slotted to the time intervals shown in the table below, based on the date relative to the date of Betalutin administration (i.e. study day).

Table 1: LYMRIT-37-01 study, Part A Visit Windows

Visit window	**Target day of assessment ***	**Dataset**	**Days relative to the date of Betalutin administration ***
Screening	N/A	FACT_Lym	Days < -1
		WHO ECOG	
Day -1 to Day 0	1	WHO ECOG	Days -1 to 1
Month 1	31	WHO ECOG	Day 2 to 46
Month 2	62	WHO ECOG	Days 47 to 77
Month 3	92	FACT_Lym	Days 2 to 138
		WHO ECOG	Days 78 to 138
Follow Up - Month 6	184	FACT_Lym	Days 139 to 229
		WHO ECOG	
Follow Up - Month 9	275	FACT_Lym	Days to 230 to 320
		WHO ECOG	
Follow Up - Month 12	366	FACT_Lym	Days 321 to 457
		WHO ECOG	
Follow Up - Month 18	549	FACT_Lym	Days 458 to 641
		WHO ECOG	
Follow Up - Month 24	734	FACT_Lym	Days 642 to 826
		WHO ECOG	
Etc			

* (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).

For the data where two or more assessments are slotting into the same visit interval, the data recorded closest to the target visit day will be used for the summary tables and analyses. If two assessments are equally close to the target day, the later of the two assessments will be used in summary tables and analyses. Data from the assessment(s) not used will be listed only.

Data from all assessments (scheduled and unscheduled), including any multiple assessments will be listed including the assigned visit window.

- Month windows

For the efficacy analysis and laboratory shift and nadir outputs, to take account of the potential for out of window assessments being conducted, the following Month labels will be rederived using the table below.

Table 2: LYMRIT-37-01 study, Part A 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
Durable response of 6 months (from first observation of response (CR or PR) to most recent response (CR or PR))	>= 154 days

* (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

In Phase I, each study arm represents a pre-dose regimen administered on the nominal Day 0 visit (study Day 1), the same day of Betalutin administration:

- Arm 1: Lilotomab 40 mg
- Arm 2: No pre-dosing
- Arm 3: Rituximab 375 mg/m^2
- Arm 4: Lilotomab 100 mg/m^2
- Arm 5: Lilotomab 60 mg/m^2

The Betalutin dose was incrementally increased in a 3+3 design until DLT was observed in >20% of treated participants. The regimen(s) that completed 6 participants without DLTs enrolled additional participants in Phase IIa.

The data will be summarised in tabular form by study arm and Betalutin dose apart from disposition of participants, protocol deviations and background and demographic data which will be summarised by arm and Betalutin dose and overall participants, unless otherwise stated.

For all data, apart from efficacy data, will be summarised separately for the phase I and phase IIa study parts and using pooled data from the phase I and phase IIa parts for those arms and Betalutin doses that match across both phases.

Efficacy data will be summarised for the Phase IIa study FL participants only.

For phase I, the data will be summarised by arm and Betalutin dose as follows:

- Arm 1 (with lilotomab 40 mg pre-dose): 10 MBq/kg b.w., 15 MBq/kg b.w., 20 MBq/kg b.w.
- Arm 2 (without pre-dose): 10 MBq/kg b.w., 15 MBq/kg b.w.
- Arm 3 (with rituximab pre-dose): 15 MBq/kg b.w.
- Arm 4 (with lilotomab 100 mg/ m2 pre-dose): 15 MBq/kg b.w., 20 MBq/kg b.w.
- Arm 5 (with lilotomab 60 mg/ m2 pre-dose): 20 MBq/kg b.w.

From protocol version 5.0, participants in Arms 1 and 2 receive a pre-treatment with 375 mg/m^2 rituximab on day -28 and day -21, and Arm 3, 4 and 5 participants receive a pre-treatment with 375 mg/m^2 rituximab on day -14. Lilotomab pre-dosing was not mandated in Protocol versions 1.0 – 4.0 (but no participant recruited under versions 1.0 to 4.0). Participants in Arm 1 receive a pre-treatment of rituximab on day -7.

The phase IIa part expansion-only participants and the combined phase I/IIa data will be summarised by arm and Betalutin dose as follows:

Arm 1 (with lilotomab 40 mg): 15 MBq/kg b.w.

Arm 4 (with lilotomab 100 mg/ m^2): 20 MBq/kg b.w.

Where an overall participant summary is included for the combined phase I/IIa data, this will include all participants regardless of arm or Betalutin dose.

Results from both scheduled visits and slotted visits will be tabulated. Unscheduled visits will be included in assessments of maximum post-baseline, shift since baseline/nadir. All assessments will be listed, as well all clinically significant values.

- Completion and withdrawals, demographic characteristics, eligibility, analysis set and screen failure listings will be based on the enrolled set.
- Safety, protocol deviations and demographic characteristics listings will be based on the SAF set. Efficacy listings will be based on the ITT analysis set.
- Listings will be sorted by arm, Betalutin dose group, participant number and date/time of assessment.
- Graphical presentations of the data will also be provided where appropriate.
- Disposition will be summarised using the enrolled set. Efficacy data will be summarised and statistically analysed using the PPS and ITT analysis sets. Demographic characteristics will be summarised using the ITT, the SAF and the SAF for Betalutin analysis sets, background characteristics will be summarised using the ITT analysis set and AEs will be summarised using the SAF and the SAF for Betalutin analysis sets. All remaining data will be summarised using the SAF.

3.5 Participant Disposition

3.5.1 Participant Enrolment

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

Eligibility for participants that were recruited but did not meet all criteria will be listed, the protocol version number at the time of screening and any inclusion/exclusion criteria not met.

3.5.2 Participant Disposition

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

- Enrolled, including screen-failures with reason
- SAF analysis set
- SAF for Betalutin analysis set
- ITT analysis set
- PPS analysis set
- Participants ongoing at the time of data cut-off, with time to data cut off segmented as follows:

    - Study treatment period (≤ 3 months)
    - Follow-up period
        - >3 to ≤6 months
        - >6 to ≤9 months
        - >9 to ≤12 months
        - >12 to ≤18 months
        - >18 months
- Participants who completed the study treatment period.
- Participants who discontinued the study treatment period (with summary of reasons for withdrawal).
- Participants who discontinued the follow-up period (with summary of reasons for withdrawal), with time to withdrawal segmented as follows:
    - >3 to ≤6 months
    - >6 to ≤9 months
    - >9 to ≤12 months
    - >12 to ≤18 months
    - >18 months
- Participants who complete the study (5-year follow-up).
- Subsequent anti-cancer therapy (for Phase IIa only where participant withdrew due to start of further anti-cancer therapy after Betalutin injection).

Participants with the Completion/Withdrawal eCRF page completed up to and including 92 days after Betalutin dosing are assumed to have withdrawn in the Study Treatment Phase.

Participants with the Completion/Withdrawal eCRF page completed greater than 92 days after Betalutin but who did not complete the study are assumed to have withdrawn in the Follow-up Phase.

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

All duration derivations 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*

Descriptive statistics for the duration of follow-up (months) for all participants and for participants with current status subtype of FL 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*

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

3.6 Protocol Violations

Clinical protocol violations will be captured outside the eCRF in ICON's ICOTrial CTMS system. Output will be provided by ICON as a log in excel format and reviewed according to the ICON Protocol Deviation Plan and classified as key or non-key severity.

The number and percentage of participants with any protocol violation and at least one key protocol violation will be summarised. Details of all protocol violations (start date, violation category, specific details and classification of key or non-key severity) will be listed.

Note that the Data Management Plan and Protocol Deviation Plan refer to deviation rather than violation, but these will be reported as violations in-line with the protocol.

3.7 Baseline Data

3.7.1 Demographics and Baseline Characteristics

Demographic characteristics (age, sex, ethnic origin and race) and body measurements (height, weight, body mass index (BMI) and body surface area (BSA)) will be summarised. Weight, BMI and BSA will be summarised for both study baseline and Betalutin baseline.

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)*

Body mass index (BMI) is calculated as: *(weight (kg)/height (m)²).*

Body surface area (m^2) will be calculated based on the DuBois and DuBois formula [Dubois, 1916] as: *(Weight (kg)$^{0.425}$ x Height (cm)$^{0.725}$ x 0.007184).*

Demographic and baseline characteristics will also be summarised for the subgroup of FL participants only in the ITT analysis set.

Individual participant demographic characteristics, including informed consent, and body measurements data will be listed.

3.7.2 Medical History

Medical history events will be coded using the latest MedDRA dictionary version utilised at the time of the reporting for PART A primary analysis i.e. up to 31-July-2021. The same version will continue to be used for the future reporting of all parts (A to C and cross-part) of LYMRIT-37-01. The version used will be indicated in the data listings. All events will be listed.

The unique MedDRA coded terms will undergo a clinical review by the sponsor to determine major protocol deviations of ongoing concomitant cancer for PPS assignment. Please see Section 3.2.3 for more details.

3.7.3 Disease History

There are differences between the recording of information relating to the initial NHL diagnosis and the current NHL status between the phase I and phase IIa parts, where the phase IIa part records more information. Therefore, some information where indicated below will be summarised for the phase IIa part only.

Disease history (initial diagnosis of NHL and current status of NHL) will also be summarised for the subgroup of FL participants only.

All disease history and previous treatments for non-Hodgkin lymphoma details will be listed including any derived variables.

3.7.3.1 Initial diagnosis of NHL

The following initial diagnosis information will be summarised and where indicated, will be summarised for the phase IIa part only:

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

  12[date of informed consent – date of diagnosis + 1]/365.25.*

  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: follicular grade I-IIIA, marginal zone, small lymphocytic, lymphoplasmacytic or mantle cell
- Subtype at initial diagnosis for current status subtype for FL participants only: follicular grade I-IIIA, marginal zone, small lymphocytic, lymphoplasmacytic or mantle cell
- Ann Arbor staging at initial diagnosis: I, II, III, IV, or unknown (phase IIa only)
- Whether B symptoms were present at initial diagnosis: No, Yes or Unknown (phase IIa only)

3.7.3.2 Current status of NHL

The following current status of NHL information will be summarised and where indicated, will be summarised for the phase IIa part only:

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

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

  If partial dates are reported for date of most recent relapse, the 15th will be used when day is missing and 1st July when day and month are missing.
- Current NHL status at screening (recorded as Relapse incurable NHL subtype for Phase I)
- Whether CD37 positive. CD37 homogeneous intensity and strength will additionally be listed.
- Whether bulky disease. Where bulky disease is defined as the longest diameter of lesion at baseline being >= 6 cm.
- Bone marrow involvement: Yes/No, where No is where the percentage of tumour cells in bone marrow sample is 0, otherwise Yes. Where a bone marrow biopsy has not been performed, it will be missing.
- Extranodal involvement (Yes/No) (phase IIa only). Where extranodal involvement is determined from the baseline PET examination question “Extranodal lesions?”.

The number of unique nodal areas of disease at baseline was not collected on the eCRF at baseline. It was thought a clinical review of the unique locations for target lesions at baseline collected on the baseline CT examinations eCRF page may be used by the sponsor to derive a

unique list of nodal area of disease. This list could then be used to derive the number of nodal areas of disease at baseline for each participant. However, upon conducting the clinical review, this task has proved to be more complex with nodal area and nodular involvement and the true number of unique target nodal areas of disease at baseline cannot be verified. Due to this fact, data on nodal areas at baseline will not be reported for the Part A Phase IIa statistical analyses.

The Ann Arbor staging at study entry (i.e. current status) has not been collected on the eCRF for the Part A Phase IIa study. The Ann Arbor staging was only collected at initial diagnosis and captured on the eCRF at screening.

The Follicular Lymphoma International Prognostic Index (FLIPI) score calculation at baseline requires both the number of unique target nodal areas of disease at baseline and the Ann Arbor staging at baseline. For the reasons described above, the FLIPI score and classification of FLIPI score will not be calculated for the Part A (Phase I and Phase IIa study).

3.7.3.3 Previous treatment for NHL

The following previous treatment for NHL information will be summarised, previous treatments are entered under regimens with components of the regimen being entered separately with the same regimen number.

- Time since last treatment for NHL (months): calculated as:

  12 [date of first study drug administration – date of last course of last treatment for NHL prior to date of informed consent + 1]/365.25.*

  Where partial dates are reported, the 15th will be used when day is missing and 1st July when day and month are missing.

- The response after last treatment (Complete remission (CR), Partial Remission (PR), No change, Progressive disease (PD), Unknown, Not applicable)
- Number of lines of prior systemic therapies for NHL (derived by counting the number of distinct regimen numbers entered into the eCRF for previous treatments for NHL. Radiotherapy and regimen number 99 which corresponds to previous LYMRIT-37-01 PART A exposure to rituximab for any participants re-enrolled should be excluded. 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).
- Number of lines of prior therapies (including radiotherapy) for NHL (derived by counting the number of distinct regimen numbers entered into the eCRF for previous treatments for NHL). This will include all therapies e.g. systemic therapy, radiotherapy, other.
- Participants with 2 or more lines of prior systemic therapies for NHL (Yes/No)
- Whether received prior Bendamustine (yes/no), determined following clinical review of unique WHO Drug coding*.
- Whether received prior PI3K inhibitor (yes/no), determined following clinical review of unique WHO Drug coding *.
- Whether received prior alkylating agents (yes/no), determined following clinical review of unique WHO Drug coding*.

- Whether received prior rituximab / anti-CD20 (yes/no), determined following clinical review of unique WHO Drug coding*.
- Last therapy refractory (yes/no) where refractory to last previous therapy is defined as no response (i.e. either "No change" (i.e. stable disease) or 'Progressive disease' response to the last regimen that the participant received).
    - For participants with last therapy refractory the regimen that was the last therapy will be reported. This will be reported according to the components of the last regimen classified as 'Rituximab' (including rituximab or any anti-CD20 agent), 'Alkylating agent', 'Rituximab and alkylating agent' or 'Other'. Whether 'Rituximab' and 'Alkylating agent' were components of the last regimen will be determined using the rules above and regimens assigned as follows 'Rituximab' if rituximab but no alkylating agent component, 'Alkylating agent' if alkylating agent but no rituximab component, 'Rituximab and alkylating agent' if last regimen has both rituximab and alkylating agents as components or 'Other' for all other regimens.
- Rituximab (anti-CD20) refractory (yes/no) where response is recorded on the eCRF and refractory to any prior rituximab treatment/rituximab-containing regimen defined as: no response (no complete remission (CR) / partial remission (PR)) during therapy or a response (CR/PR) lasting less than 6 months after the completion of a regimen of rituximab therapy (including occurrence of progressive disease (PD) during rituximab/anti-CD20 maintenance therapy, or within 6 months of completion of maintenance therapy).

** A clinical review of the unique coded WHO drug terms will be conducted by the sponsor to set the regimes into individual components (prior PI3K inhibitor, alkylating agents, bendamustine and rituximab/anti-CD20) and to provide a standardised regimen name for each unique verbatim term.*

Additionally, the 'standardised regimen name' (per the clinical review) for all prior systemic therapies for NHL will be summarised, sorted in descending frequency of the total number of participants taking the regimen.

3.7.4 HAMA test

The presence of pre-existing (human anti-murine antibody) HAMA at screening visit will be assessed as part of participant eligibility, with a positive HAMA test being an exclusion criterion. The frequency of screen failure due to HAMA test positivity will reported in the disposition summary.

Whether the HAMA test was positive will be summarised by arm over time. A contingency table of the central versus local HAMA test results will be provided in order to assess concordance over time. Details of test conducted i.e. the type of test used, and the status (positive or negative) will be listed using the Enrolled set.

3.7.5 Pregnancy test

Details of the pregnancy test conducted at Screening will be listed.

3.7.6 Protein Electrophoresis - Gamma-globulin

Details of Screening Gamma-globulin levels, analysed via protein electrophoresis, will be listed.

3.7.7 Serology

All serology data collected at Screening will be listed.

3.7.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the latest World Health Organization Drug dictionary (WHO Drug) (Standard) version utilised at the time of the survival follow-up to 31-July-21 reporting of PART A. The same version will continue to be used for the future reporting of all parts (A to C and cross-part) of LYMRIT-37-01. The version used will be indicated in the data summaries and listings.

3.7.8.1 Prior Medications

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

3.7.8.2 Concomitant Medications

- Concomitant medications are those which are indicated as 'Ongoing' on the date of the first administration of rituximab,
- or those with a start date on or after the first administration of rituximab,
- or those with a start date before the first administration of rituximab and a stop date on or after the first administration of rituximab.

There will be no imputation of unknown dates. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

The number and percentage of participants who took any concomitant cancer-related therapies (for phase I participants only) will be summarised separately by WHO drug class and WHO Drug name sorted in descending frequency of the total number of medications taken using the safety analysis set.

All prior and concomitant medications and separately concomitant cancer-related therapies (for Phase I only) will be listed. Concomitant medications will be flagged in the listing.

3.7.9 Electrocardiography (ECG)

Details of the standard 12-lead ECG, performed at baseline only, will be listed.

3.7.10 Administration of Study Treatment and Exposure

BSA (m^2) used in the derivations in this section will be programmatically derived using the DuBois and DuBois formula (see Section 3.7.1). The derived body surface area will also be summarised and listed. Body surface area as collected on the eCRF will not be summarised or listed or used in any derivations.

3.7.10.1 Betalutin

The investigational product, Betalutin, is injected once on the nominal Day 0 visit (Study Day 1). The 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.

Administration of Betalutin will also be summarised for the subgroup of FL participants only.

Details relating to administration of the investigational product, including whether Betalutin was administered within 4 hours of lilotomab administration, the radioactivity in syringe prior to injection and after injection (converted to MBq/kg b.w. i.e. standardising for body weight), total radioactivity injected (MBq/kg.b.w), overall radioactivity injected (MBq/kg.b.w) and variance from prescribed dose 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.)] × 100

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

3.7.10.2 Rituximab

Participants are pre-treated with 375 mg/m^2 rituximab as detailed in Section 3.4. The actual rituximab dose administered (mg) and the actual rituximab dose standardised by body surface area (mg/m^2), as well as weight and body surface area at rituximab infusion, will be summarised by visit.

Rituximab dose administered (mg/m^2) = Rituximab dose (mg)/Body surface area (m^2)

Administration of Rituximab will also be summarised for the subgroup of FL participants only.

Details relating to administration of rituximab will be listed separately.

3.7.10.3 Lilotomab

Lilotomab will be infused within 4 hours prior to Betalutin administration, in all arms except Arms 2 and 3 where no lilotomab pre-dosing is given. The lilotomab dose (mg) standardised by both body weight (kg) and BSA (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)/ Body surface area (m^2)

Administration of Lilotomab will also be summarised for the subgroup of FL participants only.

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

3.7.11 PK Sampling

Details of the plasma PK sampling collection times will be listed.

3.8 Efficacy Analyses

For the Phase I part of the study and for the Phase IIa non-FL participants, all data relating to the efficacy endpoints detailed below, including derived variables, will only be listed based on the ITT set.

For the Phase IIa part of the study for the FL participants only, analyses of efficacy will primarily be based on the PPS. Analyses of RR, ORR, CRR, DRR, DoR, DoCR, PFS and OS will be repeated on the ITT. All sensitivity analyses using alternative censoring schemes will be based on the PPS only. All efficacy figures and listings will be based on the ITT only. All data relating to the efficacy endpoints detailed below, including derived variables, will be listed based on the ITT set.

Imaging-based tumour assessment with PET/CT and bone marrow will be performed at baseline prior to the start of study treatment. On-study tumour assessment will be performed at month 3 (CT/PET), 6 (CT/PET), 9, 12, 18, 24, 36, 48 and 60 (CT only).

Imaging-based tumour assessments include site of lesion and bi-dimensional measures for the largest diameter and the perpendicular diameter CT and Deauville 5-point score (D 5-PS) by PET as per Section 12 of the protocol. Tumour response assessments will be based on integrated CT and PET response at 3 and 6 months, and CT for months 9-60. If integrated CT and PET response is missing at 3 and 6 months but CT response is available, CT response will be used.

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.

3.8.1 Efficacy subgroups

Participant subgroups will be explored in the LYMRIT-37-01 cross-part SAP only.

3.8.2 Response Rate, Overall Response Rate (ORR) and Complete Response Rate (CRR)

3.8.2.1 Definitions

A response of CR, CR unconfirmed (CRu), PR, Stable Disease (SD), 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.

Response is defined as a disease assessment of CR, CRu or PR. The response rate at 3 months and within the first 6 months will be assessed. If disease assessments for a participant are not available then the response rate for the relevant timepoint will be set to Not Done (ND).

Overall Response Rate (ORR) is defined as the proportion of participants who achieve a best response rate of CR, CRu or PR independent of time. Complete Response Rate (CRR) is defined as the proportion of participants who achieve a best response rate of CR or CRu independent of time. If all disease assessments for a participant are not available then ORR/CRR will be set to NE.

For the primary analysis, to take account of the potential for out of window tumour assessments being conducted, the assigned month label for Month 3 will be rederived using the rules defined in the table in Section 3.3. Only tumour assessments which fall within Month 3 window will be included. As a sensitivity analysis, the Month 3 label as per the eCRF will be used in the analysis.

3.8.2.2 Analysis

The following will be presented using the Phase IIa data for participants with FL only, by arm and Betalutin dose and overall participants.

For Response Rate at Month 3, Response Rate within the first 6 months and ORR, the following will be presented for each arm and Betalutin dose:

- The responses of CR, PR, SD, PD, NE and ND (ND for ORR only).
- The number and percentage of responders with the exact 95% confidence interval (CI) using the Clopper-Pearson method.

For CRR, the following will be presented for each arm and Betalutin dose:

- The number and percentage of responders with the exact 95% CI using the Clopper-Pearson method.

The response at all timepoints will be listed for all participants.

3.8.3 Progression-Free Survival and Duration of Response

3.8.3.1 Definitions

3.8.3.1.1 Progression-free survival

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

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

Documented disease progression is defined as a Relapse (after CR or CRu) or progression (after PR or SD) and is indicated at the earliest date when the response assessment is given as 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 assessments: censor at date of Betalutin administration (study day 1).
- No documented disease progression: censor at date of last tumour assessment where progression was not shown.
- Received further anti-cancer therapy:
    - censor at date of last tumour assessment where progression was not shown before the further anti-cancer therapy was given. If no post-baseline tumour assessment then censor at study day 1.
- 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*

In order to show robustness of the PFS analyses the following sensitivity analysis will be explored:

- Alternative censoring scheme 1
    - Participants who received further anti-cancer therapy are considered to have had progression at the start date of the new anti-cancer therapy.
    - Participants with death or progression after two or more missed tumour assessments are not censored. These participants will be considered to have events on the date of death or progression.
- Alternative censoring scheme 2
    - Participants who received further anti-cancer therapy are censored at the start date of the new anti-cancer therapy.
    - Participants with death or progression after two or more missed tumour assessments are censored at the date of their first missed tumour assessment (i.e. last adequate tumour assessment + 84 days).

3.8.3.1.2 Tumour response duration - Duration of Response (DoR) and Duration of Complete Response (DoCR)

DoR is the time from when first criteria for response (CR, CRu or PR) are met to the time of relapse of progression and 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/CRu/PR response: censored at the date of the last CR/CRu/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.*

In order to show robustness of the DoR analyses the following sensitivity analysis will be explored.

- Alternative censoring scheme 1
    - Participants who received further anti-cancer therapy are considered to have had progression at the start date of the new anti-cancer therapy.

- Participants with death or progression after two or more missed tumour assessments are not censored. These participants will be considered to have events on the date of death or progression.

- Alternative censoring scheme 2
  - Participants who received further anti-cancer therapy are censored at the start date of the new anti-cancer therapy.
  - Participants with death or progression after two or more missed tumour assessments are censored at the date of their first missed tumour assessment (i.e. last adequate tumour assessment + 84 days).

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

3.8.3.2 Analysis

The following will be presented for all FL participants from all arms and Betalutin doses from the phase IIa study for the main and sensitivity analyses.

- 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 / tumour response durations (months) and corresponding 95% CI.
- The progression free survival rate / duration of response rate at 3, 6, 9, 12 and 15 months.

The corresponding plot of the probability of being progression free / remaining relapse or progression free against time will also be presented.

3.8.4 Overall Survival and Deaths

3.8.4.1 Definition

OS time (months) is defined as:

*(Date of death – date of Betalutin administration +1)*12/365.25.*

Participants still alive or lost to follow-up will be censored where the censoring time will be defined as:

*(Last date participant known to be alive – date of Betalutin administration +1)*12/365.25*

Where last date the participant is known to be alive is obtained from the latest date of response data or latest date from survival follow-up.

3.8.4.2 Analysis

The following will be presented overall participants, including participants from all arms and Betalutin doses from the phase IIa study for FL participants only.

- The number of participants included in the analysis, those with event and those who are censored.
- The Kaplan-Meier estimate of the median survival time and corresponding 95% CI.

- The overall survival rate at 3, 6, 9, 12 and 15 months.

The corresponding Kaplan-Meier survival plot will also be presented.

A clinical review of the free text primary cause of death from the death report form eCRF page will be conducted by the sponsor to code deaths to one of the following reason categories (Adverse Event, Progressive Disease or Other).

The number of deaths and number of deaths per reason category will be summarised for the SAF set overall and by the following groupings: ≤3 months, >3 to ≤12 months and > 12 months.

Time to death (months) is defined as:

*(Date of death – date of Betalutin administration +1)*12/365.25.*

Overall survival and death report form eCRF page information will be listed using the SAF set.

3.8.5 Durable Response Rate (DRR)

3.8.5.1 Definition

A Durable Response Rate (DRR) is defined as a response of CR/CRu or PR lasting continuously for 6 months, where 6 months is defined as 22 weeks or 154 days.

3.8.5.2 Analysis

The following will be presented overall participants, including participants from all arms and Betalutin doses from the phase I and phase IIa studies.

- The number and percentage of responders
- The number and percentage of DRR responders with the exact 95% CI using the Clopper-Pearson method. The denominator for the percentage will be the number of responders.

3.8.6 Response profile follow-up of participants

The response profile of participants will be presented in swimmer plots with separate plots for FL and non-FL participants. These plots will show months from Betalutin administration on the x-axis and a bar for each participant on the y-axis. Participants will be presented in order of follow-up, longest duration at the bottom and shortest at the top. The start of PD, SD, PR, CR and CRu will be indicated on the bar at the appropriate timepoint. Whether the response ended, the response continued or whether the participant withdrew at the last follow-up time will be indicated at the end of the bar.

3.8.7 Tumour Assessment via Sum of product of diameters (SPD)

The SPD will be calculated at each visit as:

SPD= $\sum_{i=1}^{6}(longest\ diameter \times shortest\ diameter$ where i is one of up to six target lesions)

The best percentage change per participant will be determined as the minimum percentage change over time. The percentage will be derived as:

*(Change from study baseline – study baseline value)*100*

A waterfall plot of the best percentage change will be produced with separate plots for FL and non-FL participants. These plots will show % change from baseline on the y-axis and a bar for each participant on the x-axis. The colour of the bars presented will represent the subtype at baseline and participants that had a CR and/or PR will be annotated under each bar. Any changes greater than 100% will be plotted as 100% and will have the actual change described in the footnote.

All CT examination data will be listed including SPD. The best percentage change, as indicated by the minimum percentage change, will be flagged.

3.8.8 Lesion SUVmax

The maximum standardised uptake value (SUVmax) for the most active lesion at baseline (lesion with maximum SUVmax at baseline) and its change from baseline will be derived and presented in a listing along with other collected PET examination data.

3.8.9 Overall PET Response According to Deauville Score

From PET/CT scans performed at baseline, 3 months and 6 months, images will be scored according to the 5-point scale based on the Deauville criteria for nodal lesions (see Section 12.2.2 of Protocol version 15.1) as follows:

- Negative
  1. No uptake
  2. Uptake ≤ mediastinum
  3. Uptake > mediastinum but ≤ liver
- Positive
  4. Moderately increased uptake compared to liver at any site
  5. Markedly increased uptake compared to liver at any site

  X. New areas of uptake unlikely to be related to lymphoma

Overall PET Response According to Deauville Score will be presented in a listing.

3.9 WHO (ECOG) Performance Status

Summary tables will be based on the ITT overall participants, this will include participants regardless of arm and Betalutin dose from the Phase I and Phase IIa studies. Visit slotting will be employed for the WHO ECOG. See Section 3.3 for more details.

The WHO (ECOG) performance status is a 6-point scale (0=fully active to 5=dead).

A value of the WHO performance status can be missing at a scheduled study visit for reasons which are either related to the participant's quality of life or where no evidence of relationship can be assumed and where the data may be considered "missing completely at random". A summary of WHO performance status at a study visit that inappropriately assumes that all missing data are missing completely at random, or which is limited to only those participants who attended the visit may result in biased and misleading estimates. To mitigate potential sources of bias arising from participant death in summaries, the WHO performance status of all participants in the study will be assigned a value at all scheduled study visits for which there is a missing value as follows:

- If the participant has died during the study or withdraws from the study for any reason and subsequently dies, a score of 5 will be given for all (unattended) scheduled study visits after the time of death. The date of a scheduled visit will be determined using the target study

day from the schedule of assessments (Tables 6.5 and 6.7 the study protocol), e.g. the target date of the "Month 9" scheduled visit is at Week 39 which is Day 273 of the study.

- If the participant has withdrawn from the study and has not attended a subsequent study visit and there is no evidence that the participant has died prior to the scheduled date of the visit, they will be assigned a score of "unknown" for the visit.
- If the participant has not withdrawn from the study, a value of "missing" will be assigned.

A shift table of study baseline versus post-baseline visits will be provided for the ITT analysis set showing the number and percentage of participants for the different performance status categories (0 to 5) at study baseline and post-baseline visits.

Additionally, the number of participants who experienced an improvement (decrease of ≥1 point), no change, and a worsening (increase of ≥1 point) in WHO performance status from study baseline will be provided at each visit.

All WHO performance status data will be listed.

3.10 FACT-Lym Quality of Life Questionnaire

Summary tables will be based on the ITT. Visit slotting will be employed for the FACT-Lym. See Section 3.3 for more details. The Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) quality of life questionnaire (version 4) is completed only for the phase IIa participants at screening, Month 3 and Month 12 and consists of 42 items (statements about quality of life) which each belong to one of five separate domains. The participant is asked to indicate how true each statement has been for them during the past seven days. Answers range from 0 (not at all) to 4 (very much). The responses are used to calculate the following subscale scores, where a higher score is indicative of a better quality of life:

- Physical Well-Being Score (PWB): If there are at least 4 non-missing responses to the 7 items, then PWB=7 x [4 - mean response], else it is missing. PWB ranges from 0 to 28.
- Social / Family Well-Being Score (SWB): If there are at least 4 non-missing responses to the 7 items, then SWB=7 x [mean response], else it is missing. SWB ranges from 0 to 28.
- Emotional Well-Being (EWB): If the item "I am satisfied with how I am coping with my illness" is responded to, the response is inverted by subtracting it from 4 before proceeding. If there are at least 3 non-missing responses to the 6 items, then EWB=6 x [4-mean response] else it is missing. EWB ranges from 0 to 24
- Functional Well-Being Score (FWB): If there are at least 4 non-missing responses to the 7 items, then FWB=7 x [mean response], else it is missing. FWB ranges from 0 to 28.
- Additional Concerns / Lymphoma Subscale Score (LYMS): if there are at least 8 non-missing responses to the 15 items, then LYMS = 15 x [4 - mean response], else it is missing. LYMS ranges from 0 to 60.

In addition to the five subscale scores, the following three composite scores are derived:

- FACT-Lymphoma Trial Outcome Index (TOI): if PWB, FWB and LYMS are all non-missing, then TOI=PWB+FWB+LYMS, else it is missing. TOI ranges from 0 to 116.
- FACT-General Total Score (FACT-G): if PWB, SWB, EWB and FWB are all non-missing, then FACT-G=PWB+SWB+EWB+FWB, else it is missing. FACT-G ranges from 0 to 108.

- FACT-Lymphoma Total Score (FACT-L): if FACT-G and LYMS are both non-missing, then FACT-L=FACT-G + LYMS, else it is missing. FACT-L ranges from 0 to 168.

Participants who have died prior to the 6 or 12-month visit will be assigned a value of 0 for all scores at the relevant time point. Participants who withdrew for a reason other than death will be included in the summary by carrying forward the calculated value from the most recent previous visit.

The values of the five domain subscale scores and three composite scores, together with their change from study baseline (where baseline is the value at the screening assessment) will be summarised for the phase IIa participants at each time point for participants in the ITT analysis set. In this table, FACT-Lym domain subscale scores (including the number of non-missing items) and composite scores will be listed.

3.11 Biodistribution/Pharmacokinetics

All biodistribution and pharmacokinetic data will be analysed and presented in a separate report.

3.12 Safety Analyses

3.12.1 Adverse Events and Deaths

Adverse events (AEs) will be coded using the MedDRA dictionary version utilised at the time of the survival follow-up to 31-July-21 reporting of PART A. The same version will continue to be used for the future reporting of all parts (A to C and cross-part) of LYMRIT-37-01.

The start of the adverse event (AE) reporting for a study participant will coincide with signing of the 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.

3.12.1.1 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 injection 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 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 be derived separately for Betalutin, rituximab and lilotomab. For participants in Arms 2 and 3 in phase I, missing relationship to lilotomab will not be assumed to be related to lilotomab.

AEs will be classed as occurring in one of four 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), 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).

A summary table will present the following for phase I, phase IIa and the combined phase I/IIa separately:

3.12.1.2 Pre-treatment Adverse Events

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

3.12.1.3 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 phase by System Organ Class (SOC) and Preferred Term (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.

3.12.1.4 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)
- TEAE onset from Day 93 (Month 3) onwards

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 4: LYMRIT-37-01 study, Part A Adverse Event Summary Tables

Summary Table	AE onset from Day 1 onwards	AE onset from Day 1 to Day 92 (Month 3)	AE onset from Day 93 onwards (Month 3)
TEAEs by SOC and PT	X	X	X
Serious TEAEs	X	X	X
TEAEs of special interest	X	X	X
Study drug related TEAEs (Betalutin, rituximab or lilotomab)	X	X	X
TEAEs by relationship to Rituximab	X	X	
TEAEs by relationship to Lilotomab	X	X	
TEAEs by relationship to Betalutin	X	X	
Serious study drug related TEAEs (Betalutin, rituximab or lilotomab)	X	X	X
Serious TEAEs by relationship to Rituximab	X	X	
Serious TEAEs by relationship to Lilotomab	X	X	
Serious TEAEs by relationship to Betalutin	X	X	
TEAEs by CTCAE grading	X	X	
Most frequent TEAEs (reported in at least 5% of participants)	X	X	X
Most frequent TEAEs (reported in at least 5% of participants) where CTCAE grade is >=3	X	X	X
Most frequent study drug related TEAEs (reported by at least 5% participants overall)	X	X	X
Most frequent study drug related TEAEs where CTCAE grade is >=3 (reported in at least 5% of participants overall)	X	X	X
Most frequent serious TEAEs (reported in at least 2% of participants overall)	X	X	X
Dose Limiting Toxicities (DLTs)		X	

Adverse event data will be listed in full and will also include a treatment emergent flag, 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.

3.12.1.5 Rituximab Exposure Period Treatment-Emergent Adverse Events

A summary table will present the following for overall participants:

- TEAEs (events and participants).
- Serious TEAEs (events and participants).
- TEAEs of special interest (AESI) (events and participants).
- TEAEs by CTCAE grade (events and participants).
- TEAEs leading to withdrawal from study (participants only).
- TEAEs leading to death (participants only).

- TEAEs by relationship (probable/possible/unrelated) to each study treatment (Betalutin, rituximab, and lilotomab) and the pooled study treatment related (possible or probable) category (events and participants).

3.12.2 Relationship of Adverse Events and Other Listings

Separate listings will also be presented for: AEs, related TEAEs ('possible' or 'probable') to Betalutin or rituximab or lilotomab, TEAEs which lead to withdrawal from the study, serious TEAEs, TEAEs of special interest, and related TEAEs (separately for each study drug: Betalutin, rituximab, lilotomab). All CTCAE grades collected will be included in these listings.

3.13 Laboratory Evaluations

Common Terminology Criteria for Adverse Events (CTCAE, version 5) grades will be assigned to the laboratory results using the normalised laboratory results. For sodium, calcium and potassium two grades will be derived, one for hyper and one for hypo. E.g. Sodium = 125 mmol/L is Grade 2 hyponatremia but Grade 0 is hypernatremia.

Conversion factors will be applied where needed to report all laboratory results in International System of Units (SI) units.

Laboratory parameters will be listed in the following order:

- Haematology: haematocrit, haemoglobin, platelet count, red blood cell count, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, lymphocyte subsets.
- Serum biochemistry: sodium, potassium, calcium, creatinine, uric acid, blood urea nitrogen (BUN), alkaline phosphatase (total ALP), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), LDH, Gamma Glutamyl Transferase (γGT), glucose, bilirubin (total), albumin, quantitative serum immunoglobulins, human anti-murine antibody (HAMA).

3.13.1 Summaries of Numeric Laboratory Results

- Study Baseline Betalutin baseline values for all laboratory parameters.
- Values at each post-study baseline analysis window (scheduled visit).
- Change from Betalutin baseline at each post-baseline analysis window (scheduled visit) for all laboratory parameters.
- Shift tables in relation to the CTCAE grade from Betalutin baseline over first 3 months, the first 6 months and worst post-Betalutin baseline. Worst post-Betalutin baseline is defined as worst grade on any day after study Day 1 up to and including Day 92 (i.e. study treatment period). There will be two tables for sodium, calcium and potassium to deal with the two toxicities hyper and hypo.
- Shift tables in relation to the CTCAE grade from study baseline to Betalutin baseline for all laboratory parameters. There will be two tables for sodium, calcium and potassium to deal with the two toxicities hyper and hypo.

A summary table based on the ITT analysis set will be produced for neutrophil, lymphocytes and platelet counts for combined phase I/IIa. The calculations will only be derived within the timeframe of Day 1 up to and including Day 92 (i.e. study treatment period). This will include the following:

Neutrophil count

- Descriptive statistics for neutrophil nadir (where nadir is defined as the lowest post-Betalutin baseline neutrophil count)
- Descriptive statistics for Time (days) to nadir from Betalutin administration. Include all values from and including study day 1, which is pre-Betalutin. If nadir at study day 1 then time to nadir equals 1 day.
- Number (%) participants with neutrophil count < 1 x 10^9/Lat any time post-Betalutin baseline (where 1 x 10^9/L=1 000/mm^3)
- Number (%) participants with neutrophil count < 0.5 x 10^9/L at any time post-Betalutin baseline (where 0.5 x 10^9/L=500/mm^3)
- Number (%) participants with a nadir equivalent to grade 2, 3 or 4 at any time from study day 1 (this would include the pre-Betalutin dose on study day 1).
- Number (%) participants with a nadir of grade 2, 3 or 4, but without recovery to grade 0 or 1.
- Number (%) participants with a nadir of grade 2, 3 or 4, and with recovery to grade 0 or 1 (i.e. recovery to >= 1.5 x 10^9/L, where 1.5 x 10^9/L =1500/mm^3).
- Descriptive statistics for time to recovery (days). Where time to recovery (days) is number of days from nadir neutrophil count to subsequent date the neutrophil count is Grade 1 or above (including the time of nadir, i.e. if the nadir count is Grade 1 time to recovery will be 0 days).
- Descriptive statistics for time to recovery (days) for participants with a nadir equivalent to grade 2, 3 or 4, and with recovery to grade 0 or 1 subsequently.
- Number (%) participants at Week 8 and Week 12 with grade 0 or 1, grades 2-4 or a missing grade. Week 8 is defined as Days 53 to 61 and Week 12 is defined as Days 81 to 89. See Section 3.3.

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

- platelet count < 50 x 10^9/L (where 50 x 10^9/L =50 000/mm^3)
- platelet count < 25 x 10^9/L (where 25 x 10^9/L=25 000/mm^3)
- Recovery to grade 0 or 1 (i.e. recovery to >=75 x 10^9/L, where 75 x 10^9/L=75 000/mm^3)

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

- Lymphocyte count < 0.2 x 10^9/L (where 0.2 x 10^9/L=200/mm^3)
- Recovery to grade 0 or 1 (i.e. recovery to 0.8 x 10^9/L, where 0.8 x 10^9/L= 800/mm^3)

Individual haematological data will be plotted (using the Safety Analysis Set for Betalutin) for neutrophil count, platelet counts, lymphocytes, and possibly other parameters based on results.

3.13.2 Dose Limiting Toxicity

A Dose Limiting Toxicity (DLT) will be confirmed for a Phase I participant following a clinical review by the sponsor of the following data:

Haematological:

1. A haematological parameter with a grade 4 toxicity recorded post-baseline that does not recover to grade 3 within 7 days.

2. A TEAE term of PT = "THROMBOCYTOPENIA" or "FEBRILE NEUTROPENIA" or "PLATELET COUNT DECREASED" or any PT containing either "HAEMORRHAGE" or "BLEEDING".

Non-haematological:

- A serum biochemistry parameter with a grade 3 toxicity or more.

Confirmed DLT AEs from study Day 1 to Day 92 (Month 3) will be summarised by SOC and PT for Phase I only).

All confirmed DLTs for Phase I participants only will be summarised.

All confirmed DLTs will be listed (for Phase I only) detailing date recorded, whether haematological or non-haematological, the laboratory parameter (where applicable), the laboratory value (where applicable), the toxicity grade (where applicable) and the adverse event detail (where applicable).

3.13.3 Haematological Episode

For Phase IIa participants a haematological episode will be confirmed from the following data:

1. A haematological parameter with a grade 4 toxicity recorded post-baseline that does not recover to grade 3 within 7 days.
2. A TEAE term of PT = "THROMBOCYTOPENIA" or "FEBRILE NEUTROPENIA" or "PLATELET COUNT DECREASED" or any PT containing either "HAEMORRHAGE" or "BLEEDING".

All confirmed haematological episodes for Phase IIa participants will be summarised and listed.

3.14 Vital Signs

Details of vital signs data will be listed, including unscheduled assessments and change from baseline.

3.15 Physical Examination

An abbreviated physical exam (consisting of heart, lung, and other physical findings) occurs at baseline, dosing day and Days 1, 2 and 4. A full physical exam is carried out at other visits.

All physical examination data will be listed.

3.16 Bone Marrow Biopsy

Details of the bone marrow biopsy data will be listed, including change from baseline.

3.17 Long-term Toxicity

Details of the long-term toxicity data will be listed.

3.18 Biopsy of Tumour Tissue at Relapse or Progression

Details of the biopsy of tumour tissue at relapse or progression will be listed.

3.19 Whole Body Imaging

Details of the whole-body imaging will be listed.

3.20 Disease Status

Disease status information will be listed.

3.21 Changes from the Protocol Planned Analysis

1) The analysis population section in the protocol (Section 14.1.3) defines 3 analysis sets: the ITT analysis set, the Safety set and the Per-protocol set. To allow for screen-failure participants to be included in TFLs of participant completions and withdrawals, eligibility, screen failure and analysis sets, an enrolled set defined as all participants who provided informed consent, was added to this SAP.
2) The protocol Section 12.1.7 states that ORR will be assessed at 3 months and best ORR will also be evaluated, taking the best response rate achieved independent of time point for image evaluation. These definitions in this SAP were updated to define RR at 3 months and within the first 6 months and ORR as being the best response achieved independent of time.

4 REFERENCES

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