LYMRIT-37-01

EudraCT number: 2011-000033-36

IND number: 128959

CLINICAL STUDY PROTOCOL

A phase I/II study of lutetium (^{177}Lu)-lilotomab satetraxetan (Betalutin®) antibody-radionuclide-conjugate for treatment of relapsed non-Hodgkin lymphoma.

Final Protocol:	
Version 15.1	19 February 2021
Supersedes:	
Amendments 11 and 12 (Versions 14 and 15)	31 July 2020; 26 January 2021
Contains:	
Final Protocol (Version 4)	14 September 2012
Amendment 1 (Version 5)	30 January 2013
Amendment 2 (Version 6)	11 March 2014
Amendment 3, Phase 1 only (Version 6B)	18 February 2015
Amendment 4 (Version 7)	26 November 2015
Amendment 5 (Version 8)	04 July 2016
Amendment 6 (Version 9)	28 November 2016
Amendment 7 (Version 10)	04 July 2017
Amendment 8 (Version 11)	27 October 2017
Amendment 9 (Version 12)	22 October 2018
Amendment 10 (Version 13)	13 March 2020
Amendment 11 (Version 14)	31 July 2020
Amendment 12 (Version 15)	26 January 2021

Study Coordinating Investigator:
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Statement about Proper Study Conduct

This study will be conducted in compliance with Good Clinical Practices, according to ICH Harmonized Tripartite Guideline.

Confidentiality Statement

SUMMARY OF CHANGES FROM CLINICAL STUDY PROTOCOL VERSION 14

REASON(S) FOR THIS AMENDMENT

The primary reasons for this amendment are to amend LYMRIT-37-01 as follows:

1. To add Part C (Pharmacokinetic Cohort) to better characterise the pharmacokinetics of Betalutin and total lilotomab antibodies in patients treated with Betalutin 15 MBq/kg and lilotomab 40 mg, who are willing and able to provide pharmacokinetic samples due to limited available data from Part A and Part B. This change affects the entire protocol, including clarifications to inclusion and exclusion where appropriate to define applicability to Parts A,B and C of the study; Section 7.1.1 and Section 7.2.1. Section 4.8.6 has been introduced to clarify the rationale for the Part C population.
2. To clarify the management of dose finding in the subpopulations of patients in Part B with prior autologous stem cell transplant (SCT) and/or platelet count $\geq 100\times10^9$/L but $<150\times10^9$/L, including determination of the recommended dose regimens for these populations. Protocol Version 14 introduced the possibility to adapt the dose regimen in these subpopulations, without specific rules. Dose determination in the defined subpopulations will be managed using a "modified "3+3" design. The first 3 patients in each subpopulation will be treated with a lower dose of Betalutin and treatment decisions for subsequent patients will be made following review of the data by the SRC (as planned in Version 14). This change predominantly affects Section 4.2.3, Section 4.2.4, Section 4.8.7.1, Section 4.8.10, Section 6.1 and Section 6.2. A major related clarification has been added throughout the protocol that the subpopulations with a lower platelet counts have counts in the range $\geq 100\times10^9$/L but $<150\times10^9$/L.
3. To update the study hypothesis and objectives of Part B subsequent to the selection of the recommended phase II dose for further development implemented in Version 14 of the protocol:
    - Update to the Part B primary and secondary objectives to clearly identify those specific to the randomised section and those specific to the selected dose for further development; Section 5.3.1 and Section 5.3.2
    - Revision to the Part B sample size to reflect termination of dosing with the "100/20" treatment regimen and set a hypothesis and sample size for assessment of the "40/15" treatment regimen selected for further development. Patient enrolment in Part B will be completed when a total of 87 patients have received the regimen selected for further development (including patients from the randomised section of Part B) Section 6.1 and Section 14.1.2
    - Addition of secondary objectives and endpoints for Part B (complete response rate [CRR] and duration of complete response [DoCR]); Section 5.3.2, Section 5.6 and Section 14.1.7. Specification that overall response rate (ORR) will be evaluated by the investigator as a secondary endpoint (this was an omission) and that CRR, duration of response (DoR), DoCR and progression free survival (PFS) will be assessed by independent review and by the investigator.

Other key changes included in the amendment are detailed below. The rational for each change is:

4. Change of Chief Medical Officer and biostatistician and removal of the telephone number of the Coordinating Investigator from the signature page as subject to changes between versions of the protocol.

5. Introduction of (i) flexibility to the screening period (based on Sponsor approval) beyond 4 weeks due to unforeseen delays and (ii) possibility of performing study visits without key assessments as non-hospital visits, Section 6.3. These changes do not impact the assessment of the key study endpoints but allow for a safer management of patients affected by the Coronavirus Disease 19 (COVID-19) pandemic restrictions.

6. Revisions to inclusion and exclusion criteria based on queries and feedback from study sites and to clarify ambiguities, without changing the overall study population characteristics and requirements Section 7.1.2 and Section 7.2.2. This includes:

    - Clarification of the definitions of refractoriness and prior 2 lines of therapies qualifying for study entry. The inclusion requirements have not been changed, only reworded to prevent misinterpretation.
    - Acceptance that systemic anti-neoplastic regimens including agents such as idelalisib or other PI3K inhibitors qualify as a prior line of therapy.
    - Removing the requirement for a patient to be without grade≥1 Graft versus Host Disease when they have had prior autologous-SCT which was previously included in error; Section 4.2.4, Section 4.7 and Section 7.2.2.
    - Modifying the exclusion criterion for prior cancers. Exceptions to this inclusion criterion were imprecise and not adapted to changes in treatment outcomes for certain cancers since protocol was first written. Exceptions have been clarified and homogenised, still ensuring that only patients with no or very low risk of relapse during the course of the study are entered.
    - Ensuring that absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L and platelet count $\geq 100\times10^9$/L (Part B) and $\geq 100\times10^9$/L (Part C) are satisfied within 72 hours of the administration of rituximab. Haematology testing has been added prior to administration of rituximab to fulfill this requirement (Section 6.3 – Table 6.8 and Section 9.6.2.1).

7. Starting further therapy has been removed as an option for withdrawal from the study; Section 8. Patients enter limited (long term) follow-up when they have disease progression or start another cancer treatment (whichever comes first). This follow-up allows for long-term toxicities of Betalutin, to be captured and managed which is important for the patient and the study. The consent form will ensure that all situations when a patient goes into limited (long term) follow-up (including disease progression or start of a new anticancer treatment) are clearly explained. The patient's right to fully withdraw from the study at any time, including from long term follow-up, is not compromised by this change.

8. Clarification of testing requirement for human anti-murine antibodies (HAMA) detection at study entry, indicating that any commercially available test can be used as part of inclusion criteria verification. Clear differentiation between the HAMA test that is to be performed part of inclusion criteria verification and the test that is performed at screening

and over time during the study to monitor for the occurrence of HAMA directed to lilotomab (Section 4.5 and Section 9.6).

9. Clarification of the different study periods, up to 3 months, from 6 to 12 months and thereafter with clear separation of what is required during follow-up until disease progression or start of further cancer treatment (extensive follow-up involving hospital visits) versus after disease progression or further therapy (limited follow-up which may be conducted by telephone). The prior structure and wording of this section was leading to misinterpretation. Clearly highlighting what does not require hospital visits is important in the context of the COVID-19 pandemic.

10. Addition that Betalutin treatment may be administered by any other specialist physician authorised to administer radioactive treatments per local regulations (not just of a nuclear medicine specialist) to reflect local regulations for the administration of radiopharmaceuticals; Section 9.5.

11. Additional biobanking facilities specified to meet global requirements; Section 11.3.

12. Clarification added that for Part B and C, an investigator assessment of tumour response will initially be made but tumour response determined by independent central review will be used as the basis for patient decision making in relation to disease status *wherever possible*; Section 12. Throughout the protocol, it has further been clarified that patients should continue to undergo tumour assessments until disease progression assessed by central review. This is to ensure the primary objective of ORR and the secondary objective of duration of response assessed by independent central review are not compromised by early discontinuation of tumour assessments, where investigator and independent central review assessments of response differ.

    The possibility has been kept for the investigator to make treatment decision based on investigator's assessment, where the patient's condition requires immediate action at time of progression.

13. Clarification to adverse event (AE) reporting requirements and reporting of potential long-term toxicity; Section 13.2 and Section 13.4.8 to improve understanding and reporting compliance.

14. Modification in Common Terminology Criteria for Adverse Events (CTCAE) grade allocation for laboratory results and clarified that this will be derived as part of the statistical analysis rather than allocated by the study site; Section 13.4.5.

15. Revision of the statistical analysis section (i) to group all details in a single place to facilitate readability of it and (ii) clarify some requirements.

    - Statistical analysis methodology restructured and clarification added to explain that results from Part A (Phase I and Phase IIa), Part B and Part C will be summarised separately due to differences in study design, dose regimens and patient populations. However analyses in specific populations and for specific dose regimens may be performed in the overall study population.
    - Efficacy endpoint definitions moved to the statistical section only, removing the duplicate definitions from Section 5.6 and removing Section 12.4 from protocol Version 14; Section 14.1.7. There is no change in the definitions and no loss of information.

- Timing of analyses for Part B more clearly identified. Clarification added that the statistical analysis would be fully described in a Statistical Analysis Plan (SAP) prior to database lock; Section 14.1.5.
- "Not evaluable" added as an option for tumour response for completeness; Section 14.1.7.
- Requirement to present the primary endpoint at each timepoint removed as not necessary; Section 14.1.7.
- Handling tumour response data from patients who withdraw or are lost to follow-up as disease progression at the time of the last assessment removed; Section 14.1.12. These data will be handled as censored data and relevant sensitivity analyses will be conducted.
- Clarifications added to the definitions of the efficacy endpoints and of analysis of time-to event endpoints; Section 14.1.7.

16. Addition of a new section on collection of IMP dosing errors previously omitted; Section 16.3.6.

Further changes to improve sense, readability and prevent misunderstanding have also been made *without changes to overall protocol requirements*:

17. Clarifications to the rationale for a lower dose of Betalutin for patients with prior autologous-SCT and/or lower platelet counts, including the consolidation of text previously in the study design section; Section 4.8.11. There is no change to the rationale previously described in Version 14.
18. Clear presentation of the design of each part of the study and of the assessments to be performed. Where procedures differ between different parts of the study, these have been separated; Section 6.1.
19. Clear wording of the definition of dose limiting toxicities (DLTs) and the dose definition procedures in Part B subpopulations; Section 6.2.
20. Separation of the study procedures into study periods and parts of the study, where applicable to aid understanding (as the reading of this section generated multiple queries from investigators and led to protocol deviations); Section 9.6. This includes separating the biodistribution and pharmacokinetics from the main procedures as they are only applicable to a subset of patients.
21. Clarification that the biopsy collected at relapse and/or disease progression is subject to the patient's willingness to have this biopsy; Section 11.1.
22. Consolidation of key information relating to the Safety Review Committee (SRC) in one section and removal of unnecessary duplication; Section 16.4.

Correction of typographical errors, introduction of abbreviations and formatting throughout the document. Section headings were simplified throughout the document so the parts of the study each section is applicable to is now only stated when this is not Parts A, B and C.

Changes made to the body text have been reflected in the synopsis.

LIST OF CHANGES IN THIS AMENDMENT

Changes from Version 14 are detailed in Appendix I.

COORDINATING INVESTIGATOR SIGNATURE PAGE

Study Number: LYMRIT-37-01

Study Title: A phase I/II study of lutetium (^{177}Lu)-lilotomab satetraxetan (Betalutin®) antibody-radionuclide-conjugate for treatment of relapsed non-Hodgkin lymphoma.

Study Centre: Department of Oncology, Oslo University Hospital, Radiumhospitalet, Norway.

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, including any study protocol amendments, informed consent, Ethics Committee procedures, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and the local regulations governing the conduct of clinical studies.

Signature: …… Date: 23-Feb-2021
Printed name: ARNE KOLSTAD
Title: Chief physician, M.D

Address: Oslo University Hospital,
Radiumhospitalet, Montebello
N-0310 Oslo
Norway

Email: ARNEK@ous-hf.no

SPONSOR SIGNATURE PAGE

Study Number: LYMRIT-37-01

Study Title: A phase I/II study of lutetium (^{177}Lu)-lilotomab satetraxetan (Betalutin®) antibody-radionuclide-conjugate for treatment of relapsed non-Hodgkin lymphoma.

On behalf of Nordic Nanovector ASA:

Christine Wilkinson Blanc
Chief Medical Officer
Nordic Nanovector ASA
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N-0884 Oslo, Norway

Signature: 

Date: 23-Feb-2021

Christine Wilkinson Blanc, MD

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Datacision Limited
55 Station Road
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HP9 1QL, United Kingdom

Signature: 

Date: 23-Feb-2021

Albert Chau, CStat, CSci

Contact details for all the study personnel are provided in the study procedures manual.

1 PROTOCOL SYNOPSIS

Study Title:

A phase I/II study of lutetium (^{177}Lu)-lilotomab satetraxetan (Betalutin®) antibody-radionuclide-conjugate for treatment of relapsed non-Hodgkin lymphoma

Name of Sponsor/Company: Nordic Nanovector ASA, Oslo, Norway

Name of Drug Substance: lutetium (^{177}Lu)-lilotomab satetraxetan (Betalutin)

Name of Drug Substance used for pre-dosing: lilotomab or rituximab

Name of Drug Substance used for pre-treatment: rituximab

Study Centre(s) in phase I:

Coordinating Investigator: Arne Kolstad, MD

Oslo University Hospital, Radiumhospitalet, Oslo, Norway; Principal Investigator: Arne Kolstad, MD

Study centres may be added up to a total of approximately 10 centres.

Study Centre(s) in phase IIa:

Study centres may be added up to a maximum of approximately 24 centres.

Study Centre(s) in phase IIb:

Study centres may be added up to a maximum of approximately 90 centres.

Phase of Development: phase I and phase IIa (referred to as Part A) and IIb (referred to as Part B)

Key Dates:

Part A (phase I and phase IIa):

Phase I, Arm 1: Patient enrolment started in December 2012. The accrual time was 2 years and the arm is now closed.

Phase I, Arm 2: Patient enrolment started in July 2015. The arm is now closed.

Phase I, Arm 3: Patient enrolment started in May 2016 and the arm is now closed.

Phase I, Arm 4: Patient enrolment started in May 2016 and completed in March 2017. The arm is now closed.

Phase I, Arm 5: Enrolment of patients into this arm started in May 2017. The arm is now closed.

Phase II, Arm 1: Patient enrolment started in October 2015 and completed in March 2017. The arm is now closed.

Phase II, Arm 4: Patient enrolment started in May 2017. The arm is now closed.

For closed arms patients are still in follow-up.

Part B (FL phase IIb) – "PARADIGME":

Enrolment was opened upon approval of Protocol Version 11.

Part C (Pharmacokinetic Cohort phase IIa):

Enrolment will open at selected sites (capable of collecting pharmacokinetic samples) upon approval of this version of the protocol (Version 15).

Patients in Part B and Part C will be followed up for up to 5 years after the Betalutin dose. Extensive follow-up will take place for all patients for at least the first year (Months 6, 9 and 12) (see "Study Evaluations").

Study Objectives:

Part A, phase I (Arms 1, 2, 3, 4, and 5):

Primary Objective:

- To define maximum tolerated dose (MTD) of Betalutin.

Secondary Objectives:

- To establish a recommended dose of Betalutin for phase IIa.
- To investigate safety and toxicity of Betalutin.
- To investigate biodistribution and pharmacokinetics of Betalutin.

- To explore the efficacy of Betalutin.

Part A, phase IIa:

Primary Objective:

- To explore tumour response rates in patients receiving Betalutin.

Secondary Objectives:

- To confirm the recommended dose of Betalutin from Part A, phase I.
- To investigate safety and toxicity.
- To estimate progression-free survival (PFS).
- To estimate overall survival (OS).
- To investigate quality of life (QoL).

Part B, FL phase IIb "PARADIGME":

Primary Objectives:

Randomised section of Part B

- To evaluate the efficacy of the "40/15" dose regimen (40 mg lilotomab / 15 MBq/kg Betalutin) compared with "100/20" dose regimen (100 mg/m^2 lilotomab/ 20 MBq/kg Betalutin) based on an Independent Review Committee (IRC) assessment of tumour response rates in adult patients with relapsed rituximab/anti-CD20-refractory follicular lymphoma (FL).

Selected regimen for further development:

- To evaluate the overall response rate (ORR) of the regimen selected for further development based on the Independent Review Committee (IRC) assessment of tumour response rates in adult patients with relapsed rituximab/anti-CD20 refractory FL.

Secondary Objectives:

To compare the"40/15" and "100/20" treatment regimens in the randomised section and to evaluate the regimen selected for further development, in terms of the following:

Efficacy

- ORR by investigator assessment
- Complete response rate (CRR) by independent review and investigator assessment
- Duration of response (DoR) by independent review and investigator assessment
- Duration of complete response (DoCR) by independent review and investigator assessment
- PFS by independent review and investigator assessment
- OS.

Safety

- Incidence and severity of adverse events (AEs).

Exploratory objectives:

- QoL.
- Pharmacokinetics.

Part C, phase IIa (Pharmacokinetic Cohort)

Primary Objective:

To further characterise the pharmacokinetics of Betalutin (total radioactivity measurements in blood) and total lilotomab antibodies (antibodies measured in serum).

Secondary Objectives:

- To investigate safety and toxicity.
- To explore efficacy

Population

Part A (phase I and phase IIa): Adult patients with relapsed indolent non-Hodgkin B-cell lymphoma (iNHL).

Part B (FL phase IIb):

Adult patients with relapsed FL who have received ≥2 prior anti-neoplastic or immunotherapy-based regimens, and are refractory to any previous anti-CD20 based regimen. Prior therapy must include an anti-CD20 therapy and an alkylating agent. Anti-CD20 refractory disease is defined as lack of a complete remission (CR) or partial remission (PR), or PD within 6 months of last dose of an anti-CD20 containing regimen. Prior exposure to idelalisib or other PI3K (Phosphatidylinositol 3-kinase) inhibitors is allowed. The eligibility criteria were widened under protocol Version 14 to allow enrolment of patients with a prior autologous stem cell transplant (SCT) (if at least two years have elapsed since transplantation) and/or platelet count ≥100×10^9/L but <150×10^9/L at study entry.

Part C (phase IIa Pharmacokinetic Cohort):

Adult patients with relapsed iNHL who are willing and able to provide pharmacokinetic samples (samples for Betalutin total radioactivity and total lilotomab antibodies).

Investigational Products:

Betalutin is an antibody-radionuclide-conjugate (ARC) composed of the radioisotope lutetium-177 (^{177}Lu), the linker p-SNC-benzyl-DOTA (also referred as satetraxetan) and the murine anti-human CD37 immunoglobulin G_1 (IgG_1) antibody, lilotomab. The active moiety is the beta-particle emitting nuclide ^{177}Lu. Lutetium-177 has a physical half-life of 6.7 days. The antibody lilotomab recognises epitopes on the human CD37 antigen, which is abundant on the cell surface of tumours of B-cell origin, including non-Hodgkin lymphoma (NHL). Betalutin is prepared as a solution for intravenous administration. The amount of Betalutin (also referred as lutetium (^{177}Lu)-lilotomab satetraxetan) injected per patient will depend on dose level and patient's weight; however, the dose is capped for patients who weigh more than 130 kg (patients heavier than 130 kg will receive the dose for a 130 kg patient). The concentration of lilotomab satetraxetan in the Betalutin formulation is 0,78 mg/mL, and the amount injected is dependent on how many days after production the product is given, up to a maximum of 18 mg of lilotomab. Betalutin will be supplied in vials containing a ready-to-use solution.

The investigational medicinal product (IMP) will be referred to as Betalutin or lutetium (^{177}Lu)-lilotomab satetraxetan in the protocol.

Rituximab, a chimeric anti-CD20 antibody, will be used to clear the circulating normal peripheral B-lymphocytes in the blood and in the spleen before administering Betalutin. This may secure better access for Betalutin to less accessible compartments such as lymph nodes and larger tumour masses. Rituximab targets CD20 and will not block the binding of Betalutin to CD37 on the B-lymphocytes or tumour cells.

Pre-medication consisting of an antipyretic and antihistamine should be administered before infusion of rituximab. The types of pre-medication will be in accordance with each hospital's routine, including any use of corticosteroids. For detailed guidance on use of rituximab and possible side effects, see the summary of product characteristics or prescribing information.

Lilotomab is a murine anti-human CD37 antibody, and the same antibody, as used in Betalutin, that will be used to block the binding on remaining B-cells, in the lymphoid organs following the rituximab pre-treatment. Administration of lilotomab will be performed within 4 hours before administration of Betalutin on Day 0. Pre-medication consisting of an antipyretic and antihistamine medication should be administered before infusion of lilotomab.

Study Design:

Part A:

Phase I: Open-label, non-randomised, single injection ascending dose study to assess safety, biodistribution and PK of Betalutin.

A 3+3 dose-escalation design was used to determine the MTD and/or Recommended phase 2 dose (RP2D) for Betalutin and the optimal pre-treatment and pre-dosing regimen with rituximab and lilotomab for further phase IIa evaluation. Dose-limiting toxicity (DLT) criteria are defined in Section 6.2.1.

Phase IIa: Two phase IIa expansion cohorts were added to Arms 1 and 4 for confirmatory safety and efficacy assessment. Thirty (30) patients were enrolled in the Arm 1 phase IIa cohort. Approximately 10-15 patients will be enrolled in the Arm 4 phase IIa cohort.

Part B (FL phase IIb)-"PARADIGME"

Open label, randomised 1:1 (stratified for double-refractory patients, where double-refractory is defined as refractory to both an anti-CD20 therapy and an alkylating agent therapy – see Section 9.1.7.2 for full definition) to receive one of the 2 RP2Ds (40 mg lilotomab + 15 MBq/kg Betalutin (referred to as "40/15") or 100 mg/m^2 lilotomab + 20 MBq/kg Betalutin (referred to as "100/20"). The patients will receive a single dose of rituximab 375 mg/m^2 on Day -14, and then sequential administration of lilotomab followed by Betalutin within 4 hours on Day 0. . An interim analysis of efficacy and safety data was planned after approximately 50 patients (see 'Statistical

Methods and Planned Analysis'). This was performed after the first 47 patients. Following the interim analysis, the single regimen of 40mg lilotomab and 15MBq/kg Betalutin ("40/15") was selected for all subsequent patients having platelets ≥150×10^9/L (and without a prior autologous-SCT (see below) Patient enrolment will be completed when a total of 87 patients have received the "40/15" regimen (including patients in the randomised section).

The eligibility criteria for Part B were also widened (under protocol Version 14), to allow enrollment of patients 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 will be divided into 3 subpopulations. The dose of Betalutin administered to the first 3 first patients treated each subpopulation will be reduced:

- Patients with a prior autologous-SCT and platelet count ≥150×10^9/L will receive Betalutin at the reduced dose of 12.5 MBq/kg
- Patients with a prior autologous-SCT and platelet count ≥100×10^9/L but <150×10^9/L will receive Betalutin at the reduced dose of 10 MBq/kg
- Patients without a prior autologous-SCT and platelet count ≥100×10^9/L but <150×10^9/L will receive Betalutin at the reduced dose of 12.5 MBq/kg

All patients will be followed for 6 weeks. The SRC will review the safety data (in particular, the number of dose limiting toxicities [DLTs]) of each subpopulation and recommend the current reduced dosing level be maintained, a dose escalation (including escalation to Betalutin 15 MBq/kg with lilotomab 40 mg), an evaluation of an additional 3 patients, a dose-decrease, a different dose or to stop the recruitment of further patients with a prior autologous-SCT and/or lower platelet count.

Part C (phase IIa Pharmacokinetic Cohort):

Open label phase IIa expansion cohort to enable the collection of samples for Betalutin pharmacokinetics and total lilotomab antibodies pharmacokinetics in patients receiving the "40/15" regimen.

Number of Patients Planned:

Part A (phase I and phase IIa): iNHL patients

Up to 35 phase I patients

In phase IIa, 30 patients have been enrolled in Arm 1 and approximately 10-15 patients have been enrolled in Arm 4.

Part B (FL phase IIb):

Randomised section of Part B

Up to 130 patients with FL were planned to be enrolled and randomised 1:1 (stratified for double-refractory patients, where double-refractory is defined as refractory to both an anti-CD20 therapy and an alkylating agent therapy– see Section 9.1.7.2 for full definition) to receive dose "40/15" or dose "100/20" until the selection of one of the 2 regimens for further assessment in clinical development.

Assessment of dose selected for further development

Following the interim analysis and selection of the "40/15" regimen for future development, patient enrolment will be completed when 87 patients have received this regimen (including patients treated with the "40/15" regimen in the randomised section). **Part C (phase IIa Pharmacokinetic Cohort): iNHL patients**

At least 10 patients (up to a maximum of 20 patients) from selected sites willing and able to collect pharmacokinetic samples.

Inclusion Criteria: Part A (phase I and phase IIa) and Part C (phase IIa Pharmacokinetic Cohort)

1. Histologically confirmed (by World Health Organization [WHO] classification) relapsed incurable non-Hodgkin B-cell lymphoma of following subtypes; follicular grade I-IIIA (for Part C, this excludes patients meeting Part B criteria, who should enter Part B), marginal zone, small lymphocytic, lymphoplasmacytic, mantle cell.
2. Age ≥ 18 years.
3. Part A: A pre-study WHO performance status of 0-1; Part C: WHO performance status of 0-2.
4. Life expectancy should be ≥3 months.
5. <25% tumour cells in bone marrow biopsy (biopsy taken from a site not previously irradiated).
6. Measurable disease by radiological methods.
7. Women of childbearing potential must:

   a) understand that the study medication is expected to have teratogenic risk.

	b) have a negative pregnancy test.
	c) agree to use, and be able to comply with, effective contraception without interruption, 4 weeks before starting study medication, throughout study medication therapy and for 12 months after end of study medication therapy, even if she has amenorrhoea.
8.	Male patients must agree to use condoms during intercourse throughout study medication therapy and the following 12 months.
9.	Patients previously treated with native rituximab are eligible.
10.	The patient is willing and able to comply with the protocol, and agrees to return to the hospital for follow-up visits and examination.
11.	The patient has been fully informed about the study and has signed the informed consent form.
Exclusion criteria: Part A (phase I and phase IIa) and Part C (phase IIa Pharmacokinetic Cohort)	
1.	Medical contraindications, including uncontrolled infection, severe cardiac, pulmonary, neurologic, psychiatric or metabolic disease, uncontrolled asthma/allergy requiring systemic steroids, known to be human immunodeficiency virus (HIV) positive.
2.	Laboratory values within 15 days pre-registration:
	a. Absolute neutrophil counts (ANC) $\leq 1.5\times10^9$/L.
	b. Part A: Platelet count $\leq 150\times10^9$/L; Part C: Platelet count $<150\times10^9$/L.
	For Part C, criteria 2a and 2b must be satisfied within 72 hours of the administration of rituximab
	c. Total bilirubin ≥30 mmol/L (Part A only).
	Total bilirubin > 1.5×ULN (except patients with documented Gilbert's syndrome [≥3.0 mg/dL]) (Part C only).
	d. Alkaline phosphatase (ALP) and alanine transaminase (ALT) ≥4×normal level (Part A only).
	Aspartate transaminase (AST), ALT or ALP >2.5×ULN (or >5.0×ULN with liver involvement by primary disease). (Part C only).
	e. Creatinine ≥115 µmol/L (men), 97 µmol/L (women) (Part A only).
	Serum creatinine ≥1.5×ULN (Part C only).
	f. Haemoglobin <9.0 g/dL (Part C only).
3.	Known central nervous system (CNS) involvement of lymphoma.
4.	Previous total body irradiation.
5.	Positive test for human anti-murine antibody (HAMA) at screening.
6.	Chemotherapy or immunotherapy received within the last 4 weeks prior to start of study treatment. Pre-treatment with rituximab is allowed.
7.	Pregnant or lactating women.
8.	Previous hematopoietic stem cell transplantation (autologous and allogenic).
9.	Part A: Previous treatment with radioimmunotherapy. Part C: Not applicable.
10.	Actively participating in another study or received an IMP within 4 weeks prior to enrolment.
11.	Receipt of live-attenuated vaccine within 30 days prior to enrolment.
12.	Part A and Part C: Test positive for hepatitis B (HBsAg and anti-HBc). Part C only: Test positive for hepatitis C and human immunodeficiency virus (HIV).
13.	A known hypersensitivity to rituximab, lilotomab, Betalutin or murine proteins or any excipient used in rituximab, lilotomab, or Betalutin.

Inclusion Criteria: Part B (FL phase IIb)

1. Histologically confirmed (by WHO classification) relapsed non-Hodgkin B-cell FL (grade I-IIIA).
2. Male or female aged ≥18 years.
3. Received at least 2 prior systemic anti-neoplastic or immunotherapy-based regimens (maintenance therapy following a CR/PR is not considered to be a separate line of therapy). Systemic regimens including agents such as idelalisib or other PI3K inhibitors qualify as a prior line of therapy.
4. Prior therapy must have included a rituximab/anti-CD20 agent and an alkylating agent – which may be been administered in separate regimens.
5. Patients must be refractory to any at least one previous regimen that contained rituximab or an anti-CD20 agent, with refractoriness defined as:
   i. no response (no CR or PR) during therapy, or
   ii. a response (CR/PR) lasting less than 6 months after the completion of a regimen including rituximab/anti-CD20 therapy (including occurrence of progressive disease (PD) during rituximab/anti-CD20 maintenance therapy, or within 6 months of completion of maintenance therapy).
6. WHO performance status of 0-2.
7. Life expectancy of ≥3 months.
8. Bone marrow tumour infiltration <25% (in biopsy taken from a site not previously irradiated).
9. Measurable disease by CT or MRI: longest diameter (LDi) >1.5 cm for nodal lesion, LDi >1.0 cm for extra nodal lesion on an assessment performed during the screening period.

Criteria 10 and 11 must be satisfied within 72 hours of the administration of rituximab:

10. ANC ≥1.5×10^9/L.
11. Platelet count ≥100×10^9/L.

Criteria 12 to 15 must be verified at time of eligibility review within 2 weeks prior to rituximab administration:

12. Haemoglobin ≥9.0 g/dL.
13. Total bilirubin ≤1.5×upper limit of normal (ULN) (except patients with documented Gilbert's syndrome [<3.0 mg/dL]).
14. Liver enzymes: AST; ALT or ALP ≤2.5×ULN (or ≤5.0×ULN with liver involvement by primary disease).
15. Adequate renal function as demonstrated by a serum creatinine <1.5×ULN.
16. Women of childbearing potential must:
    a) understand that the study medication is expected to have teratogenic risk.
    b) have a negative serum beta human-chorionic gonadotropin (ß-HCG) pregnancy test at screening.
    c) commit to continued abstinence from heterosexual intercourse (excluding periodic abstinence or the withdrawal method) or begin a highly effective method of birth control with a Pearl-Index <1%, without interruption, from 4 weeks before starting study medication, throughout study medication therapy and for 12 months after end of study medication therapy, even if she has amenorrhoea. Apart from abstinence, highly effective methods of birth control are:
       i. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
       ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
       iii. Intrauterine device (IUD).
       iv. Intrauterine hormone-releasing system (IUS).
       v. Bilateral tubal occlusion.
       vi. Vasectomised partner.
17. Male patients must agree to use condoms during intercourse throughout study treatment administration and for 12 months following administration of Betalutin.
18. The patient is willing and able to comply with the protocol, and agrees to return to the hospital for follow-up visits and examination.
19. The patient has been fully informed about the study and has signed the informed consent form.

20. Negative HAMA test at screening.
21. Negative test at screening for Hepatitis B (negative HBsAg and anti-HBc), Hepatitis C and HIV.

Exclusion Criteria: Part B (FL phase IIb)

1. Prior hematopoietic allogenic stem cell transplantation.
2. Patients with a prior autologous SCT are excluded unless at least two years have elapsed since transplantation.
3. Evidence of histological transformation from FL to diffuse large B-cell lymphoma (DLBCL) at time of screening (transformation to grade IIIB that was successfully treated with recurrence of grade I-IIIA initial clone is accepted).
4. Previous total body irradiation.
5. Prior anti-lymphoma therapy (chemotherapy, immunotherapy or other systemic agent including any investigational agent) within 4 weeks prior to start of study treatment (corticosteroid treatment at doses of ≤ 20 mg/day, topical or inhaled corticosteroids, granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor [GM-CSF] are permitted up to 2 weeks prior to start of rituximab)..
6. Patients who are receiving any other investigational medicinal products.
7. Patients with known or suspected CNS involvement of lymphoma.
8. History of malignancy other than FL within 5 years prior to screening(i.e. patients with cancer diagnosed within 5 years prior to screening or who were diagnosed prior to 5 years and were not in CR or were on treatment within 5 years prior to screening), with the exception of malignancies with a negligible risk of metastasis or death (e.g. 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localised prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.

.9. Pregnant or breastfeeding women.

10. Exposure to another CD37 targeting drug.
11. A known hypersensitivity to rituximab, lilotomab, Betalutin or murine proteins or any excipient used in rituximab, lilotomab, or Betalutin.
12. Has received a live-attenuated vaccine within 30 days prior to enrolment.
13. Evidence of severe or uncontrolled systemic diseases:
    a. Uncontrolled infection including evidence of ongoing systemic bacterial, fungal, or viral infection (excluding viral upper respiratory tract infections) at the time of initiation of study treatment.
    b. Pulmonary conditions e.g. unstable or uncompensated respiratory disease.
    c. Hepatic, renal, neurological, or metabolic conditions - which in the opinion of the investigator would compromise the protocol objectives.
    d. Psychiatric conditions e.g. patients unlikely to comply with the protocol, e.g. mental condition rendering the patient unable to understand the nature, scope, and possible consequences of participating in the study.
    e. History of erythema multiforme, toxic epidermal necrolysis, or Stevens-Johnson syndrome.
    f. Cardiac conditions in the previous 24 weeks (before date of consent), including
        i. history of acute coronary syndromes (including unstable angina).
        ii. class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
        iii. known uncontrolled arrhythmias (except sinus arrhythmia).

Concomitant Medication:

Warfarin should be changed to low-molecular heparin. The dose of low-molecular heparin should be temporarily reduced if platelets are below 50×10^9/L, and be temporarily stopped if platelets are below 25×10^9/L.

Prophylaxis with allopurinol for tumour lysis will be permitted at the discretion of the investigator.

Study Evaluation:

The patients will attend study centre visits during the screening, treatment and follow-up period.

The treatment period is defined from the time of rituximab pre-treatment until 12 weeks after administration of Betalutin. Soft tissue imaging (chest/abdominal/pelvic computed tomography [CT] and/or positron-emission tomography [PET]/CT scan) and clinical evidence of disease progression will be measured. Pharmacokinetics, dosimetry and biodistribution will be assessed in selected patients in Part A Phase I. These assessments may also be performed for Part A phase IIa and Part B patients at selected sites that are experienced and equipped to perform these assessments; however, they are not mandatory for all patients. Pharmacokinetics is mandatory for all patients enrolled in Part C.

The follow-up period for Part A is defined from 12 weeks to a maximum of 5 years after administration of Betalutin, or until further anticancer therapy is given. During the follow-up period, serious adverse events (SAE) related to treatment, and AEs related to study medication, haematology, serum biochemistry, and long-term safety will be collected every 3 months after end of study treatment until 12 months after start of study treatment. Thereafter, at 6 month intervals until the patient has been through their 5-year visit or until need of other cancer-related treatment. At these visits, soft tissue imaging and clinical evidence of disease progression will be assessed.

Survival and long term safety data will be collected for all consenting patients up to a maximum of 5 years from the date that they were administered study drug.

Part B and Part C - up to 5 years after Betalutin administration.

Extensive follow-up (hospital visits) will take place for all patients every 3 months for the first year (Months 6, 9 and 12). Tumour imaging assessments are only required until the patient has further anticancer treatment after Betalutin administration or disease progression prior to further anticancer therapy as assessed by central imaging review. All other scheduled assessments should be performed.

After Month 12, follow-up will continue every 6 months up to 5 years after the Betalutin dose. Extensive follow-up (hospital visits) must be performed until the patient has further anticancer treatment after Betalutin administration or disease progression prior to further anticancer therapy as assessed by central imaging review. Thereafter, the patient will continue limited follow up every 6 months for potential long-term toxicity (new onset adverse events of special interest [AESIs], ADRs and study treatment-related SAEs), OS, further anticancer treatment and ADA testing (only if ADA test is positive at Month 12; testing to be continued until a negative result is obtained). Unless blood sampling is required for ADA testing, limited follow-up visits can be performed by telephone.

Endpoints - Part A (phase I and phase IIa)

Safety Endpoints:

- Incidence and severity of AEs and SAEs graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE Version 4.0 or later as applicable).
- 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 and Pharmacokinetic Endpoints:

Evaluation of biodistribution includes whole-body radioactivity assessment, the counts in region-of-interest (ROIs) from anterior and posterior whole-body images, and the assay of total radioactivity in blood. 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.

Efficacy Endpoints:

- Tumour response rate.
- Tumour response duration.
- PFS.

- OS.

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.
- QoL assessed using the FACT-Lym questionnaire (Version 4).

The QoL forms will be used in those countries where the forms are translated and validated.

Endpoints – Part B (FL phase IIb)

Primary Endpoint:

- Overall response rate (ORR) as assessed by an independent review committee based on Cheson criteria (Version 2014).

Secondary Endpoints:

Efficacy:

- ORR by investigator assessment.
- CRR by independent review and investigator assessment.
- DoR by independent review and investigator assessment.
- DoCR by independent review and investigator assessment.
- PFS by independent review and investigator assessment.
- OS.
- Change from baseline in the sum of the product of the greatest perpendicular diameters (SPD) of target lymph nodes as documented radiographically.

Safety:

- Incidence and severity of AEs.

Exploratory Endpoints:

- Changes in QoL as reported by patients using the FACT-Lym questionnaire (Version 4).
- Pharmacokinetic assessments e.g. total lilotomab antibodies measurements in serum (total lilotomab antibodies pharmacokinetics) and total radioactivity measurements in blood (Betalutin pharmacokinetics).

Endpoints - Part C (phase IIa Pharmacokinetic Cohort)

Pharmacokinetic Endpoints:

- Pharmacokinetic assessments e.g. total lilotomab antibodies measurements in serum (total lilotomab antibodies pharmacokinetics) and total radioactivity measurements in blood (Betalutin pharmacokinetics).

Safety Endpoints:

- Incidence and severity of AEs.

Efficacy Endpoints:

- Tumour response rate.
- Tumour response duration.
- OS.

Statistical Methods and Planned Analysis:

Part A (phase I and phase IIa)

Phase I: The results from this study will be presented using descriptive statistical methods.

Phase IIa: The response rate will be presented along with the 95% confidence interval. The response rate will be presented for all dose groups combined and separately for the extended dose level group.

An interim analysis was conducted when 15 patients have received MTD in the Arm 1 treatment regimen.

Part B (FL phase IIb)

Comparison of "40/15" and "100/20" regimens

The study is a randomised, 2-arm, open-label study to further differentiate the risk/benefit of 2 candidate dose regimens of lilotomab and Betalutin in patients with relapsed non-Hodgkin B-cell FL.

Once approximately 50 patients have been treated (approximately 25 per dose regimen), an interim analysis was performed to evaluate the possibility of study modifications or continuation of both regimens.

The intent-to-treat (ITT) population will consist of all patients who were randomised to one of the dose groups. The primary efficacy endpoint is ORR. Scans will be performed at baseline, 3, 6, 9, 12, 18 and 24, 36, 48 and 60 months after Betalutin injection for all patients to assess tumour response as follows:

- CR
- PR
- No change/stable disease (SD)
- PD
- NE

Response rates will be presented as percentage of patients in the ITT population with the exact 95% confidence interval (Clopper-Pearson).

Assessment of ORR in the "40/15" treatment regimen.

A total of 87 patients, including the ones in the interim analysis, will be recruited and treated with the "40/15" regimen.

The response rate under the null hypothesis is set at 30%, versus the response rate of 48% under the alternative hypothesis will be compared. A 2-sided exact test with a significance level of 0.05 will be used to compare the observed response rate against the hypothesis. In addition, a complete response rate of 8% under the null hypothesis versus a complete response rate of 20% under the alternative hypothesis will also be tested.

Descriptive and summary statistics will be calculated for each pharmacokinetic parameter. Further analyses may be conducted, as appropriate. Pharmacokinetic data and/or parameters from patients who received lilotomab 40 mg and Betalutin 15MBq/kg in Part B may be combined with data from Part C.

Safety Review Committee:

Part A:

The recommendation to increase or decrease the dose in Part A has been made by the SRC based on the safety data in the database at the time until the last patient in the current cohort has onset of blood counts recovery. The SRC consists of 3 to 4 relevant experts including the coordinating investigator for the study.

Part B:

The SRC will periodically monitor the safety data.

In line with its Charter, the Safety Review Committee reviewed the results of the interim analysis and provided a recommendation to the Sponsor to continue or terminate treatment arms or to perform other modifications. The recommendation was based on the totality of safety, efficacy, and other available data (e.g., immunogenicity data) based on the following guidelines:

- If ORR ≥ 40% in each treatment regimen, the study may complete its targeted enrolment of up to 130 patients (around 65 per arm).
- If ORR < 40% in either regimen then the regimen with ORR <40% may be terminated.
- If both regimens have ORR <40%, the study may be terminated for futility or modified. The regimen(s) with ORR ≥40% will proceed to enrol the remaining patients, up to 65 patients per regimen (including the patients in the interim analysis). The final decision lies with the Sponsor.

To facilitate decision to keep or drop treatment arms based on ORR rates, the boundary of 40% ORR was non-binding and for guidance only. Following the interim analysis, the SRC recommended to discontinue the "100/20" treatment regimen and continue with further recruitment in the "40/15" treatment regimen.

For patients included with prior autologous-SCT and/or with platelet counts $\geq 100 \times 10^9$/L but $<150 \times 10^9$/L, the SRC will evaluate the emerging safety data (in particular, DLTs) from the first 3 patients in each of the 3 subpopulations (see "Study Design" section)

- If no DLT is observed, the dose of Betalutin may be escalated as follows:
  - to 15MBq/kg in the subpopulation with prior autologous-SCT and platelet count ≥150×10^9/L.
  - to 15MBq/kg in the subpopulation without a prior autologous-SCT, and platelet count ≥100×10^9/L but <150×10^9/L.
- to 12.5MBq/kg in the subpopulation with a prior autologous-SCT and platelet count ≥100×10^9/L but <150×10^9/L. If 1 DLT is observed in a given subpopulation, a further 3 patients will be treated at the initial dose in this subpopulation and the SRC will review the overall safety of the cohort prior to establishing the dose to be recommended.
- If 2 DLTs are observed in any given subpopulation, the SRC may consider a dose reduction to "40/10" for the 2 subpopulations treated with "40/12.5" or may decide to close enrolment in the subpopulation. There will be no dose reduction of Betalutin below 10 MBq/kg.

The SRC will evaluate the safety data from each set of 3 patients (either 3 or 3+3) in each subpopulation and may request a subsequent review of safety data.

Part C:

The SRC will periodically monitor the safety data in line with Part B review of safety data.

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AE	Adverse events
AESI	Adverse events of Special Interest
ADA	Anti-drug antibody
ADL	Activities of daily living
ADR	Adverse drug reaction
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AUC	Area under the plasma drug concentration-time curve
β-HCG	beta human-chorionic gonadotropin
BSA	Body surface area
b.w.	Body weight
CCLS	Covance Central Laboratory Services
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CHOP	Cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone
C_{max}	Maximum plasma drug concentration;
CNS	Central nervous system
COVID-19	Coronavirus Disease 19
CR	Complete response
CRR	Complete response rate
CRu	Complete response unconfirmed
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	Decay correction factor
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoCR	Duration of complete response
DoR	Duration of response
DOTA	Abbreviation/company code for the chelator p-SCN-benzyl-DOTA IUPAC name: 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid, 2-[(4-isothiocyanatophenyl)methyl]
DTPA	Diethylenetriaminepentaacetic acid
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
E_{max}	Maximum energy
EU	European Union
FACT-Lym	Functional Assessment of Cancer Therapy–Lymphoma
FcγRIIa	Fc-gamma-Receptor IIa
FDA	Food and Drug Administration

FDG	(^{18}F) Fluorodeoxyglucose
FFPE	Formalin fixed paraffin embedded
FL	Follicular lymphoma
GCP	Good clinical Practice
GDPR	General Data Protection Regulation
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HAMA	Human anti-murine antibody
HBsAg	Hepatitis B surface antigen
Anti-HBc	Antibody to hepatitis B core antigen
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
I	Iodine
ICH	International Council for Harmonisation
IFMA	Immuno-Fluorometric Bridging Assay
IHC	Immunohistochemistry
IgG	Immunoglobulin G
IMP	Investigational medicinal product
In	Indium
iNHL	Indolent non-Hodgkin B-cell lymphoma
INR	International Normalised Ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
i.v.	Intravenous
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LDi	Longest diameter
Lu	Lutetium
Max	Maximum
MB-1	Murine monoclonal antibody
MBq	Mega becquerel
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MoAb	Monoclonal antibody
MRT	Mean residence time
MS	Mass spectrometry
MTD	Maximum tolerated dose
NHL	Non-Hodgkin Lymphomas
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PET	Positron-emission tomography
PFS	Progression-free survival
PI3K	Phosphatidylinositol-3-kinase

PK	Pharmacokinetic
PPD	Individual product of the perpendicular diameters
PR	Partial response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QoL	Quality of Life
RIA	Radio-immune assay
RIC	Radioimmunoconjugate
RIT	Radioimmunotherapy
RNA	Ribonucleic acid
ROIs	Regions-of-interest
RP2D	Recommended phase II dose
SAE	Serious adverse event
SCID	Severe combined immune deficient
SCT	Stem Cell Transplant
SD	Stable disease
SDV	Source data verification
SOP	Standard Operating Procedure
SPD	Sum of products of the 2 target tumour diameters
SPECT	Single Photon Emission Computed Tomography
SRC	Safety Review Committee
SUL	Lean body mass
SUV	Standardized uptake value
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
$T_{½}$	Half-life
T_{max}	Time to maximum plasma drug concentration
ULN	Upper limit of normal
US	United States
Y	Yttrium
WHO	World Health Organization
WHO PS	WHO Performance Status

4 INTRODUCTION

4.1 Background

Non-Hodgkin Lymphomas (NHL) as a group comprise the most common malignant haematological disease. NHLs are a diverse group of blood cancers that include any kind of lymphoma except Hodgkin lymphoma. NHLs are tumours developed from lymphocytes, a type of white blood cells. NHLs vary in their clinical behaviour, morphologic appearance, immunologic and molecular phenotype. The various types represent neoplastic lymphoid cells arrested at different stages of differentiation. Based on their natural history, NHLs can be clinically classified as indolent, aggressive, and highly aggressive. Diffuse large B-cell and follicular lymphoma (FL) are the most common subtypes.

NHLs are the fifth most common cause of cancer in the United States, with an estimated incidence of 70,130 cases in 2012. Follicular centre cell lymphomas are the second most common subtype, comprising approximately 40% of all NHLs. Since 1950, the incidence of NHL has steadily increased at approximately 4% per year (1).

Treatment usually depends on the type of lymphoma and its stage, as well as other prognostic factors. The different treatment options are radiation therapy, chemotherapy, immunotherapy, radioimmunotherapy (RIT) and bone marrow or peripheral stem cell transplantation. In B-cell and follicular lymphoma, rituximab (immunotherapy) combined with chemotherapy or a combination of drugs such as CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone) regimen is used. Treatment options for patients with relapsed indolent non-Hodgkin B-cell lymphoma (iNHL) are rituximab, chemotherapy combined with anti-cluster of differentiation (CD)20 agents or other chemotherapy combinations, or phosphatidylinositol-3-kinase (PI3K) inhibitors, although the proportion responding and duration of response (DoR) decreases with each relapse.

The aim of RIT is to use a monoclonal antibody (MoAb) to target an isotope for radiation to tumour tissue while limiting the toxicity to normal cells. Beta-emitting radioimmunoconjugates (RIC) possess high levels of clinical activity in patients with relapsed or refractory B-cell lymphomas (2), including those refractory to rituximab (3, 4) and chemotherapy (5). Clinical data have validated that RIT is both more cost effective and more efficacious than nonradioactive immunotherapy (6, 7). More recently, several single-arm studies have demonstrated that upfront RIT administered either alone or with chemotherapy to previously untreated iNHL patients produces overall response rates (ORRs) of 90-100%, complete response (CR) rates of 60-95% and durable remissions (8-11). A phase III study of RIT as part of frontline therapy for iNHL reported that consolidation therapy with yttrium-90 (^{90}Y)-ibritumomab tiuxetan (Zevalin®) after induction chemotherapy markedly prolonged progression-free survival (PFS) in patients with previously untreated stage II or IV FL (12). In another study, patients with indolent and aggressive NHLs received 4 cycles of chemotherapy followed by high myeloablative dose ^{90}Y-ibritumomab tiuxetan followed by autologous stem cell support (13). After a follow-up time of 30 months, the overall survival (OS) rate was 87% and the event free survival was 69%. Although myeloablative doses of ^{90}Y-ibritumomab tiuxetan were given, the RIT was well tolerated. The low dose-rate permits RIT to be effective for haematologic malignancies while causing minimal non-haematological toxicity.

When anti-CD20 RIT is given to patients, they are administered with large quantities of unlabelled cold anti-CD20 antibody immediately before radiolabelled anti-CD20 antibodies. Such a priming dose is necessary to optimise radiolabelled antibody concentrations in tumour

(14, 15), presumably by partially saturating easily accessible B-cells in the blood and the spleen and permitting sufficient radiolabelled antibody to bypass these sites and penetrate less accessible compartments such as lymph nodes and large tumour masses. However, too much cold anti-CD20 antibody over a long time can result in blocking of the CD20 antigen on tumour cells and thus reduce the effect of anti-CD20 RIT. Both clinical and non-clinical studies have shown that in some circumstances quite low rituximab concentrations in the blood can reduce tumour cell targeting and thus impair the clinical efficacy of CD20-directed RIT (16). A solution to this problem might be to omit cold rituximab from the last cycles of therapy before RIT. Alternatively; one could choose to target another B-cell surface antigen such as CD37.

RIT with CD37 as the target antigen has been explored previously using a Iodine-131 (^{131}I)-labelled murine monoclonal antibody (MB-1) both in a mouse model and in patients with low, intermediate and high-risk NHLs (17-22). CD37 antibodies were compared with CD20 antibodies and a higher grade of internalisation and degradation of ^{131}I-labeled RIC was found for CD37 than for CD20 (22). Furthermore, a favourable biodistribution was obtained in 59% of the patients for CD20 and for 50% of the patients for CD37. The amount of cold priming with antibody necessary to get a favourable biodistribution was higher for CD37 than for CD20. All six patients treated with ^{131}I-MB-1 (against CD37 antibody) had a complete response and three of the patients received bone marrow transplantation. Of twelve patients that were treated with ^{131}I labelled antibody against CD20, ten had a complete response and eleven needed bone marrow transplantation (22). Despite the clinical responses observed in this study, the data for CD20 was evaluated to be marginally better than for CD37. CD20 was therefore chosen as the target antigen for further development of a commercially available RIC. This development resulted in Food and Drug Administration (FDA) approval of Bexxar® and Zevalin in 2003. No subsequent efforts have been made to target CD37 with RICs, although anti-CD37 agents (otlertuzumab and BI836 826 for chronic lymphocytic leukemia and anti-CD37 antibody-drug conjugates IMGN529 and AGS67E for lymphoid malignancies) are currently in early clinical development (23). Previous studies thus show that CD37 is a potent target for both immunotherapy and RIT.

The chloramine T method of ^{131}I-labeling was used in the early studies of anti-CD37 RIT described above (22). ^{131}I labelled to antibodies with the iodogen or the chloramine T method are not being contained in the cells if the antigen-antibody complex is internalised (24, 25). Inside the cells the nuclide is removed from the antibody by intracellular enzymes and diffuses out and away from the tumour cells (26). The same so-called dehalogenation has been shown with CD22 antibodies, which are also internalised (27). Metallic radionuclides labelled to antibodies with so-called chelators are however more stable and remain contained inside the cells to a much higher degree (28). By using metallic radionuclides internalising antigens can be used for tumour targeting and tumour uptake may also be higher than for non-internalising antibodies as well.

4.2 Lutetium (^{177}Lu)-lilotomab Satetraxetan (Betalutin) and Lilotomab

At the Norwegian Radium Hospital, an anti-CD37 antibody (lilotomab) was developed in the 1980s (29). Lilotomab and the anti-CD20 antibody rituximab have been labelled with both ^{125}I and indium-111 (^{111}In) and measured cell bound activity after 4 days of incubation with a lymphoma cell line. The results show that the problem of catabolism of RIC can be circumvented by labelling with metallic nuclides such as ^{111}In or lutetium-177 (^{177}Lu) which confirms the result of Press et al. mentioned in Section 4.1 (23, 24).

The most common radiopharmaceuticals used in therapy today utilise substances that disintegrate resulting in the emission of a beta-particle. Beta-particles are electrons emitted from the nucleus of an atom. Beta emitters approved for therapy include ^{131}I (half-life ($T_{½}$) = 8 days), ^{90}Y ($T_{½}$ = 2.7 days), and ^{177}Lu ($T_{½}$ = 6.7 days). ^{177}Lu has been selected for use in Betalutin since it has proven to be suitable for labelling of the antibody and has an appropriate energy of the emitted β-particle (maximum energy (E_{max}) = 0.497 MeV, $T_{½}$ = 6.7 days). Furthermore, it has a low abundance of photons with almost ideal energy for imaging (E = 113 keV, abundance = 6.5%; E = 208 keV, abundance = 11%).

Betalutin (lilotomab labelled with ^{177}Lu via the chelator p-SCN-benzyl-DOTA), is the product to be tested in this clinical study. Betalutin has been developed by Nordic Nanovector in collaboration with the Norwegian Radium Hospital for the treatment of relapsed NHL.

RIT permits delivery of a therapeutic dose of radiation directly to the deoxyribonucleic acid (DNA) of tumour cells. The radionuclide ^{177}Lu is a beta-particle emitter. The beta particles are electrons with energy and range in tissue suitable for treating NHLs. The absorbed radiation results in DNA damage and tumour cell death. The radiation emitted from the radiolabelled antibody affects not only the antibody-binding cell, but also neighbouring cells. This mechanism of action of RIT may be especially beneficial in treating patients with bulky or poorly vascularised tumours.

Betalutin has been tested for targeting, therapeutic and toxic effect in cells and in mice. Lilotomab has similar or better binding properties to CD37 as rituximab has to CD20. Therapy against single cells showed a significantly better effect of Betalutin than of ^{177}Lu-rituximab. The maximum tolerated dose (MTD) of Betalutin in severe combined immune deficient (SCID) mice with tumour cells in the bone marrow was between 50 and 100 MBq/kg, and 530 MBq/kg in nude mice (55). Biodistribution studies with Betalutin have shown high uptake in tumour and uptake in normal organs similar to the uptake of ^{177}Lu-rituximab. The preclinical data to date indicate that Betalutin has a suitable biodistribution profile with high uptake in tumour cells, and that the efficacy results in the mouse models show promise of potentially interesting clinical results.

Relevant animal species that shares a cross-reactive or identical target antigen as humans have not been found. The antibody lilotomab did not elicit a response by human immune effectors *in vitro*. No significant antibody-dependent effect of lilotomab was observed by complement activation or immune cell cytotoxicity. The human tissues cross-reactivity studies showed that the morphology and distribution of cells stained with lilotomab were consistent with that of B-cells.

The antibody part of Betalutin, lilotomab is administered as pre-treatment within 4 hours before Betalutin administration in Arm 1, Arm 4 and Arm 5. The few CD37 antigen positive cells that are left after rituximab treatment can then be blocked by infusion of lilotomab, within 4 hours before Betalutin. It is assumed that lilotomab will bind to the most easily accessible CD37 positive cells in the lymphoid organs. The binding capacity in tumour seems more difficult to saturate (21), pre-treatment with lilotomab should increase the possibility that Betalutin binds to the tumour cells. Clinical data with the radiolabelled murine anti-CD37 MB-1 antibody indicates that 10 mg/kg can be given without saturating tumour uptake in patients with non-lysed B-cells (21). Xenograft studies in nude mice indicate that 1 mg/kg lilotomab does not saturate tumour uptake of Betalutin.

4.2.1 Part A - Phase I

In Part A of the study, the safety and preliminary efficacy of Betalutin in combination with

administration of different pre-treatment/pre-dosing regimens of rituximab and lilotomab were investigated using a traditional 3+3 study design. Patients were enrolled into one of 4 arms to identify the MTD/recommended phase II dose (RP2D) of Betalutin. An additional arm (Arm 5) was added to further characterise the pharmacokinetic profile of Betalutin.

4.2.2 Part A – Phase IIa

Phase II of Part A expanded the number of patients added to Arms 1 and 4 to confirm safety and further evaluate the efficacy of the RP2Ds 40 mg lilotomab/15 MBq/kg Betalutin and 100 mg/m^2 lilotomab/20 MBq/kg Betalutin respectively in additional patients (see Section 6.1 for patient disposition).

4.2.3 Part B – FL Phase IIb

Following a review of the clinical safety, efficacy, dosimetry, and pharmacokinetic data from the treatment regimens used in Part A, the 2 candidate RP2D dosing regimens from Arms 1 and 4 emerged as contenders for the selection of the RP2D for future clinical development. Therefore, a phase IIb randomised sub-study (hereafter referred to as **Part B**, or **"PARADIGME"**) was added to further delineate the risk: benefit profile of these candidate RP2D treatment regimens in a population of FL patients with ≥2 prior lines of therapy who are refractory to rituximab/anti-CD20 therapy.

Following an interim analysis of 47 patients with FL, randomised to either 40 mg lilotomab and 15MBq/kg Betalutin ("40/15"), or 100mg/m^2 lilotomab and 20MBq/kg Betalutin ("100/20"), the Safety Review Committee (SRC) recommended that the "40/15" dose be selected for subsequent patients entered to Part B (which was formalised in Version 14 of the protocol).

Version 14 of the protocol also allowed for a relaxation of 2 selection criteria i.e. minimum accepted level of platelets at study entry and restriction on prior autologous stem cell transplantation (SCT) (note: the Betalutin dose will be lower for patients entered with a prior autologous SCT and/or platelets <150×10^9/L - see Section 4.2.4).

4.2.4 Part B – Inclusion of Patients with a Prior Auto-SCT and Inclusion of Patients with Lower Platelet Threshold

Patients with a prior autologous-SCT, for whom at least two years have elapsed since transplantation before the date of consent can be entered to Part B.

Patients with a platelet count ≥100×10^9/L but <150×10^9/L can be entered to Part B.

Patients with both a prior autologous-SCT and/or a platelet count ≥100×10^9/L but <150×10^9/L can be entered to Part B. The Betalutin dose is to be adapted for these patients.

Patients will be divided into in 3 subpopulations and the first 3 patients in each will receive the following doses:

- Patients with a prior autologous-SCT and platelet count ≥150×10^9/L will be followed for at least 6 weeks. These patients will receive Betalutin at the reduced dose of 12.5 MBq/kg with lilotomab 40 mg.
- Patients with a prior autologous-SCT and platelet count ≥100×10^9/L but <150×10^9/L will be followed for at least 6 weeks. These patients will receive Betalutin at the reduced dose of 10 MBq/kg with lilotomab 40 mg.

- Patients without a prior autologous-SCT and platelet count ≥100×10^9/L but <150×10^9/L) will be followed for at least 6 weeks. These patients will receive Betalutin at the reduced dose of 12.5 MBq/kg with lilotomab 40 mg.

Emerging safety data (in particular, dose limiting toxicities [DLT]) from the first 3 patients in each subpopulation will be reviewed by the SRC.

The SRC may request a subsequent review of safety data (see Section 16.4). The SRC can recommend the current reduced dosing level be maintained, a dose escalation (including escalation to Betalutin 15 MBq/kg with lilotomab 40 mg), an evaluation of an additional 3 patients, a dose-decrease, a different dose or to stop the recruitment of further patients with a prior autologous-SCT and/or lower platelet count.

4.2.5 Part C - Inclusion of a Cohort Dedicated to Pharmacokinetic Assessments

Although pharmacokinetic assessment is an exploratory objective in Parts A and B, measurement of total lilotomab antibodies was not included in Part A. Part C has therefore been introduced to further measure total lilotomab antibodies and to assess the total radioactivity of Betalutin in the blood to inform future development activities. Part C will be performed at selected sites that are able to perform blood sampling under the restrictions necessary due to the Coronavirus Disease 19 (COVID-19) pandemic. Adult patients with relapsed indolent non-Hodgkin B-cell lymphoma (iNHL) (according to the broader Part A entry criteria) who are willing and able to provide pharmacokinetic samples will be enrolled to improve recruitment to this part of the study.

All patients treated in Part C will be treated with the selected RP2D ("40/15" dose regimen).

4.3 Rituximab or Anti-CD20 Antibody Therapy

Rituximab/anti-CD20 agent is used as a standard treatment for patients with B-cell NHL either as monotherapy or in combination with chemotherapy. The description of rituximab can be found in the prescribing information and package insert if not otherwise referred to.

Rituximab binds specifically to the trans membrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B-lymphocytes. The antigen is expressed on >95% of all B-cell NHL.

For patients with B-cell NHL, a dose of 375 mg/m^2 is administered once weekly. As monotherapy, weekly doses and 4 cycles are standard. In combination with chemotherapy 3 to 8 cycles with 2 to 4 weeks interval is most commonly used.

Figure 6-1 shows the study design and pre-treatment regimens of rituximab (375 mg/m^2), to clear circulating normal peripheral B-lymphocytes in the blood and spleen to optimise the biodistribution of Betalutin. Rituximab is shown in several studies to have substantial effect of depleting normal circulating B-cells. It is likely that the dead B-cells in the circulation are filtered through the spleen, bone marrow and liver. After rituximab treatment, many of these cells may be retained in the spleen over a certain period before they are eliminated, however literature is limited. The concentration of normal B-cells is higher in the spleen than in the blood, and the depletion of B-cells in the spleen is expected to take a longer time than for blood.

For a description of the scientific rationale for the use of rituximab on Day 0 see Section 4.8.4.2 and see rationale for dose selection, Section 4.8.3. For a summary of risks associated with rituximab, please see Section 4.4.

4.4 Potential Benefits and Risks

Intravenous administration of Betalutin is an experimental treatment for patients with NHL. The following benefit–risk assessment is anticipated.

Disease and patient population

Indolent B-cell (low-risk group) NHL is not curable with standard treatment approaches, perhaps with the exception of curative potential for stage I/II indolent lymphomas using radiotherapy. Conventional first line therapy is commonly associated with a high rate of clinical response, which is followed by disease relapse. Subsequent remissions may occur in association with standard care; however, such remissions tend to occur at progressively lower rates and with shorter remission durations across patients.

Patients included in **Parts A and C** of this study are adults with histologically confirmed relapsed iNHL of any of the following subtypes; a) follicular grade I-IIIA, b) marginal zone, c) small lymphocytic, d) lymphoplasmacytic, or e) mantle cell, considered to have experienced treatment failures from prior treatment regimens, including chemotherapy and immunotherapy treatment regimens.

Patients included in **Part B** of this study are adult patients with a diagnosis of histologically confirmed relapsed rituximab/anti-CD20 refractory B-cell FL (follicular grade I-IIIa) who have received at least 2 prior chemotherapy or immunotherapy-based regimens, including alkylating agents. Prior exposure to idelalisib or other PI3K inhibitors is also allowed.

Following a protocol amendment (Protocol Version 7), the inclusion criterion for testing for CD37 positive cells was removed in order to remove the delay in treating patients while the biopsy testing was completed. This amendment was supported by Dahle et al. showing that CD37 was expressed in 216 out of 217 tumour biopsies from patients with B-cell lymphoma (37) and suggestion that the one case with no CD37 expression (a patient with chronic lymphocyte leukaemia) may have been due to technical reasons associated with the assay. All pre-treatment biopsies that were available for testing in the Part A of the LYMRIT-37-01 study (65/74 patients) stained positive for CD37.

Non-clinical risk assessment of Betalutin

There are no directly-relevant animal models available to evaluate fully the non-clinical safety of Betalutin - as there are no animals with cross-reactivity to the lilotomab antibody. Safety has been evaluated by use of the most relevant studies to determine tolerability and target organ toxicity namely, combined toxicity and therapy studies in immune-compromised mice. There are no therapies in current use which target the lilotomab antibody so there are no additional data from which potential risks may be identified.

Betalutin is a β-emitting antibody-radionuclide-conjugate designed specifically for the treatment of NHL. The radionuclide ^{177}Lu was chosen since it allows effective irradiation of single cells as well as micro-metastases and larger tumours. The antibody lilotomab was chosen for its excellent properties in binding to the CD37 antigen. The radionuclide, antibody and chelator used for radiolabelling are prepared in compliance with Good Manufacturing Practice regulations.

From cell cytotoxicity assays *in vitro,* and antitumour studies *in vivo,* effective antitumour activity of Betalutin has been demonstrated at dose levels that were well tolerated in the sensitive SCID mouse model.

The pharmacological rationale of lutetium (^{177}Lu)-lilotomab satetraxetan is considered

sufficiently evaluated to provide evidence to support a favourable benefit: risk assessment for the investigational medicinal product (IMP). The expression of CD37 in human NHL has been demonstrated, thereby identifying this receptor as a target for treatment of NHL. The binding properties of lilotomab to lymphoma cells *in vitro* and *in vivo* have been evaluated and the cytotoxic activity of the IMP has been evaluated in animal models of NHL. The selection of the ^{177}Lu metallic radionuclide is considered optimal, as the half-life of the isotope is 6.7 days, consistent with the rate of localisation of Betalutin to the CD37 antigen. After binding of Betalutin to the CD37-antigen, the antibody-antigen complex may be internalised to some degree. The antibody lilotomab has not been shown to elicit a response by human immune effectors *in vitro* and no antibody-dependent effect of lilotomab has been observed by complement activation or immune cell cytotoxicity, indicating that the mechanism of cytotoxicity of the IMP Betalutin is due to the radiation effect mediated by delivery of ^{177}Lu to the site of action.

Even though there is a lack of pharmacologically-relevant animal models for the evaluation of Betalutin mechanism of action or safety studies there is a considerable clinical experience with CD37 targeted antibodies, ^{177}Lu radiolabelled agents and the DOTA chelator. Human experience is considered more relevant to the development of Betalutin and can provide significant insight into the anticipated clinical response. ^{177}Lu-labelled rituximab, prepared using the same DOTA procedure as for Betalutin, has recently been administered clinically (30, 31). The maximum tolerated dose was 50 mCi/m^2 (approximately 48 MBq/kg body weight) and efficacy results in NHL patients were promising. This report confirms that the radiolabelling procedure for Betalutin is compatible with human administration and provides supportive evidence of the safety of both satetraxetan and ^{177}Lu.

It is anticipated that benefits of administration of the IMP will include a targeted antitumour response, evidenced by improvements in progression-free survival and OS. Furthermore, the targeted binding of lilotomab to CD37 expressed on lymphoma cells is anticipated to increase delivery of ^{177}Lu to the desired site of action, thus minimising general systemic toxicity typically associated with external radiation therapy.

Risk with rituximab pre-treatment

The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera® are infusion-related reactions which occur in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after 8 doses of MabThera. Infectious events (predominantly bacterial and viral) occurred in approximately 30-55% of patients during clinical studies in patients with NHL. ADRs reported as very common (≥1/10) are infections (bacterial and viral), reduction in haematological parameters, infusion-related reactions such as angioedema, nausea, pruritus, rash, alopecia, fever, chills, asthenia, headache, and decreased immunoglobulin G (IgG) levels. Please refer to the prescribing information for further details.

Risk with lilotomab pre-dosing

In order to improve the biodistribution of Betalutin the patients will receive an infusion of 40 mg, 60 mg/m^2 or 100 mg/m^2 (up to a maximum of 270 mg) of lilotomab within 4 hours before administration of Betalutin. The infusion rate will be 100 mL/hour. The same procedure as used with rituximab will be used for lilotomab. If the patient experiences adverse events (AEs) such as a drop in blood pressure, chills, fever, or dyspnoea the infusion will be stopped. When the symptoms disappear, the infusion will start again with 50% reduced infusion rate.

The patients will benefit from an improved biodistribution of Betalutin, which will decrease the

uptake in spleen and bone marrow. This could lead to improved circulation $T_{½}$ of the product, which could facilitate better tumour uptake of the radioimmunoconjugate as suggested from development studies with CD37 targeting with ^{131}I-MB-1 (21).

Risk with omitting lilotomab as pre-dosing

In Part A, phase I Arm 1, the first patient enrolled received 10 MBq/kg Betalutin without lilotomab pre-dosing. The patient did not experience a DLT and stayed in remission for approximately 4 years.

In Arm 2, patients did not receive lilotomab pre-dosing. Two patients enrolled into Arm 2 who received 15 MBq/kg of Betalutin experienced haematological DLTs (grade 4 thrombocytopenia/neutropenia enrolment), and 1 patient received a de-escalated dose of Betalutin 10 MBq/kg. The arm was discontinued as omitting pre-treatment with lilotomab had a negative impact on the safety of Betalutin.

In Arm 3, patients received a pre-dose with rituximab instead of lilotomab on Day 0 (see Section 4.8.4.2 for the rationale). Three (3) patients were dosed with Betalutin 15 MBq/kg. Arm 3 was subsequently discontinued as rituximab pre-dosing appeared to have an inferior safety profile compared to both 40 mg and 100 mg/m^2 lilotomab.

4.5 Immunogenicity Risk Assessment of Lilotomab and Betalutin

Pre-existing and/or development of a human anti-murine antibody (HAMA) response has been described to influence the effectiveness of immunotherapy using murine or chimeric monoclonal antibodies (44). In addition, allergic reactions could occur, stressing the importance of assessing pre-existing HAMA as one of the patient inclusion criteria in clinical studies for murine therapeutic monoclonal antibodies (43). In Part A phase I and phase IIa and Part B (FL phase IIb) and Part C (Pharmacokinetic Cohort phase IIa), patients will therefore be tested for pre-existing HAMA, with a positive HAMA test being considered as an exclusion criterion (see Section 7.1.1 and Section 7.2.1 respectively). In addition, all patients will be monitored for the development of an anti-drug antibody (ADA) response after injection of lilotomab and Betalutin.

In Part A, monitoring of the immune response post-treatment was performed at Day 7 (phase I only), month 1, 3, 6 and 12 after Betalutin administration, using either the Milenia® Quickline HAMA test on-site and/or at a central laboratory using an immuno-fluorometric bridging assay (IFMA) for human antibodies specific to lilotomab (ADA test). The development of an immune response after administration of lilotomab and ^{177}Lu-lilotomab satetraxetan was reported for 7 out of 74 subjects overall. Five of the observed responses were detected one month after treatment, three had resolved at the 3-month visit and one at the 6-month visit (data not available for one patient). Two additional immune responses were detected at 12-month follow-up visits. No reported side-effects could be associated with the development of an immune response. Details can be found in Table 4-1.

Table 4-1 LYMRIT-37-01 Part A. Immunogenicity assessment

Patient	Treatment	Immunogenicity assessment

Number	Arm	Day 7	Month 1	Month 3	Month 6	Month 12
001-006[1]	1	-ve	+ve	+ve	-ve	NA
001-007[1]	1	-ve	+ve	-ve	-ve	+ve
001-017[1]	3	-ve	+ve	+ve	NA	NA
001-020[1]	4	-ve	+ve	-ve	-ve	NA
001-022[1]	4	-ve	+ve	-ve	NA	NA
016-007[2]	1	NA	-ve	-ve	-ve	+ve
027-002[2]	1	NA	-ve	-ve	-ve	+ve

+ve: positive; -ve: negative; NA = not assessed
1 IFMA test
2 Milenia Quickline® HAMA test

In Part B and Part C, screening for pre-existing HAMA will be performed using a commercially available test prior to inclusion (such as the Milenia® Quickline HAMA kit or a HAMA-ELISA test commercially available).

An exploratory HAMA test to assess HAMA specificity vs. lilotomab (IFMA test) will also be performed at baseline for research purposes. The IFMA test result may be used to verify a negative HAMA test at baseline in cases, where HAMA testing using a commercially available test is not feasible.

A tiered approach using a bridging enzyme-linked immunosorbent assay (ELISA) format will be used to monitor the development of an ADA response (https://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf). Conjugation of satetraxetan to lilotomab before further chelation with ^{177}Lu to obtain Betalutin occurs randomly via one of the 92 lysine present in lilotomab sequence (45) As all promiscuous neo-epitopes identified for lilotomab are predicted to contain one or more lysine, one could speculate, taking into account the described *in vitro* stability of the conjugation between lilotomab and satetraxetan, that one or more of these neo-epitopes could be masked for Betalutin. To ensure the maximum sensitivity e.g. detection of all potential ADA, lilotomab and not Betalutin will be used in the *in vitro* bridging assay. This strategy will be implemented in Part B.

4.6 Alternative Treatments versus Betalutin Treatment

Alternative treatments for the patient population to be included in this study are rather limited and would be restricted to continuation of chemotherapy either alone, or in combination with rituximab/an anti-CD20 agent administration, or PI3K inhibitors. The major disadvantages with chemotherapeutic approaches to treatment are the AEs and discomfort experienced by patients, including but not limited to: a) haematological toxicities, b) nausea, c) malaise, d) infections, and e) alopecia. It is considered highly likely that, in most cases, patients will remain on medical leave during the treatment period which may extend from 6 to 8 weeks.

An additional alternative treatment to Betalutin therapy may be the use of the radioimmunoconjugate Zevalin. This therapeutic agent has demonstrated acceptable efficacy with respect to NHL treatment, with the advantage of fewer AEs presenting relative to conventional chemotherapy. Importantly, Zevalin targets the same antigen CD20 as the antibody rituximab, as compared to Betalutin, which target the antigen CD37 on B-cells; consequently, Betalutin provides potential advantages from a dual-targeting approach, which would not be afforded by Zevalin.

Betalutin administration is expected to result in less patient discomfort as compared to standard treatments involving chemotherapy and rituximab. Betalutin therapy will be administered as a single treatment event – fundamentally as an outpatient procedure; the patients will not require hospitalisation following treatment (unless local laws stipulate otherwise). Following administration of Betalutin, it is anticipated that significant impacts on patient lifestyle will not be experienced; for example, patients may continue working if the disease in itself does not preclude them from doing so. The overall patient's quality of life (QoL) following administration of rituximab, lilotomab and Betalutin treatment is realistically and reasonably anticipated to be improved in comparison to treatment regimens involving chemotherapy in conjunction with rituximab.

In this clinical phase I/II study there will be a higher clinical burden for the patients enrolled on study with respect to frequency of hospital visits, blood sampling and imaging procedures than would otherwise be experienced by patients not participating in the clinical trial. Though the follow-on burden to treatment may be greater for study participants, patients who are enrolled on study will receive more thorough monitoring.

4.7 Clinical Risk-benefit Summary

The main objective in the first part of this study (Part A) was to define an appropriate dosing regimen for further phase II evaluation. Two candidates have emerged for comparison based on available efficacy, safety and dosimetry data. The RP2D of Betalutin for Arm 1 (lilotomab 40 mg pre-dose) was 15 MBq/kg; 30 patients were enrolled in the phase IIa arm, and follow-up is ongoing. For Arm 4 (lilotomab 100 mg/m^2 pre-dose), the RP2D of Betalutin was 20 MBq/kg. A phase IIa expansion cohort has completed enrolment.

To summarise the safety profile, neutropenia and thrombocytopenia were the most commonly reported grade 3/4 AEs, and were generally transient in nature with recovery to grade 1 by 3 months in the majority of patients. The mean platelet and neutrophil nadirs occurred at Day 40 (range Day 34 to Day 43) for platelets and Day 49 (range Day 43 to Day 56) for neutrophils after Betalutin administration. There were no reports of febrile neutropenia. The preliminary safety profile of both Arms 1 and 4 is promising, with the higher lilotomab pre-dose having a favourable impact on the degree of neutropenia and thrombocytopenia. The number of patients receiving platelet transfusions in Arms 1 and 4 was balanced. Two Arm 1 patients required prophylactic platelet transfusions for grade 4 thrombocytopenia, and 1 Arm 4 patient received a platelet transfusion for haematuria/grade 3 thrombocytopenia. Lilotomab pre-dosing mitigates hematologic toxicity; 2/3 patients in Arm 2 without lilotomab pre-dosing had haematologic DLTs. Preliminary efficacy data show ORRs of 64% for all enrolled patients (CR 28%) (53).

Taken together, the risk: benefit profile of Betalutin is favourable.

Potential risk factors of Betalutin and proposed risk minimisation activities are presented in Table 4-2. The dose-escalation design and definition of DLTs are described in Section 6.2.

Table 4-2 Potential Risks Factors of Betalutin Treatment and Proposed Risk Minimisation Activities

Anticipated Risk Factors	Proposed risk minimisation treatment activities	Pharmacovigilance
Myelosuppression, transient reduction of haematological parameters.	• A pre-defined minimum value for platelet counts and neutrophil counts are to be verified prior to inclusion. • Only patients with <25% tumour cells in bone marrow biopsy (biopsy taken	• The inclusion and exclusion criteria in this clinical study protocol must be followed.

Anticipated Risk Factors	Proposed risk minimisation treatment activities	Pharmacovigilance
	from a site not previously irradiated) will be included. • Patients with previous total body irradiation will be excluded. • Patients with a previous haematopoietic allogenic stem cell transplantation will be excluded. • Patients with a previous haematopoietic autologous-SCT will be excluded if <2 years prior to inclusion but eligible if ≥2 years prior to enrolment) . These patients will receive Betalutin 12.5MBq/kg until the SRC confirms the dose for this subpopulation. • Patients with platelet count ≥100×10^9/L but <150×10^9/L are at risk of Grade 3 or 4 thrombocytopenia. These patients will also receive Betalutin 12.5MBq/kg until the SRC confirms the dose for this subpopulation. • Patients with both a prior autologous-SCT and platelet count ≥100×10^9/L but <150×10^9/L will receive Betalutin 10MBq/kg until the SRC confirms the dose for this subpopulation.	• Haematological parameters will be closely followed as a safety measure. • The SRC will review the safety data from the first 3 patients enrolled with a history of autologous-SCT or with platelets ≥100×10^9/L but <150×10^9/L who have been treated with Betalutin and after they have been followed for at least 6 weeks. • The SRC will review the safety data from the first 3 patients with platelets that are below 150 x10^9/L who have been treated with Betalutin and who have been followed for at least 6 weeks.
Carcinogenicity, Betalutin is a radioactive drug and may in longer term induce secondary malignancies, including myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) and other primary cancers.	Avoid giving treatment to children/juvenile to reduce life time risk.	The patients will be followed up to 5 years.
Treatment with Betalutin also leads to temporary depletion of normal $CD37^+$ B-cells.		White blood cells will be followed closely.
Betalutin administration includes pre-treatment with rituximab.	The study personnel should be familiar with rituximab administration, and the prescribing information of rituximab.	
Betalutin administration includes pre-treatment with lilotomab.	The study personnel should be familiar with rituximab administration, as the same procedure will be used for lilotomab administration.	
Betalutin should not be given to pregnant or lactating women.	Pregnant or lactating women are excluded from the study.	The exclusion criterion should be followed.
The adverse event profile is not established for Betalutin.	Emergency treatments and specialist medical staff will be available during injection.	The patient will be closely followed by the study personnel. All reported events will be recorded up to 12 weeks after injection; thereafter all adverse reactions will be reported, including potential late toxicity.

Anticipated Risk Factors	Proposed risk minimisation treatment activities	Pharmacovigilance
Lilotomab is a murine antibody.	The patients are screened for antibodies against lilotomab before inclusion in the study.	
Lilotomab is a murine antibody. *In silico* MHC class II-peptide binding prediction analysis identified promiscuous overlapping T-cell neo-epitopes in the sequence of lilotomab e.g. a risk to develop an ADA response in patients after lilotomab and/or Betalutin dosing	The patients are screened for pre-existing HAMA against lilotomab before inclusion in the study with exclusion of patients with a positive test.	Immunogenicity assessment will be performed from pre-dose up to 1 year after dosing. Additional measurements will be implemented to characterise any observed ADA response (tiered approach) and the HLA class II haplotype of the targeted patients.
Radiopharmaceutical agent	Written instructions concerning safety precautions will be given to the patients, (with recommendations for them, their relatives and other close contacts) before administration and to the hospital staff before handling.	

4.8 Rationale and Dose Selection

4.8.1 Estimation of Start Dose of Betalutin with Pre-dosing of Lilotomab

As described in Section 4.2, preclinical studies performed with SCID mice showed that the Betalutin MTD was between 50 and 100 MBq/kg body weight (b.w), and 530 MBq/kg in nude mice. SCID mice lack B-cells and T-cells and are often used as a model organism since they easily accept growth of human tumour xenografts and cells. However, because of the SCID mutation, SCID mice are not able to repair DNA damage. This type of mouse is therefore very sensitive to ionising radiation. As a result, the MTD in SCID mice may not be representative for the patients that are to be included in this study.

DOTA-conjugated rituximab has been labelled with ^{177}Lu using the same labelling procedure as for Betalutin, and tested in clinical studies (30, 31). MTD was 50 mCi/m^2 (approximately 48 MBq/kg b.w.). The starting dose of 20 mCi/m^2 (approximately 19 MBq/kg b.w.) was well tolerated and no grade 3/4 non-haematological toxicity or anaemia was observed.

Phase I data from treatment of NHL indicate similar dose tolerability for ^{131}I radiolabelled anti-CD20 and anti-CD37 antibodies, in studies where trace labelled pre-dosing were used to estimate acceptable whole-body radiation dose for each patient (21, 32). It is assumed that a similar relationship between ^{177}Lu radiolabelled versions of rituximab (chimeric anti-CD20 antibody) and lilotomab (murine anti-CD37 antibody) may exist. It was therefore expected that the MTD for lutetium (^{177}Lu)-lilotomab satetraxetan may approximate that of ^{177}Lu-DOTA-rituximab, i.e. 48 MBq/kg b.w. The amount of pre-dose with cold antibody was 250 mg/m^2 for ^{177}Lu-rituximab, so the MTD for Betalutin with 40 mg or 100 mg/m^2 predosing was expected to be lower.

The recommended doses, absorbed radiation dose per decay and half-lives for Bexxar and Zevalin are known, and it is possible to estimate a range for the MTD for Betalutin based on the MTDs for Bexxar and Zevalin. To make the estimate it is assumed that the pharmacokinetics in blood and bone marrow are similar for the three compounds, under these assumptions the MTD for Betalutin was predicted to be in the range of 52 to 72 MB/kg b.w. With the cold antibody pre-dosing of 250 mg/m^2 for Zevalin and 450 mg for Bexxar compared to lilotomab 40 mg and 100 mg/m^2 (i.e. 10 and 2.5 fold lower), it was expected that the Betalutin MTD would be lower.

In summary, a starting dose of 10 MBq/kg for Betalutin was predicted to be well tolerated, based on the above mentioned clinical studies with ^{177}Lu-DOTA-rituximab, Zevalin and Bexxar.

4.8.2 Justification of Cold Antibody (Lilotomab) Dose in Betalutin

The goal of this study is the investigation of radiation-induced toxicity and associated anti-tumour activity of Betalutin via stepwise escalation of the amount of radioactivity, with and without pre-dosing with the cold antibody lilotomab.

In the phase I arms, the administered amount of radioactivity was increased with increasing doses of Betalutin. This was obtained by radiolabelling each vial of antibody conjugate (lilotomab satetraxetan) with increasing amounts of ^{177}Lu-, while the amount of lilotomab satetraxetan remained at a fixed level of 7.8 mg per vial. For Betalutin doses above the maximum allowable radioactive concentration, 2 vials of Betalutin would be administered. The amount of lilotomab satetraxetan that would be administered (on a per patient basis) varied over a range 5.5-7.8 mg [single vial of Betalutin] and 11.0-15.6 mg [2 vials of Betalutin], as the injected volume of Betalutin is dependent on the time from manufacturing to the actual injection due to the decay of ^{177}Lu.

Preclinical data supportive of the proposed dosing levels were generated using Betalutin with a specific activity level between 100 and 400 MBq/mg. From a practical standpoint, the upper limit of ^{177}Lu that can be conjugated to 7.8 mg of lilotomab satetraxetan is equivalent to a patient dose of 40 MBq/kg. This limit is based on the fact that there are approximately 2 satetraxetan molecules per antibody, which thereby limits the total amount of ^{177}Lu atoms that can be conjugated to a fixed number of lilotomab satetraxetan molecules. In addition, specific activity levels substantially greater than 400 MBq/mg would be anticipated to increase the radiolysis of the therapeutic product and could possibly reduce overall product integrity.

In addition, experimentation performed to assess tumour targeting, relative to the concentration of administered antibody, was performed using murine xenograft tumour models. Preclinical data from nude mice implanted with Daudi tumours has demonstrated that varying antibody doses over the range 0.01 to 1 mg/kg does not impact overall biodistribution of the administered radioimmunoconjugate. Consequently, and on the basis of these preclinical findings, a relevant antibody dose range of 0.01 to 1 mg/kg was recommended for consideration.

As administered levels of antibody are directly relevant to potential clinical therapeutic benefit, it is worth noting that CD37 antigen expression is of a similar pattern to that of CD20 antigen. It is therefore appropriate to compare the antibody dosage identified for Betalutin (7 - 20 mg/patient) with the antibody dose levels used for both Zevalin (3.2 mg/patient) and Bexxar (35 mg/patient) treatment. Both Zevalin and Bexxar have demonstrated significant and clinically meaningful results in association with treatment administered at the indicated antibody dose levels. Consequently, it is reasonable to anticipate that an antibody dose of 7-20 mg/patient, in the case of Betalutin administration, is reflective of a relevant clinical antibody dose.

4.8.3 Justification of Pre-treatment with Rituximab and Selection of Dose

All patients received pre-treatment with rituximab to clear circulating peripheral B-lymphocytes from the blood and spleen in order to optimise the biodistribution of Betalutin. It was envisaged that, as a consequence of peripheral B-lymphocyte clearance, the radiolabelled antibodies would bind to remaining CD37 antigens in tumour masses. Importantly, as rituximab targets CD20, this treatment was not considered likely to block the binding of Betalutin CD37 expressed on either B lymphocytes or tumour cells, which has subsequently been confirmed in preclinical

murine xenograft tumour models with implanted human tumour xenografts (54).

Rituximab is used as a standard treatment for patients with B-cell NHL either as monotherapy, or in combination with chemotherapy, at a dose of 375 mg/m^2 on a weekly basis. The conventional monotherapy approach utilises four cycles of weekly administration of rituximab. In contrast, combination therapy utilises weekly dosing for 3 to 8 cycles with administration of rituximab commonly occurring at 2 to 4-week intervals. In the setting of B-cell NHL, rituximab treatment has been shown to deplete tumour cells via antibody-dependent cell cytotoxicity (30% depletion) and by apoptotic mechanisms (30% relative cytotoxicity) within as little as 3 hours following treatment (33).

It was initially considered that injecting 375 mg/m^2 of rituximab on Days 28 and 21 prior to Betalutin was necessary to ensure clearance of B-cells from the lymphoid organs (Arms 1 and 2). This was subsequently modified to a single rituximab pre-treatment dose on Day 14 (Arms 3, 4, and 5), due to the reported rapid onset of action of rituximab for B-cell depletion (within 24 to 72 hours; continuing for at least 2-3 months) (39), and to shorten the time to Betalutin administration from enrolment for these patients with advanced disease. Dosimetry data from phase I patients subsequently indicated that pre-dosing with lilotomab was potentially even more important than rituximab for the biodistribution of Betalutin. For a summary of the rituximab pre-treatment regimens per arm, please refer to Table 6-1.

4.8.4 Justification of Pre-Dosing with Lilotomab and Selection of Dose for Part A

4.8.4.1 Rationale for Pre-dosing: Arm 1

In our development of radioimmunotherapy against CD37 antigen positive lymphoma, we did not have the option of using an epitope analogue antibody to lyse cells as a pre-treatment, because the antibody does not cause significant cell lysis. Rituximab causes cell lysis, and is thus another reason for using rituximab in the study. The cell lysis properties of lilotomab were evaluated using *in vitro* assays of complement dependent cytotoxicity and antibody-dependent cellular toxicity.

The few CD37 antigen positive cells that are left following B-cell depletion with rituximab pre-treatment can then be blocked by infusion of lilotomab within 4 hours before Betalutin. It was assumed that lilotomab would bind to the most easily accessible CD37 positive cells in the lymphoid organs and thus facilitating Betalutin binding to the tumour cells.

Our *in vitro* data indicated that an effective blocking of the CD37 antigen could be obtained with 1-5 µg/mL of lilotomab (equivalent to 1-5 mg/L blood) with as little as 1-hour pre-treatment. Unlabelled lilotomab was given within 4 hours before Betalutin to obtain sufficient blocking. A modest pre-dose of 40 mg* lilotomab was used in Arm 1 for the blocking, equivalent to 10 mg/L of blood, assuming a patient blood volume of 5 L. This concentration was anticipated to result in blocking of 95 - 97% of the CD37 positive cells based on the *in vitro* blocking data. In conclusion, a lilotomab pre-dose of 40 mg was thus selected for Arm 1.

* Termed as 50 mg previously due to use of incorrect extinction coefficient (see amendment 5, protocol Version 8).

4.8.4.2 Rationale for Pre-dosing: Arms 2 and 3

In Arm 2, no pre-dosing with lilotomab was used. It was demonstrated that pre-dosing with a cold antibody was necessary due to increased haematologic toxicity without it; Arm 2 was subsequently discontinued due to haematologic DLT. Dosimetry data from patients in Arm 2 compared with patients in Arms 1 and 4 (with lilotomab pre-dosing) showed increased red

marrow absorbed radiation doses in Arm 2, which correlated with the increased haematologic toxicity observed.

Arm 3 was added to examine the use of rituximab as a Day 0 pre-dosing regimen (within 4 hours prior to Betalutin administration) instead of lilotomab. The scientific rationale for the administration of rituximab as pre-dosing on Day 0 was unrelated to the clearing of peripheral B-lymphocytes from the blood and spleen. Betalutin contains a murine monoclonal antibody which has been shown from *in vitro* analysis to bind to the human Fc-gamma-Receptor IIa (FcγRIIa), which is expressed on most leukocytes including neutrophils, eosinophils, B-lymphocytes, platelets, mast cells, Langerhans cell and dendritic cells among other cell types. The binding of Betalutin to the FcγRIIa will alter its biodistribution, potentially resulting in a decrease in the circulating half-life of Betalutin. While rituximab binds to CD20 it also binds to the FcγRIIa and will therefore likely inhibit the binding of Betalutin to this receptor. If observed *in vivo* this inhibition of Betalutin binding would therefore improve the biodistribution of Betalutin without inhibiting its affinity for CD37 in the patient's tumour cells. This improved biodistribution may reduce the incidence of myelosuppressive AEs by decreasing the radioactivity in the bone marrow and spleen. In addition, preclinical data from immune deficient xenograft mice with implanted human lymphoma tumour cells show an increased duration of survival for animals administered a combination of rituximab and Betalutin, compared with animals administered either antibody alone.

As a result of the potential to both improve the efficacy of Betalutin and reduce the incidence of myelosuppression, Arm 3 was added to examine the effect of rituximab administered on Day 0 on the safety-efficacy profile of Betalutin. As compared with Arm 2, there was a small improvement in the platelet/neutrophil nadirs, while the absorbed radiation dose to the red marrow was the same. Arm3 was subsequently closed as the clinical profile was inferior to use of lilotomab pre-dosing.

4.8.4.3 Rationale for Pre-dosing: Arm 4

In Arm 4, the lilotomab pre-dosing was increased to 100 mg/m^2. Using the same radioisotope as Betalutin, Forrer et al 2010 conducted a phase I/II dose-escalation trial of ^{177}Lu-labelled rituximab in follicular and mantle cell lymphoma patients (38). Using a Day 0 dose of unlabelled rituximab of 250 mg/m^2 (~475 mg total dose) patients were able to receive up to 1850 MBq/m^2 of radioactivity isotope equivalent to approximately 45 MBq/kg. By linear extrapolation of the observed MTD of 15 MBq with 40 mg of lilotomab from Arm 1 compared to the results of Forrer et al, increasing the dose of unlabelled antibody to approximately 100 mg/m^2 was considered to allow an MTD of approximately 25 MBq/kg of Betalutin. In addition, increasing the dose of lilotomab may further improve the biodistribution of the labelled antibody allowing a greater concentration of radioactivity to be targeted to the tumour and away from the patient's bone marrow.

In addition, as an *in vitro* analysis of the binding of both lilotomab and Betalutin to the FcγRIIa (that 40 mg of lilotomab may not be sufficient to block binding to CD37 positive cells in the spleen, bone marrow and any remaining circulating lymphocytes, as well as block binding to the FcγRIIa, increasing the lilotomab pre-dose may improve the biodistribution of Betalutin allowing a greater concentration of radioactivity to be targeted to the tumour and away from the patient's bone marrow.

Furthermore, as previously described, the cold antibody pre-dosing used for Zevalin is 250 mg/m^2, more than 10-fold higher than the lilotomab pre-dose used in Arm 1 (40 mg). It was considered that this magnitude of increase for a lilotomab pre-dose (i.e. from 40 mg to

250 mg/m^2) was too large, while an increase to 100 mg/m^2 would be large enough to give a measurable effect. As blood volume depends on the size of the patient, and as Betalutin blood concentration is considered important for its uptake into tumours, pre-dosing was evaluated on a body surface area (BSA) adjusted dose rather than a fixed dose.

In conclusion, a lilotomab pre-dose of 100 mg/m^2 was thus explored in Arm 4 (up to a maximum of 2.7 m^2). The RP2D of Betalutin in Arm 4 was determined to be 20 MBq/kg. The rationale for dosing per m^2 is to explore both a fixed pre-dose (in Arm 1) and a BSA adjusted dose.

4.8.4.4 Rationale for Arm 5

The dose of 60 mg/m^2 of lilotomab for Arm 5 has been selected to be intermediate between the lilotomab dose in Arm 1 (40 mg) and Arm 4 (100 mg/m^2), and is also being tested in an ongoing study of Betalutin in diffuse large B-cell lymphoma (DLBCL) patients (LYMRIT 37-05). If the dose of lilotomab used in Arm 4 is excessive the cold antibody may inhibit the uptake of Betalutin, thus decreasing efficacy. Therefore, Arm 5 was modified to test a lower dose of lilotomab which may provide equivalent protection to the cells of the spleen and bone marrow without inhibiting radioactivity uptake in the tumour. Testing this dose will also provide an additional assessment point in the dose effect curve of lilotomab pre-dosing with patients having then been tested at 0 mg, 40 mg, 60 mg/m^2, and 100 mg/m^2 in 4 different treatment arms. Up to 6 patients will receive rituximab on Day-14 (375 mg/m^2) and lilotomab (60 mg/m^2) followed by Betalutin 20 MBq/kg on Day 0.

4.8.5 Rationale for the Selection of Patients with Follicular Lymphoma in Part B (FL phase IIb)

Data presented at the American society of hematology annual conference in 2018 showed that patients across all arms of the phase 1 study experienced encouraging efficacy alongside a carefully managed safety profile that was deemed to be favourable (60).

Table 4-3 Overall Response Rates from Part A (all Patients)

Subtype	Objective Response Rate N (%)	Complete Response N (%)	Partial Response N (%)	Stable Disease N (%)	Progressive Disease n (%)
All patients	61%	28%	32	19%	20%
FL (n=57)	37 (65%)	16 (28%)	21 (37%)	10 (18%)	10 (18%)
MZL (n=9)	7 (78%)	4 (44%)	3 (33%)	2 (22%)	-
MCL (n=7)	1 (14%)	1 (14%)	-	2 (28%)	4 (57%)
SLL (n=1)	-	-	-	-	1

MCL=Mantel Cell Lymphoma; SLL=Small Lymphocytic Lymphoma

Table 4-4 Treatment Emergent AEs (Grade ≥3) from Part A (all Patients)

Adverse Event	Grade 3 N (%)	Grade 4 N (%)
Neutropenia	26 (35%)	14 (19%)
Thrombocytopenia	21 (25%)	15 (20%)
Leukopenia	30 (40%)	4 (5%)
Lymphopenia	23 (31%)	2 (3%)
Infections:	1 (1%)	

Adverse Event	Grade 3 N (%)	Grade 4 N (%)
• Urinary Tract Infection • Pneumonia • Sepsis/neutropenic sepsis	1 (1%)	2 (3%)
Bleeding: • Epistaxis • Hematuria	 1 (1%) 1 (1%)	
Hyperglycaemia	2 (3%)	
Lymphoma progression	4 (5%)	1 (1%)

4.8.6 Rationale for Part C and Selection of Patients with Indolent NHL in Part C

Initial pharmacokinetics data were collected in Part A in a broad population of iNHL. Collection of further pharmacokinetics data was included in Part B to better characterise the pharmacokinetics of Betalutin and total lilotomab antibodies. Pharmacokinetic sampling in Part B is to be performed at selected centres and only for patients consenting for pharmacokinetic sample collection. Pharmacokinetic sample collection is not feasible at all sites participating in study 37-01 and ability to perform adequate sample collection is currently further limited due to restrictions related to COVID-19.

As of January 2021, no Part B patient has consented to pharmacokinetic sample collection, which may have been partly due to patients' reluctance to attend additional hospital visits during the COVID-19 pandemic.

Part C is added to specifically assess the pharmacokinetics of Betalutin and total lilotomab antibodies and is to be conducted at selected centres able and willing to perform adequate pharmacokinetic sample collection. In order to recruit enough patients in Part C, the population has been aligned with the population of Part A population, which is broader than Part B population and should allow for a sufficient amount of patients to be included at each participating site. Preliminary results from Part A have shown responses to study treatment in all populations of iNHL included in Part A (53), which allows their further inclusion in Part C.

4.8.7 Rationale for Dose Selection(s) in Parts B and C

4.8.7.1 Part B (FL phase II)

Following a review of the clinical safety, efficacy, dosimetry and Betalutin pharmacokinetics (total radioactivity in blood) from Arms 1 through 4 in Part A of this study, 2 dosing regimens emerged as candidates for the RP2D: from Arm 1, a pre-dose of 40 mg lilotomab followed by 15 MBq/kg Betalutin ("40/15"), and from Arm 4, a pre-dose of 100 mg/m^2 lilotomab followed by 20 MBq/kg Betalutin ("100/20").

Arm 2 exceeded the pre-defined acceptable DLT of 20%; and Arm 3 was closed after the enrolment of 3 patients due to an inferior clinical profile compared to Arm 1 and Arm 5 was closed after Betalutin pharmacokinetics was evaluated.

For Arm 1, 6 patients received 15 MBq/kg Betalutin in phase I; 1 patient developed grade 4 neutropenia and thrombocytopenia for 9 and 12 days respectively. A second patient developed grade 3 thrombocytopenia for 22 days. It was at this time that the SRC recommended: i) to revise the original DLT criteria so that "grade 3 haematologic toxicity that does not recover after 2 weeks" was removed, since grade 3 neutropenia and thrombocytopenia are common toxicities

with Betalutin (see Section 6.2.1 for the revised DLT definition), and ii) to continue 15 MBq/kg as the Betalutin dose for the Arm 1 phase IIa expansion cohort. Thirty (30) patients were subsequently enrolled into the phase IIa cohort, and follow-up is ongoing. In total, 36 patients have received this regimen (25 with FL); the ORR is 64% (CR 25%), and for the FL subset, the ORR is 72% (CR 28%). The most common toxicities are reversible neutropenia and thrombocytopenia (4 patients with grade 4 neutropenia >7 days, and 4 with grade 4 thrombocytopenia >7 days). There were no incidences of febrile neutropenia.

For Arm 4, (lilotomab pre-dose of 100 mg/m^2), 3 patients received Betalutin 15 MBq/kg. One patient had recovered their neutrophil count to grade 1 (1.5) by 8 weeks, but it was then 1.4 at 12 weeks, after the SRC had made the decision to allow dose escalation to 20 MBq/kg. This case was reviewed by the SRC and enrolment continued at 20 MBq/kg. Seven patients received 20 MBq/kg of Betalutin. One patient was under-dosed with lilotomab (approximately 60 mg/m^2) and an additional patient was enrolled. One patient receiving 20 MBq/kg had a DLT of haematuria (grade 3) with thrombocytopenia (platelet count of 40 x 10^9/L) and received a platelet transfusion. The higher lilotomab pre-dose in Arm 4 has a favourable effect on the degree of neutropenia and thrombocytopenia (Table 4-5).

The number of patients receiving platelet transfusions in Arms 1 and 4 was balanced; 2 patients in Arm 1 received prophylactic platelet transfusions for grade 4 thrombocytopenia, and 1 patient in Arm 4 received a platelet transfusion for haematuria/grade 3 thrombocytopenia. The SRC recommended to continue 20 MBq/kg as the Betalutin dose for the phase IIa expansion cohort, which is currently enrolling up to 15 patients. Of 8 patients enrolled, 7 were FL. The ORR is 50% for all 8 patients and 57% for the FL subset. Two FL patients have had a CR.

Table 4-5 Incidence of Grade 3/4 Neutropenia/Thrombocytopenia in Arms 1 and 4

	40 mg lilotomab pre-dose	**100 mg/m^2 lilotomab pre-dose**
	15 MBq/kg Betalutin (n=36)	**20 MBq/kg Betalutin (n=8)**
G3/4 neutropenia	20 (56%)	3 (38%)
G4 neutropenia	7 (19%)	---
G3/4 thrombocytopenia	20 (56%)	4 (50%)
G4 thrombocytopenia	6 (17%)	1 (13%)

Following commencement of Part B, an interim analysis of the emerging safety and efficacy data from the first 47 patients was assessed by the SRC who recommended that all patients enrolled after the interim analysis receive the “40/15” dosing regimen. The Sponsor followed the SRC recommendation and the study protocol was amended (Version 14) to continue with this single dose regimen only.

Protocol Version 14 also introduced changes in eligibility criteria allowing for patients with prior autologous-SCT ≥2 years prior to study enrolment and/or platelet count ≥100×10^9/L but <150×10^9/L to enter the study. The Betalutin dose is to be adapted for these patients. Patients will be divided into in 3 subpopulations and the first 3 patients in each will receive the following doses:

- Patients with a prior autologous-SCT and platelet count ≥150×10^9/L will receive Betalutin at the reduced dose of 12.5 MBq/kg with lilotomab 40 mg.

- Patients with a prior autologous-SCT and platelet count ≥100×10^9/L but <150×10^9/L will receive Betalutin at the reduced dose of 10 MBq/kg with lilotomab 40 mg.
- Patients without a prior SCT and platelet count ≥100×10^9/L but <150×10^9/L) will receive Betalutin at the reduced dose of 12.5 MBq/kg with lilotomab 40 mg.

The SRC will review the first 3 patients in each of these subpopulations and evaluate the number of DLTs observed. The SRC may recommend the current reduced dosing level be maintained, a dose escalation (including escalation to Betalutin 15 MBq/kg with lilotomab 40 mg), an evaluation of an additional 3 patients, a dose-decrease, a different dose or to stop the recruitment of further patients with a prior autologous-SCT and/or lower platelet count.

4.8.7.2 Part C (Pharmacokinetic Cohort)

Part C will start enrolment after the interim analysis and decision on the selected RP2D for future development in Part B. Therefore, all patients enrolled to Part C will receive lilotomab 40 mg followed by Betalutin 15 MBq/kg.

Note: Patients with a prior autologous-SCT and/or platelet count ≥100×10^9/L but <150×10^9/L are excluded from Part C.

4.8.7.3 Pharmacokinetics (Part A)

Betalutin pharmacokinetics, measured as total radioactivity in blood for patients in Arms 1, 2 and 4 are presented in Table 4-6. The pharmacokinetic profile of Betalutin is shown to be affected by the pre-dosing with lilotomab at the 3 doses tested (0, 40 mg and 100 mg/m^2), with lilotomab increasing the activity adjusted area under the total radioactivity in blood -time curve (AUC), and reducing the volume of distribution and rate of clearance of Betalutin, while having little effect on activity-adjusted maximum total radioactivity in blood measurement (C_{max}).

Table 4-6 Pharmacokinetics of Betalutin for Patients with and without Lilotomab Pre-dosing

	Arm 1 With 40 mg lilotomab pre-dosing N=9	**Arm 2 Without lilotomab pre-dosing N=4**	**Arm 4 With 100 mg/m^2 lilotomab pre-dosing N=9**
Activity-adjusted AUC0-∞ h*kBq/mL/(MBq/kg)	676	421	901
Volume of distribution (L)	10.48	17.56	5.39
Clearance (mL/h)	126	227	89
Activity-adjusted Cmax kBq/mL/(MBq/kg)	16.6	16.9	17.89
Effective T1/2 (h)	53.3	51.6	43.0
Biological T1/2 (h)	79.7	76.0	58.6

4.8.7.4 Dosimetry (Part A)

Dosimetry data show that the spleen, bone marrow, liver and kidneys were the organs receiving the highest absorbed radiation dose (Table 4-7). For the absorbed radiation doses to the liver and kidneys, the observed exposure with Betalutin is well below the external beam radiation therapy tolerance levels (52). Analysis of the absorbed radiation dose (dosimetry) for Arms 1, 2, and 4 support that both the 40 mg and the 100 mg/m^2 lilotomab pre-doses of Arms 1 and 4 protect the bone marrow as compared with no pre-dosing in Arm 2, since the absorbed radiation doses to red marrow are lower for Arms 1 and 4 than for Arm 2 (50, 51). This correlates with the reduced

haematologic toxicity noted in Arms 1 and 4 compared to Arm 2. The maximum absorbed radiation dose to the red marrow for all patients in Arms 1 and 4 is below the previously published radiological tolerance limit of 3 Gy (Table 4-8). The absorbed radiation dose is higher in Arm 4 compared to the other Arms; more patients are required to determine if this correlates with improved efficacy.

Table 4-7 Absorbed Radiation Doses to all Organs for Arms 1, 2 and 4

	Arm 1	Arm 2	Arm 4
	Mean (mGy/MBq) N=3	Mean (mGy/MBq) N=3	Mean (mGy/MBq) N=3
Adrenals	0.12	0.09	0.12
Brain	0.10	0.07	0.09
Breasts	0.10	0.07	0.09
Gallbladder Wall	0.12	0.09	0.12
LLI Wall	0.11	0.08	0.10
Small Intestine	0.11	0.08	0.10
Stomach Wall	0.11	0.08	0.11
ULI Wall	0.11	0.08	0.11
Heart Wall	0.11	0.08	0.11
Kidneys	0.46	0.27	0.60
Liver	0.97	0.89	1.36
Lungs	0.11	0.08	0.10
Muscle	0.10	0.08	0.10
Ovaries	0.11	0.08	0.10
Pancreas	0.12	0.10	0.12
Osteogenic Cells	0.50	0.81	0.72
Skin	0.10	0.07	0.09
Spleen	2.81	3.01	1.82
Thymus	0.11	0.08	0.10
Thyroid	0.10	0.07	0.10
Urinary Bladder Wall	0.11	0.08	0.10
Uterus	0.11	0.08	0.10
Total Body	0.14	0.12	0.16

Table 4-8 Mean Red Marrow and Tumour Absorbed Radiation Doses, Arms 1, 2 and 4

Arm	Mean (Standard Deviation) red marrow dose (mGy/MBq)	Mean (Standard Deviation) tumour dose (mGy/MBq)
1	0.96 ± 0.29 (n=4)	1.62 ± 0.67 (n=3)
2	1.57 ± 0.19 (n=3)	2.10 ± 0.60 (n=3)
4	0.88 ± 0.24 (n=4)	2.87 ± 0.98 (n=4)

In summary, the available safety, efficacy and dosimetry data support the selection of the

2 dosing regimens "40/15" and "100/20" for randomised comparison in Part B for dose selection. The preliminary results stated above indicate that the lilotomab/Betalutin regimen is highly active in patients with relapsed iNHL, particularly in patients with FL.

4.8.8 Estimation of Interval between Dose Escalations (Part A)

In preclinical studies with SCID mice administration of 100 MBq/kg b.w. of Betalutin was associated with transient reductions in while blood cell and platelet counts, nadir at 3 weeks after injection and recovered after 7 weeks. In the phase I clinical study with ^{177}Lu-rituximab the blood count nadirs were reached 7 to 8 weeks post-injection. The time to nadir may depend on the nature of the antibody. Rituximab is a chimeric antibody and is expected to be in the blood circulation longer than a murine antibody, such as lilotomab. However, for Zevalin (a murine RIC) nadir levels in humans were reported to be 7 to 9 weeks after administration. Escalation to the next dose level of Betalutin has therefore been scheduled to occur after a 12-week follow-up period after the last patient has been included in the dose group or when blood counts have recovered with neutrophils $\geq 1.5\times10^9$/L and platelets $\geq 100\times10^9$/L, provided that the other safety criteria are met.

4.8.9 Administration of Betalutin in the same Cohort (Part A)

There will be no time interval between patient dosing in the same cohort.

4.8.10 Outcome of the Interim Analysis on Patients Entered to Part B

The SRC reviewed efficacy and safety data for 47 patients who had been observed for a minimum of 3 months after Betalutin treatment. Based on the outcomes assessed and the totality of safety and efficacy, including the ORR and overall safety data including haematological adverse events, the SRC recommended that all future patients receive the regimen of lilotomab 40 mg and Betalutin 15 MBq/kg ("40/15"). There will be Betalutin dose adjustments for the first patients with a prior autologous-SCT and/or platelet count $\geq 100\times10^9$/L but $<150\times10^9$/L as follows:

- Patients with a prior autologous SCT and platelet count $\geq 150\times10^9$/L will receive Betalutin at the reduced dose of 12.5 MBq/kg.
- Patients with a prior autologous SCT and platelet count $\geq 100\times10^9$/L but $<150\times10^9$/L will receive Betalutin at the reduced dose of 10 MBq/kg.
- Patients without a prior autologous SCT, and platelet count $\geq 100\times10^9$/L but $<150\times10^9$/L will receive Betalutin at the reduced dose of 12.5 MBq/kg.

The SRC will review the safety data of the first 3 patients in each subpopulation and will further guide the determination of the recommended dose regimen for these subpopulations.

4.8.11 Rationale for Lower Betalutin Dose for Patients with Prior Autologous-SCT and/or Lower Platelet Level (Part B)

Discussion with the SRC, investigators and lymphoma experts (amendment implemented in protocol Version 14) lead to recommendation that:

- The revised inclusion criteria for platelets should not allow for the acceptable platelet threshold to be lowered too much on grounds that many of the DLTs in Part A were bleeding related.

Elderly patients who have cycled through previous therapies for FL and could potentially be treated on this protocol sometimes have platelets that are lower than would be considered 'normal' in younger, healthier reference populations. In order that this protocol includes a more representative population of FL patients there is a desire to include patients with platelets that are $\geq 100 \times 10^9$/L. This threshold represents a compromise between the desire to be more inclusive and the potential threat from radiation induced thrombocytopenia which is a recognised and reproducible AE with this therapy.

- There was a desire for inclusion of patients previously treated with autologous-SCT. The prevalence of this approach as the mainstay of first line therapy in some countries was considered. This was offset against the observation that patients with transplanted stem cells typically demonstrate more limited bone marrow reserves (61). One of the main effects of Betalutin administration, largely because of the attached radioactive lutetium is to compromised bone marrow. To retain sufficient activity to kill cancerous lymphoid tissue whilst avoiding excessive bone marrow toxicity a lower dose of Betalutin was suggested for initial assessment in this population.

The choice of the lilotomab 40 mg and Betalutin 15 MBg/kg dose regimen at the interim analysis points to a generally more efficacious and a more easily adhered to regimen with acceptable safety profile. The supposition based on interim data is that the lower dose of cold lilotomab (in the "40/15" regimen as compared to the "100/20" regimen) provides sufficient shielding of bone marrow without compromising the efficacy on tumour cells. The combination of a reduced dose of radioactivity for stem cell transplant patients and the choice of a regimen that is generally looking to be gentler on the bone marrow was considered an adequate compromise.

A further step to assess patients progress after the first 3 patients in each of the subpopulations of prior autologous-SCT, lower platelet and both prior auto-SCT and lower platelets, who have been on study for at least 6 weeks adds an extra element of supervision in considering the suitability of this new inclusion criterion. The consideration that future patients might be precluded from therapy by having previously received a mainstay approach like stem cell transplantation owing to the hitherto lack of experience dosing such patients and the desire to treat a representative population of NHL patients also factored into the rationale for the amendment introduced in protocol Version 14.

5 STUDY OBJECTIVES

5.1 Part A - Phase I (Arms 1, 2, 3, 4, and 5)

5.1.1 Primary Objective

- To define maximum tolerated dose of Betalutin.

5.1.2 Secondary Objectives

- To establish a recommended dose of Betalutin for Phase II.
- To investigate safety and toxicity of Betalutin.
- To investigate biodistribution and pharmacokinetics of Betalutin.
- To explore the efficacy of Betalutin.

5.2 Part A - Phase IIa

5.2.1 Primary Objective

- To explore tumour response rates in patients receiving Betalutin.

5.2.2 Secondary Objectives

- To confirm the recommended dose of Betalutin from Part A, phase I.
- To investigate safety and toxicity.
- To estimate progression free survival.
- To estimate OS.
- To investigate QoL.

5.3 Part B – FL Phase IIb "PARADIGME"

5.3.1 Primary Objectives

The primary objectives are:

- Randomised section:
  - To evaluate the efficacy of the "40/15" dose regimen (40 mg lilotomab/ 15 MBq/kg Betalutin) compared with the "100/20" dose regimen (100 mg/m^2 lilotomab/20 MBq/kg Betalutin) based on the Independent Review Committee (IRC) assessment of tumour response rates in adult patients with relapsed rituximab/anti-CD20-refractory FL.
- Selected regimen for further development:
  - To evaluate the ORR of the 40/15 regimen based on the IRC assessment of tumour response rates in adult patients with relapsed rituximab/anti-CD20 refractory FL.

5.3.2 Secondary Objectives

To compare the "40/15" and "100/20" treatment regimens in the randomised section and to evaluate the treatment regimen selected for further development, in terms of the following:

Efficacy

- ORR by investigator assessment
- Complete response rate (CRR) by independent review and investigator assessment
- DoR by independent review and investigator assessment
- Duration of complete response (DoCR) by independent review and investigator assessment
- PFS by independent review and investigator assessment
- OS

Safety

- To characterise the safety profile of Betalutin

5.3.3 Exploratory Objectives

- To characterise QoL as reported by patients receiving Betalutin.
- To further characterise the pharmacokinetic assessments e.g. total lilotomab antibodies measurements in serum (total lilotomab antibodies pharmacokinetics) and total radioactivity measurements in blood (Betalutin pharmacokinetics).

5.4 Part C - Pharmacokinetic Cohort

5.4.1 Primary Objective

To further characterise the pharmacokinetics of Betalutin (total radioactivity measurements in blood) and total lilotomab antibodies (antibodies measured in serum).

5.4.2 Secondary Objectives

- To investigate safety and toxicity
- To explore efficacy

5.5 Study Endpoints Part A (phase I and phase IIa)

Safety endpoints:

- Incidence and severity of AEs and serious adverse events (SAEs) graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE Version 4.0 or later, as applicable).
- 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 and pharmacokinetic endpoints:

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.

Efficacy endpoints:

- Tumour response rate.
- Tumour response duration.
- PFS.
- OS.

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.
- QoL assessed using Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) questionnaire (Version 4). The QoL forms will be used in those countries where the forms are translated and validated.

5.6 Study Endpoints Part B: FL phase IIb

Efficacy endpoints definitions are provided in Section 14.1.7.

Primary endpoint:

- ORR as assessed by an independent reviewer based on standard criteria [Cheson 2014] (40)

Secondary endpoints:

Efficacy endpoints:

- ORR by investigator assessment
- CRR by independent review and investigator assessment
- DoR and DoCR by independent review and investigator assessment
- PFS by independent review and investigator assessment
- OS
- Change from baseline in the sum of the product of the greatest perpendicular diameters (SPD) of target lymph nodes as documented radiographically.

Safety endpoints:

Incidence and severity of AEs.

Exploratory endpoints:

- Changes in QoL as reported by patients using the FACT-Lym questionnaire (Version 4).
- Pharmacokinetic assessments e.g. total lilotomab antibodies measurements in serum (total lilotomab antibodies pharmacokinetics) and total radioactivity measurements in blood (Betalutin pharmacokinetics).

5.7 Study Endpoints Part C: Pharmacokinetic Cohort

Primary endpoints:

Pharmacokinetic assessments e.g. total lilotomab antibodies measurements in serum (total lilotomab antibodies pharmacokinetics) and total radioactivity measurements in blood (Betalutin pharmacokinetics).

Pharmacokinetic parameters (weight adjusted, as appropriate) including, but not limited to: C_{max}, T_{max}, $AUC_{0-\infty}$, AUC_{0-last} and $T_{1/2}$, will be calculated for Betalutin pharmacokinetics and total lilotomab antibodies PK using actual sampling times. Activity-adjusted and dose-adjusted Cmax and AUC will also be calculated using the actual activity (Bq) or dose of total antibodies (mg) injected.

Secondary endpoints:

Incidence and severity of AEs.

Exploratory endpoints:

- Tumour response rate.
- Tumour response duration.
- OS.

6 STUDY DESIGN

6.1 Description of Study Design

This study is a phase I/II, open-label study of Betalutin in patients with relapsed NHL (Figure 6-1).

Part A of the study uses a traditional 3+3 study design for dose-escalation. Cohorts of 3 - 6 patients were enrolled into one of 4 arms evaluating different pre-dosing regimens (no pre-dose, rituximab or lilotomab 40 mg or 100 mg/m^2); dose escalation of Betalutin in each cohort continued until identification of a MTD or RP2D. All patients received pre-treatment with rituximab. Dose-escalation decisions were guided by a SRC (see Section 6.2). Additional patients (3 - 6) are being enrolled in Arm 5 to more fully characterise the PK profile of Betalutin (60 mg/m^2 lilotomab plus 20 MBq/kg Betalutin).

Table 6-1 Patient Disposition- Part A

	Rituximab Pre-treatment	Lilotomab Pre-dosing	Betalutin Dose	Number of Patients Treated	Number of Patients Planned	Cohort Status
		Day 0	Day 0			
Arm 1	D-28 D-21	40 mg	10 MBq/kg 20 MBq/kg 15 MBq/Kg	3 3 6	3 3 6	Closed
Arm 1, Phase IIa	D-28	40 mg	15 MBq/kg	30	30	Closed

	Rituximab Pre-treatment	Lilotomab Pre-dosing	Betalutin Dose	Number of Patients Treated	Number of Patients Planned	Cohort Status
		Day 0	Day 0			
	D-21					
Arm 2	D-28 D-21	-	15 MBq/kg 10 MBq/kg	2 1	3 3	Discontinued
Arm 3	D-14, D0	-	15 MBq/kg	3	3	Discontinued
Arm 4	D-14	100 mg/m^2	15 MBq/kg 20 MBq/kg	3 7	3 6	Closed
Arm 4, Phase IIa	D-14	100 mg/m^2	20 MBq/kg	12	10 to 15	Closed
Arm 5	D-14	60 mg/m^2	20 MBq/kg	3	3 to 6	Closed

Patients were then enrolled into 2 phase IIa expansion arms at the RP2D of Arm 1 (40 mg lilotomab + 15 MBq/kg Betalutin) and Arm 4 (100 mg/m^2 lilotomab + 20 MBq/kg Betalutin) to more fully evaluate safety and efficacy of the respective dosing regimen. Thirty (30) patients were enrolled into the Arm 1 phase IIa expansion arm. To further confirm the safety in phase I, the DLT rate was re-evaluated after a total of 15 patients had been treated at the RP2D of 15 MBq/kg Betalutin plus 40 mg lilotomab, and enrolment proceeded.

Part B

In **Part B** of the study, up to 130 patients with relapsed, rituximab/anti-CD20 refractory FL and platelet count ≥150×10^9/L who have received ≥2 prior lines of therapy were initially randomised in a 1:1 ratio to compare the 2 candidate RP2Ds of Arms 1 and 4 (40 mg lilotomab + 15 MBq/kg Betalutin versus 100 mg/m^2 lilotomab + 20 MBq/kg Betalutin) (65 per treatment regimen) until the selection of one of the 2 regimens for further assessment in clinical development.

An interim analysis of efficacy and safety data was planned after approximately 50 patients (see Section 14.1.2.2). This was performed after the first 47 patient and the SRC recommended that the "40/15" regimen be selected for further development. Randomisation was therefore stopped.

Patient enrolment will be completed when a total of 87 patients have received the "40/15" regimen selected for further development (including patients in the randomised section).

The eligibility criteria for Part B, were also widened (under protocol Version 14), to allow enrollment of patients with prior auto-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 (see Section 4.8.5). The Betalutin dose is to be adapted for these patients.

Patients will be divided into in 3 subpopulations and the first 3 patients in each will receive the following doses:

- Patients with a prior autologous-SCT and platelet count ≥150×10^9/L will receive Betalutin at the reduced dose of 12.5 MBq/kg with lilotomab 40 mg.
- Patients with a prior autologous-SCT and platelet count ≥100×10^9/L but <150×10^9/L will receive Betalutin at the reduced dose of 10 MBq/kg with lilotomab 40 mg.
- Patients without a prior autologous SCT with a platelet count ≥100×10^9/L but <150×10^9/L) will receive Betalutin at the reduced dose of 12.5 MBq/kg with lilotomab 40 mg.

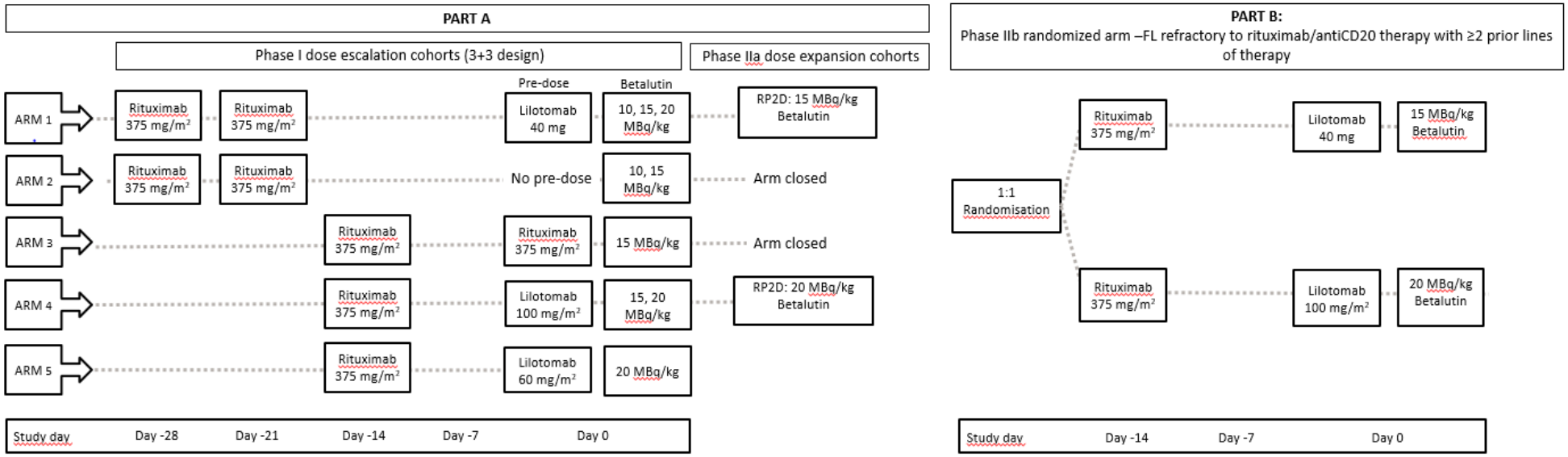
The SRC will review the emerging safety data (in particular, DLTs) from the first 3 patients in

each subpopulation after they have been followed up for at least 6 weeks and recommend the subsequent Betalutin dose, either a dose escalation, an evaluation of an additional 3 patients, a dose-decrease or to stop (see Section 6.2.3). .

Part C

Open label phase IIa expansion cohort to enable the collection of samples for Betalutin pharmacokinetics and total lilotomab antibodies pharmacokinetics in at least 10 patients (up to a maximum of 20 patients) receiving the "40/15" regimen.

Figure 6-1 ` LYMRIT 37-01 Study Design (Part A, Part B and Part C)



- Part A is closed to enrolment.
- Part B (PARADIGME) is open to enrolment for patients with FL.
- Part C (Pharmacokinetic Cohort) is open at selected sites (subject to regulatory and EC/IRB Approvals) to enrolment for patients with iNHL. All patients will receive the “40/15” regimen. Patients entering Part C will follow the same Schedule of Assessments (except QoL) as those in Part B.

Definition of study periods:

The ***study treatment period*** is defined as from the first administration of rituximab pre-treatment until 12 weeks after Betalutin administration. All patients will be closely monitored during the study treatment period.

The ***follow-up period*** is

Part A - up to 5 years or until the first anticancer treatment after Betalutin administration. Survival and potential long-term toxicity information will continue to be collected up to 5 years, even after further anticancer treatment has begun. All patients will be followed closely the first year after treatment, thereafter every 6 months (See Section 6-3 Schedule of Assessments).

Part B and Part C - up to 5 years after Betalutin administration.

Extensive follow-up (hospital visits) will take place for all patients every 3 months for the first year (Months 6, 9 and 12). Tumour imaging assessments are only required until the patient has further anticancer treatment after Betalutin administration or disease progression prior to further anticancer therapy as assessed by central imaging review. All other scheduled assessments should be performed.

After Month 12, follow-up will continue every 6 months up to 5 years after the Betalutin dose. Extensive follow-up (hospital visits) must be performed until the patient has further anticancer treatment after Betalutin administration or disease progression prior to further anticancer therapy as assessed by central imaging review. Thereafter, the patient will continue limited follow up every 6 months for potential long-term toxicity (new onset adverse events of special interest [AESIs], ADRs and study treatment-related SAEs), OS, further anticancer treatment and ADA testing (only if ADA test is positive at Month 12; testing to be continued until a negative result is obtained). Unless blood sampling is required for ADA testing, limited follow-up visits can be performed by telephone.

In Part B, Positron-emission tomography (PET)/computed tomography (CT) scans will be obtained for evaluation of tumour responses at certain intervals, see Section 6-3. Whole-body gamma camera and SPECT images will be taken for patients from Germany and in other agreed sites, at various time points.

In Part A, phase IIa, serial gamma camera scans, Single Photon Emission Computed Tomography (SPECT) imaging and pharmacokinetics measurements to evaluate dosimetry and biodistribution are optional and will only be performed at sites that are experienced and equipped to perform these assessments. If the study site does not intend to conduct dosimetry assessments, only SPECT/CT images at Day 4 will be conducted as an optional assessment.

6.2 Dose Escalation in Part A / Dose Definition in Special Populations in Part B

6.2.1 Dose-limiting Toxicity Definition

Both dose escalation decisions in Part A and dose definition decisions in Part B were made based on the incidence of DLTs. A DLT is defined as:

- Haematological:
  - Grade 4 toxicity that does not recover to grade 3 within 7 days

- or bleeding due to thrombocytopenia, or febrile neutropenia

- Non-haematological:
  - Grade 3 or more, final decision to be made by the SRC.

Toxicity is graded according to CTCAE Version 4.0 or later, as applicable

The DLT criteria were re-visited by the SRC in May 2017, and a recommendation was made to re-define "failure of platelets or neutrophils to recover to grade 1 by 12 weeks post-Betalutin" as not being a DLT event, as this is not associated with adverse clinical outcomes, is not a widely recognised haematologic DLT parameter in chemotherapy or RIT studies, and is not aligned with the DLT criteria from other Betalutin studies.

6.2.2 Dose Escalation in Part A

The dose escalation in Part A followed the traditional "3+3" design scheme shown in Table 6-2.

Table 6-2 "3+3 Design"

Outcome	Action
0 DLT out of 3 patients	Escalate dose for next cohort of 3 patients
1 DLT out of 3 patients	Expand this dose level with 3 more patients
	Halt dose escalation: treat total of 3 to 6 patients at a lower dose level, for Arms 3 and 4 consider closing enrolment into an arm and continuing enrolment into the alternative arm, according to recommendation made by the SRC
1 DLT out of 6 patients	Escalate dose for next cohort of 3 patients
≥ 2 DLT out of 6 patients	Halt dose escalation: treat total of 3 - 6 patients at a lower dose level, for Arms 3 and 4 consider closing enrolment into an arm and continuing enrolment into the alternative arm according to recommendation made by the SRC.

Phase 1 Arm 1: Dose-escalation and De-escalation

Dose escalation and De-escalation in Arm 1 was performed according to Table 6-3.

Table 6-3 Part A: Dose Escalation Phase I Arm 1 with Pre-dosing of 40 mg lilotomab

Dose level	Dose (administered activity)	Pre-set rules
1	10 MBq/kg body weight	Escalate dose when the third patient completes 8 weeks of follow-up after treatment, or when blood counts have recovered with ANC ≥1.5x10^9/L and platelets ≥100x10^9/L and no DLT occurred.
2	20 MBq/kg body weight	Escalate dose when the third patient completes 12 weeks of follow-up after treatment, or when blood counts have recovered with ANC ≥1.5x10^9/L and platelets ≥100x10^9/L and no DLT occurred.
3	Dose to be evaluated after safety results from dose level 2	To be recommended by the SRC.

An assessment of all available safety data was performed prior to allowing the study to proceed to the next dose level. A report including an overall recommendation on the next step was prepared and the final recommendation to move to the next dose level was endorsed by

the SRC in the study.

Arm 1: The recommended Betalutin dose following 40 mg lilotomab pre-dosing for phase IIa was 15 MBq/kg; a phase IIa expansion cohort enrolled 30 patients.

Arm 2: was discontinued after treatment of 3 patients (2 at 15 MBq/kg and 1 at 10 MBq/kg) due to dose-limiting haematologic toxicity.

Arm 3: was discontinued after treatment of 3 patients at 15 MBq/kg due to a sub-optimal clinical profile.

Arm 4: Following review of available safety data from 3 patients treated at the starting dose of 15 MBq/kg the SRC endorsed enrolment of patients at 20 MBq/kg in phase I. Seven (7) patients were enrolled and the RP2D of Betalutin was determined to be 20 MBq/kg. A phase IIa expansion cohort was subsequently opened.

Arm 5: Additional patients (3 - 6) were enrolled in Arm 5 to more fully characterise the pharmacokintic profile of Betalutin (60 mg/m^2 lilotomab plus 20 MBq/kg Betalutin).

6.2.3 Dose Definition in Special Populations in Part B

The dose escalation in each subpopulation of patients with prior autologous SCT and/or platelet count ≥100×10^9/L but <150×10^9/L in Part B (see Section 6.1) will follow the modified "3 + 3" design scheme shown in Table 6-4.

Table 6-4 Modified "3+3 Design" in Part B

Outcome	Action
0 DLT out of 3 patients	Escalate dose for next 3 patients in the subpopulation: • to 15MBq/kg in the subpopulation with prior autologous-SCT and platelet count ≥150×10^9/L. • to 15MBq/kg in the subpopulation without prior autologous-SCT, and with platelet count ≥100×10^9/L but <150×10^9/L. • to 12.5MBq/kg in the subpopulation with prior autologous-SCT and platelet count ≥100×10^9/L but <150×10^9/L.
1 DLT out of 3 patients	Expand this dose level with 3 more patients in the subpopulation. The SRC will review the overall safety of the cohort (6 patients) prior to establishing the dose to be recommended. Dose escalation may still be considered (same as for no DLT)
2 DLTs in a subpopulation	The SRC may consider a dose reduction to "40/10" for the 2 subpopulations treated with "40/12.5" or may decide to close enrolment in the subpopulation. There will be no dose reduction of Betalutin below 10 MBq/kg.

All patients will be followed for 6 weeks. The SRC will review the safety data from each set of 3 patients (either 3 or 3+3) (in particular, the number of DLTs) of each subpopulation and recommend the current reduced dosing level be maintained, a dose escalation (including escalation to Betalutin 15 MBq/kg with lilotomab 40 mg), an evaluation of an additional 3 patients, a dose-decrease, a different dose or to stop the recruitment of further patients with a prior autologous-SCT and/or lower platelet count.

6.3 Schedule of Assessments

There are separate tables for Part A phase I (Table 6-5), Part A phase IIa (Table 6-7), Part B FL phase IIb and Part C (Table 6-8).

Pharmacokinetic and dosimetry schedule of assessments for Part A are described in Table 6-6 and for Parts B and C in Table 6-9. In Parts B and C, pharmacokinetic assessments will be performed at selected sites only, whereas dosimetry assessments will be performed at sites in Germany and in other agreed sites.

During the coronavirus disease 19 (COVID-19) pandemic, every effort should be made to continue to perform the study visits and assessments according to the planned schedules. Where this is not possible, any deviations should be clearly documented. Any results of assessments performed remotely must be entered into the eCRF.

Part A (phase I and phase IIa):

A visit window of ± 2 days is permitted for the 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 3 week intervals will have a window of ± 3 days. During the treatment and follow-up periods, a window of ± 2 weeks for visits is acceptable. For PET/CT and CT evaluation a window of ± 2 weeks is acceptable for treatment and follow-up periods.

The investigator may perform more frequent examinations than shown in Table 6-5 and Table 6-7 if clinically needed. Data from such additional examinations are also to be recorded in the electronic Care 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.

Part B FL phase IIb and Part C (Pharmacokinetic Cohort):

Screening assessments should be performed within 4 weeks prior to administration of rituximab. In case of unforeseen delays in the planned rituximab administration, including but not limited to delay in the availability of Betalutin, or delay in HAMA testing or results availability, the screening period may be extended upon Sponsor's approval and the validity of imaging tests and bone marrow biopsy may be extended accordingly.

A visit window of ± 2 days is permitted for the 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 3 week intervals will have a window of ± 3 days. During the treatment and follow-up periods, a window of ± 7 days for visits is acceptable. For PET/CT and CT evaluation a window of ± 7 days is acceptable for treatment and follow-up periods.

The investigator may perform more frequent examinations than shown in Table 6-8 if clinically needed. Data from such additional examinations are also to be recorded in the 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 Betalutin administration.

Table 6-5 Schedule of Assessments – Part A, Phase I

	Screening	Treatment period										Follow-up period			
Test Type	Pre-study within 4 weeks before rituximab infusion	D-14 W2 prior dosing	D-1/D0 Day -1/ Dosing Day[12] **before adm**	D0 Dosing Day[13] **after adm**	D1 (24±6) hours)	D2 (48±12) hours)	D 4 (96±24) hours)	D 7 (168±24) hours)	W 2, 3, 5, 6, 7, 9, 10, 11 Local GP (±3 days)	Month 1, 2 (W 4, 8) (±3 days)	Month 3 (W 12) (±2weeks)	Month 6 (W26) (±2weeks)	Month 9 (W 39) (±2 weeks)	Month 12 (W52) (±2 weeks)	W52-5 years[1] Hospital visit every 6 months (±3 weeks)
Hospital visit	X	X	X	X	X	X	X	X		2X	X	X	X	X	8X
Informed consent	X														
Demographics	X														
Medical History	X														
Rituximab administration		X													
Lilotomab administration			X[2]												
Betalutin administration				X											
Concomitant medication/therapy	X		X	X	X	X	X	X		X	X				
Cancer related treatment only excl. analgesics												X	X	X	8X
Physical examination[8]	X		X	X[6]	X	X	X	X		X	X	X	X	X	8X
Vital signs incl. temp	X		X	X[6]	X	X	X	X		X	X				
Pregnancy test (if applicable)	X														
ECG			X												
WHO PS	X		X					X		X	X	X	X	X	8X
Hematology	X		X		X	X	X	X	8X	X	X	X	X	X	8X
Serum biochemistry[7]	X		X		X	X	X	X	8X	X	X	X	X	X	8X
Lymphocyte subset	X										X	X	X	X	
Hepatitis B test	X														
Immunoglobulin levels	X										X	X	X	X	
HAMA level	X							X		X(W4 only)	X	X		X	
CD37 expression	X[3]										(X[5])	(X[5])	(X[5])	(X[5])	(X[5])
Bone marrow biopsy	X[11]										X[10]	X[10]			
Radioactivity in blood[4]			X	3-5X	X	X	X	X	X (week 2 and 3 only)						
Gamma Camera Images, only few pts.[4]				X	X		X	X							
SPECT/CT[4]							X[13]								
Urine sampling[4]					X										
CT neck, thorax, abdomen, pelvis with contrast	X										X	X	X	X	2X 1-2 years; X 2-5 years
FDG PET/CT images	X										X	X			
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X[9]	X[9]	X[9]	8X[9]
Adverse events		X	X	X	X	X	X	X		X	X				
Adverse drug reaction, only												X	X	X	8X
Long term toxicity											X	X	X	X	8X
Survival status											X	X	X	X	8X

1) 5 years or until relapse of disease; 2) On the dosing day, within 4 hrs prior to Betalutin administration for arms 1, 4 and 5; 3) A biopsy is needed or test on existing tumour material for CD37;
4) Only at selected sites. For more details see Table 6.3.2: Pharmacokinetic and Biodistribution 5) When a patient is biopsied at relapse, CD37 expression should be asessed. CD37 biopsy at relaps is optional. 6) Measured at 2 hrs post injection;
7) Protein-electrophoresis at baseline only; 8) Abbreviated physical examination at baseline, dosing day, day 1, 2 and 4. 9) Only when judged to be related to study participation or study treatment. 10) Bone marrow biopsy required for
12) A visit window of ±2 days is permitted for Day 0 visit. 13) A visit window of ±1 day is permitted for the Day 4 SPECT/CT scan.

Table 6-6 Schedule of Assessments – Pharmacokinetic, Biodistribution and Dosimetry, Part A, Phase I/IIa

Test Type	Day -14	Day 0 relative to Betalutin dosing							Day 1	Day 2	Day 3	Day 4	Day 7	Day 14	Day 21
	2 weeks prior to dosing	Dosing Day	Pre-dose	5 min	60 min	2 hrs	4 hrs	8 hrs	24 hrs	48 hrs	72 hrs	96 hrs	168 hrs	W2	W3
Visit Window													**± 1 d**	± 1 d	± 1 d
Rituximab infusion	X														
Lilotomab infusion		X[1]													
Betalutin administration		X													
Radioactivity in blood			X	X	X	X	X[9]	X[9]	X	X	X[3]	X	X	X[4]	X[4]
Urine collection[5]		From 0 to 2-4 hrs WB scan; from 2-4 hrs WB scan to 24 hrs WB scan. First void collected separately.													
Serial whole body (WB) studies						X			X			X[6,7]	X[6]		
SPECT/CT[8]												X[7]			

In general, urine, blood samples and imaging for pharmacokinetic and biodistribution will be done until counts are not longer significant from background counts, and as long as the images are meaningful. The time points may be adjusted after experience from the first patients.

1) Lilotomab infusion within 4 hours prior to Betalutin injection; 2) One baseline blood sample before Betalutin injection; 3) Blood sampling is optional

4) Blood from biochemistry/hematology samples may be used. 5) Urine collection when feasible 6) Patients not participating in whole body study will do SPECT on Days 4 and 7

7) a visit window of ± 1 day is permitted for Day 4 SPECT/CT scans 8) For those sites not able to conduct whole body scans 9) Only for patients participating in whole-body study

Table 6-7 Schedule of Assessments – PART A, Phase IIa

	Screening										**Follow-up period**			
Test Type	Pre-study (Within 4 weeks before 1st rituximab dose)	D-14 W2 prior to dosing	D-1/D0[7] Day -1 or Dosing Day before adm	D0[7] Dosing Day after adm	D+7 W1 Local GP (±1 day)	D+21 W3 Local GP (±3 days)	D+28 W4 (±3 days)	W 5, 6, 7, 9, 10, 11 Local GP6 (±3 days)	Month 2 W8 (±3 days)	Month 3 W12 (±2 weeks)	Month 6 W26 (±2weeks)	Month 9 W 39 (±2 weeks)	Month 12 W52 (±2 weeks)	W 53-5 years[1] Hospital visit every 6 months (±3 weeks)
Hospital visit	X	X	X	X			X		X	X	X	X	X	8X
Informed consent	X													
Demographics	X													
Medical History	X													
Rituximab administration		X												
Lilotomab administration[2]			X[2]											
Betalutin administration				X										
Concomitant medication/therapy	X	X	X	X			X		X	X				
Physical examination	X		X				X		X	X	X	X	X	8X
Vital signs including temperature	X		X	X			X		X	X	X	X	X	8X
Pregnancy test (if applicable)	X													
WHO (ECOG) Performance Status	X		X				X		X	X	X	X	X	8X
Hematology	X		X		X	X	X	X	X	X	X	X	X	8X
Serum biochemistry	X		X		X	X	X	X	X	X	X	X	X	8X
Lymphocyte subset	X									X	X	X	X	
Hepatitis B test	X													
Immunoglobulin levels	X									X	X	X	X	
HAMA level	X						X			X	X		X	
CD37 expression	X[3]													(X[4])
Bone marrow biopsy	X									X[5]	X[5]			(X[5])
CT neck, thorax, abdomen, pelvis with contrast	X									X	X	X	X	2X 2nd year X yearly 3-5
FDG PET/CT images	X									X	X			
Quality of Life form	X									X			X	
Adverse events		X	X	X			X		X	X				
Adverse Drug reaction											X	X	X	8X
SAE	X	X	X	X			X		X	X				
SAE related to treatment											X	X	X	8X
Long term toxicity											X	X	X	8X
Survival status											X	X	X	8X

1) 5 years or until further anticancer therapy is given 2) On the dosing day, within 4 hrs prior to Betalutin administration

3) CD37 expression is assessed by immunohistochemistry using an archived tissue biopsy (FFPE block). If not available, a new tissue biopsy needs to be collected at patient screening

4) When patient is biopsied at relapse CD37 expression should be assessed. CD37 biopsy at relaps is optional

5) Bone marrow biopsy required for confirmation of CR if patient had bone marrow infiltration at baseline, otherwise it is optional

6) Blood samples weekly until platelet counts ≥ 100 x 109/L and neutrophil counts (ANC) ≥ 1.5 x 109/L after nadir values 7) A visit window of +/- 2 days is permitted for Day 0 visit. GP= general practitioner or local hospital

Note: during the COVIID-19 pandemic, it may be necessary to perform certain study procedures remotely. All assessments must be recorded in the eCRF

Table 6-8 Schedule of Assessments - Part B, FL Phase IIb "PARADIGME" and Part C, Pharmacokinetic Cohort Phase IIa

	Screening	**Treatment period**									**Follow-up period**			
Test type	Pre-study (Within 4 weeks before 1st rituximab dose)	D-14 W2 prior to dosing	D-1/D0 Day -1 or Dosing Day before adm (±2 day)	D0 Dosing Day after adm	D+7 W1 (±2 day)	D+21 W3 (±2 days)	D+28 W4 (±2 days)	W5, 6,7,9,10,11[6] (±2 days)	Month 2 W8 (±3 days)	Month 3 W12 (±7 days)	Month 6 W26 (±7 days)	Month 9 W 39 (±7 days)	Month 12 W52 (±7 days)	W53-5 years[1] Hospital visit every 6 months (±7 days)
Hospital visit	X	X	X	X			X		X	X	X	X	X	8X
Informed consent	X													
Demographics	X													
Medical History	X													
FL (Part B) or iNHL (Part C) disease stage and previous treatment	X													
Rituximab administration		X												
Lilotomab administration[2]				X[2]										
Betalutin administration				X										
Cancer related treatment only excl analgesics											(X)[7]	(X)[7]	(X)[7]	(X)[7]
Concomitant medication/therapy	X	X	X	X			X		X	X				
Physical examination	X		X				X		X	X	X	X	X	8X
Vital signs including temperature, weight and height	X		X	X[p]			X		X	X	X	X	X	8X
Pregnancy test (if applicable)	X[13]		X				X			X	X		X	
WHO (ECOG) Performance Status	X		X				X		X	X	X	X	X	8X
Haematology	X	X	X		X	X	X	X	X	X	X	X	X	8X
Serum biochemistry	X		X		X	X	X	X	X	X	X	X	X	8X
Coagulation parameters (PT/INR & PTT)	X									X				
Lymphocyte subset	X									X	X	X	X	
Viral serology[12]	X													
Immunoglobulin levels	X									X	X	X	X	
HAMA test	X													
Immunogenicity (ADA)			X[9]		X		X			X	X		X	X[8]
CD37 expression in tumour tissue	X[3]									(X)[4]				

	Screening	**Treatment period**									**Follow-up period**			
Test type	Pre-study (Within 4 weeks before 1st rituximab dose)	D-14 W2 prior to dosing	D-1/D0 Day -1 or Dosing Day before adm (±2 day)	D0 Dosing Day after adm	D+7 W1 (±2 day)	D+21 W3 (±2 days)	D+28 W4 (±2 days)	W5, 6,7,9,10,11[6] (±2 days)	Month 2 W8 (±3 days)	Month 3 W12 (±7 days)	Month 6 W26 (±7 days)	Month 9 W 39 (±7 days)	Month 12 W52 (±7 days)	W53-5 years[1] Hospital visit every 6 months (±7 days)
Genomic biomarkers (DNA, RNA and proteins) in tumour tissue	(X)[10]									(X)[10]				
HLA haplotyping in blood	(X)[11]													
Bone marrow biopsy	X[5]									X[5]	X[5]			
CT neck, thorax, abdomen, pelvis with contrast or MRI	X									X	X	X	X	2X 2nd year X yearly 3-5
FDG PET/CT images	X									X	X			
ECG	X													
QoL (FACT-LYM) (Part B only)	X									X			X	
Adverse events	X	X	X	X	X	X	X	X	X	X				
Adverse Drug reaction											X	X	X	8X
SAE	X	X	X	X	X	X	X	X	X	X				
SAE related to treatment											X	X	X	8X
AEs of special interest											X	X	X	8X
Survival Status											X	X	X	8X

1) 5 years or until further anticancer therapy is given
2) On the dosing day, within 4 hrs prior to Betalutin administration
3) CD37 expression is assessed by immunohistochemistry using an archived tissue biopsy (FFPE block age <5 years. If block age 2-5 years, discuss with Sponsor) at screening, or if not available, a new tissue biopsy needs to be collected at screening. Repeat at relapse and/or disease progression (optional). The tumour biopsy sample(s) can be used for genomic biomarkers analysis if separate informed consent is given (see note 10).
4) When patient is biopsied at relapse, CD37 expression should be assessed. Tumour biopsy at relapse is optional.
5) At screening: The Bone Marrow Biopsy taken up to 8 weeks before rituximab administration may be used. At Complete Response: Bone marrow biopsy required for confirmation of CR if patient had bone marrow infiltration at baseline, otherwise it is optional.
6) Blood samples weekly until platelet counts ≥ 100 x 10^9/L and neutrophil counts (ANC) ≥ 1.5 x 10^9/L after nadir values (these do not require a hospital visit).
7) If the patient receives cancer related treatment, they should continue with limited long term follow-up and record the first course of cancer related treatment.
8) Only if ADA test is positive at month 12. Blood samples to be collected at each visit until ADA-negative result.
9) ADA immunogenicity blood sample to be taken before lilotomab dose
10) Separate patient informed consent required for the analysis of genomic biomarkers (DNA, RNA, proteins) using the tumour tissue biopsy sample(s) collected for CD37 expression analysis.
11) Separate patient informed consent required for the analysis of genomic biomarkers (HLA haplotyping) using the peripheral blood sample collected at screening.
12) Hepatitis B (HBsAg and anti-HBc), Hepatitis C and HIV
13) Serum ß-HCG at screening; otherwise urine dip stick test
(X) – optional sample; p - 2 hours post-dose.

Note: during the COVID-19 pandemic, it may be necessary to perform certain study procedures remotely. All assessments must be recorded in the eCRF

Table 6-9 Schedule of Assessments – Pharmacokinetic and Dosimetry, Part B - "PARADIGME" and Part C Pharmacokinetic Cohort

Test type	Day -14	Day 0 relative to lilotomab dosing							Day 0 relative to Betalutin dosing			Day 1	Day 2	Day 4	Day 7	Day 21	Day 28	Day 35
	2 weeks prior to dosing	Pre-dose	Lilotomab Dose	5 min	30 min	60 min	120 min	Betalutin administration	5 min	60 min	2 hrs	24 hrs	48 hrs	96 hrs	W1	W3	W4	W5
Visit Window				± 2 min	± 5 min	± 10 min	± 15 min		± 2 min	± 10 min	± 15 min	± 4 hrs	± 24 hrs	± 24 hrs	± 1 day	± 2 days	± 2 days	± 2 days
Rituximab infusion	X																	
Lilotomab infusion			X[1]															
Betalutin administration								X										
Total Radioactivity in blood		X[2]							X	X	X	X	X	X	X	X	X	X
Total lilotomab antibodies in serum		X		X	X	X	X		X	X	X	X	X	X	X	X	X	X
SPECT/CT Imaging (Germany and in other agreed sites)											X +1 hr	X		X	X			

(1) Lilotomab infusion within 2-4 hours prior to Betalutin injection;
(2) One baseline blood sample before lilotomab infusion

7 SELECTION OF STUDY POPULATION

7.1 Inclusion Criteria

Patients must meet the criteria for the part of the study they will enrol into:

7.1.1 Part A (phase I and phase IIa) and Part C (Pharmacokinetic Cohort, phase IIa)

1. Histologically confirmed (by World Health Organization [WHO] classification) relapsed incurable non-Hodgkin B-cell lymphoma of following subtypes; follicular grade I-IIIA (for Part C, this excludes patients meeting Part B criteria, who should enter Part B), marginal zone, small lymphocytic, lymphoplasmacytic, mantle cell.
2. Age ≥ 18 years.
3. Part A: A pre-study WHO performance status of 0-1; Part C: A pre-study WHO performance status of 0-2.
4. Life expectancy should be ≥3 months.
5. <25% tumour cells in bone marrow biopsy (biopsy taken from a site not previously irradiated).
6. Measurable disease by radiological methods.
7. Women of childbearing potential must:
   a) understand that the study medication is expected to have teratogenic risk.
   b) have a negative pregnancy test.
   c) agree to use, and be able to comply with, effective contraception without interruption, 4 weeks before starting study medication, throughout study medication therapy and for 12 months after end of study medication therapy, even if she has amenorrhoea.
8. Male patients must agree to use condoms during intercourse throughout study drug therapy and the following 12 months.
9. Patients previously treated with native rituximab are eligible.
10. The patient is willing and able to comply with the protocol, and agrees to return to the hospital for follow-up visits and examination.
11. The patient has been fully informed about the study and has signed the informed consent form.

7.1.2 Part B (FL phase IIb)

1. Histologically confirmed (by WHO classification) relapsed non-Hodgkin B-cell FL (grade I-IIIA).
2. Male or female aged ≥18 years.
3. Received at least 2 prior systemic anti-neoplastic or immunotherapy-based regimens (maintenance therapy following a CR/PR is not considered to be a separate line of therapy). Systemic regimens including agents such as idelalisib or other PI3K inhibitors, qualify as a prior line of therapy.

4. Prior therapy must have included a rituximab/anti-CD20 agent and an alkylating agent – which may have been administered in separate regimens
5. Patients must be refractory to at least one-previous regimen that contained rituximab or an anti-CD20 agent, with refractoriness defined as:
   i. no response (no CR or PR) during therapy, or
   ii. a response (CR/PR) lasting less than 6 months after the completion of a regimen including rituximab/anti-CD20 therapy (including occurrence of progressive disease (PD) during rituximab/anti-CD20 maintenance therapy, or within 6 months of completion of maintenance therapy).
6. WHO performance status of 0-2.
7. Life expectancy of ≥3 months.
8. Bone marrow tumour infiltration <25% (in biopsy taken from a site not previously irradiated).
9. Measurable disease by CT or MRI: longest diameter (LDi) >1.5 cm for nodal lesion, LDi >1.0 cm for extra nodal lesion on an assessment performed during the screening period.

Criteria 10 and 11 must be satisfied within 72 hours of the administration of rituximab:

10. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L.
11. Platelet count $\geq 100 \times 10^9$/L.

Criteria 12 to 15 must be verified at time of eligibility review within 2 weeks prior to rituximab administration:

12. Haemoglobin ≥9.0 g/dL.
13. Total bilirubin ≤1.5×upper limit of normal (ULN) (except patients with documented Gilbert's syndrome [<3.0 mg/dL]).
14. Liver enzymes: aspartate transaminase (AST); alanine transaminase (ALT) or alkaline phosphatase (ALP) ≤2.5×ULN (or ≤5.0×ULN with liver involvement by primary disease).
15. Adequate renal function as demonstrated by a serum creatinine <1.5×ULN.
16. Women of childbearing potential must:
    a) understand that the study medication is expected to have teratogenic risk.
    b) have a negative serum beta human-chorionic gonadotropin (β-HCG) pregnancy test at screening.
    c) commit to continued abstinence from heterosexual intercourse (excluding periodic abstinence or the withdrawal method) or begin a highly effective method of birth control with a Pearl-Index <1%. without interruption from 4 weeks before starting study medication, throughout study medication therapy and for 12 months after end of study medication therapy, even if she has amenorrhoea. Apart from abstinence, highly effective methods of birth control are:
       i. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
       ii. Progestogen-only hormonal contraception associated with inhibition of ovulation. (oral, injectable, implantable)
       iii. Intrauterine device (IUD).

iv. Intrauterine hormone-releasing system (IUS).
v. Bilateral tubal occlusion.
vi. Vasectomised partner.

17. Male patients must agree to use condoms during intercourse throughout study treatment administration and the 12 months following the administration of Betalutin.
18. The patient is willing and able to comply with the protocol, and agrees to return to the hospital for follow-up visits and examination.
19. The patient has been fully informed about the study and has signed the informed consent form.
20. Negative HAMA test at screening.
21. Negative test at screening for Hepatitis B (negative hepatitis B surface antigen [HBsAg] and antibody to hepatitis B core antigen [anti-HBc]), Hepatitis C and human immunodeficiency virus (HIV).

7.2 Exclusion Criteria

7.2.1 Part A (phase I and phase IIa) and Part C (Pharmacokinetic Cohort, phase IIa)

1. Medical contraindications, including uncontrolled infection, severe cardiac, pulmonary, neurologic, psychiatric or metabolic disease, uncontrolled asthma/allergy requiring systemic steroids, known to be HIV positive.
2. Laboratory values within 15 days pre-registration:
   a. ANC $\leq 1.5\times10^9$/L.
   b. Part A: Platelet count $\leq 150\times10^9$/L; Part C: Platelet count $<150\times10^9$/L

   For Part C, criteria 2a and 2b must be satisfied within 72 hours of the administration of rituximab
   c. Total bilirubin ≥30 mmol/L (Part A only).

      Total bilirubin >1.5×ULN (except patients with documented Gilbert's syndrome [≥3.0 mg/dL]) (Part C only).
   d. ALP and ALT ≥4×normal level (Part A only).

      AST, ALT or ALP >2.5×ULN (or > 5.0 x ULN with liver involvement by primary disease). (Part C only)
   e. Creatinine ≥115 µmol/L (men), 97 µmol/L (women) (Part A only).

      Serum creatinine ≥1.5×ULN (Part C only).
   f. Haemoglobin <9.0 g/dL (Part C only).
3. Known central nervous system (CNS) involvement of lymphoma.
4. Previous total body irradiation.
5. . Positive test for HAMA at screening.
6. Chemotherapy or immunotherapy received within the last 4 weeks prior to start of study treatment. Pre-treatment with rituximab is allowed.
7. Pregnant or lactating women.
8. Previous hematopoietic stem cell transplantation (autologous and allogenic).

9. Part A : Previous treatment with radioimmunotherapy. Part C: Not applicable.
10. Actively participating in another study or received an investigational medicinal product within 4 weeks prior to enrolment.
11. Receipt of live, attenuated vaccine within 30 days prior to enrolment.
12. Part A and Part C: Test positive for hepatitis B (HBsAg and anti-HBc). Part C only: Test positive for hepatitis C and HIV.
13. A known hypersensitivity to rituximab, lilotomab, Betalutin or murine proteins or any excipient used in rituximab, lilotomab, or Betalutin.

7.2.2 Part B (FL phase IIb)

1. Prior hematopoietic allogenic stem cell transplantation.
2. Patients with a prior autologous-SCT are excluded unless at least two years have elapsed since transplantation
3. Evidence of histological transformation from FL to DLBCL at time of screening (transformation to grade IIIB that was successfully treated with recurrence of grade I-IIIA initial clone is accepted).
4. Previous total body irradiation.
5. Prior anti-lymphoma therapy (chemotherapy, immunotherapy or other systemic agent including any investigational agent) within 4 weeks prior to start of study treatment (corticosteroid treatment at doses of ≤20 mg/day, topical or inhaled corticosteroids, granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) are permitted up to 2 weeks prior to start of rituximab).
6. Patients who are receiving any other investigational medicinal products.
7. Patients with known or suspected CNS involvement of lymphoma.
8. History of malignancy other than FL within 5 years prior to screening (i.e. patients with cancer diagnosed within 5 years prior to screening or who were diagnosed prior to 5 years and were not in CR or were on treatment within 5 years prior to screening), with the exception of malignancies with a negligible risk of metastasis or death (e.g. 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localised prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
9. Pregnant or breastfeeding women.
10. Exposure to another CD37 targeting drug.
11. A known hypersensitivity to rituximab, lilotomab, Betalutin or murine proteins or any excipient used in rituximab, lilotomab, or Betalutin.
12. Has received a live-attenuated vaccine within 30 days prior to enrolment.
13. Evidence of severe or uncontrolled systemic diseases:
    a. Uncontrolled infection including evidence of ongoing systemic bacterial, fungal, or viral infection (excluding viral upper respiratory tract infections) at the time of initiation of study treatment.
    b. Pulmonary conditions e.g. unstable or uncompensated respiratory disease.
    c. Hepatic, renal, neurological, or metabolic conditions - which in the opinion of the investigator would compromise the protocol objectives.

d. Psychiatric conditions e.g. patients unlikely to comply with the protocol, e.g. mental condition rendering the patient unable to understand the nature, scope, and possible consequences of participating in the study.

e. History of erythema multiforme, toxic epidermal necrolysis, or Stevens-Johnson syndrome.

f. Cardiac conditions in the previous 24 weeks (before date of consent), including:

   i. history of acute coronary syndromes (including unstable angina).

   ii. class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.

   iii. known uncontrolled arrhythmias (except sinus arrhythmia).

8 WITHDRAWL AND TERMINATION CRITERIA

8.1 Patient Withdrawal

In accordance with the Declaration of Helsinki, each patient is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw patients from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation.

Single patient withdrawal is per definition:

- when the patient is withdrawn during the treatment period or extensive follow-up without consent to be followed up for survival, collection of long-term toxicities and anticancer therapies.
- when the patient has died.

If a patient dies, the immediate cause of death should be noted, in addition to death caused by underlying disease, the Investigator's judgement on possible relationship to study drug should be recorded in the CRF.

If a patient starts further anticancer treatment, details of the new anticancer therapy regimen should be noted and recorded in the CRF.

Should a patient decide to withdraw after administration of the IMP(s), or should the investigator(s) decide to withdraw the patient, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given of why the patient is withdrawing or being withdrawn from the study. The reason and date for withdrawal must be noted in the eCRF. If the reason for withdrawal is a clinical AE or an abnormal laboratory test result, monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF.

It is advisable to monitor the haematology parameters of the withdrawn patients after Betalutin administration until recovery to Grade 1 NCI CTCAE.

Survival information, potential long-term toxicity information and further anticancer therapy will continue to be collected on withdrawn patients unless the patient specifically withdraws their consent. Confirmation of continued consent to survival or collection of

long-term toxicities follow-up is recorded in the eCRF.

8.2 Study Termination

The whole study may be discontinued at the discretion of the investigator or Sponsor in the event of the following:

- Occurrence of AEs which by virtue of their nature, severity and duration are considered to necessitate study termination.
- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in the recruitment of patients.
- Cancellation of drug development.

9 TREATMENT PLAN

9.1 Study Treatment

Rituximab, lilotomab and Betalutin can all be administered on an outpatient basis. The patient should be under surveillance at the hospital at least 2 hours after administration of Betalutin (unless local regulations require a longer surveillance period).

In case of hypersensitivity reactions, study drug administration must be stopped immediately. Medicinal products for the treatment of hypersensitivity reactions, e.g, adrenaline, antihistamines and corticosteroids must be available for immediate use in the event of an allergic reaction during administration of rituximab, lilotomab or Betalutin.

If extravascular administration of Betalutin or lilotomab or rituximab – that is, leakage of the injection to the surrounding tissue is suspected, the administration must be immediately terminated. Rinse with isotonic saline, elevate the arm and gently massage the arm to facilitate lymphatic drainage.

Detailed written instructions on labelling and preparation will be given to the personnel prior to patient inclusion. See also Investigator's Brochure.

9.1.1 Investigational Drug Product Betalutin

The generic name for Betalutin is lutetium (^{177}Lu)-lilotomab satetraxetan. The antibody lilotomab is labelled with ^{177}Lu via the chelator p-SCN-benzyl-DOTA. ^{177}Lu is a β-particle emitter with a physical half-life of 6.7 days. The radiopharmaceutical Betalutin is a ready-to-use, sterile, non-pyrogenic, clear and slightly yellowish aqueous solution of lutetium (^{177}Lu)-lilotomab satetraxetan for intravenous administration.

The product is isotonic and has a pH of 6.4-7.4. The radioactive concentration at the reference date will depend on the dose level and the patient body weight; however, the dose is capped for patients who weigh more than 130 kg (patients heavier than 130 kg will receive the dose for a 130 kg patient). When administered on a day other than the reference day, the volume should be corrected according to the physical decay table included in the Drug Handling Plan. The measured Betalutin dose must be +/-10% of the intended prescribed dose.

The product is supplied in 20 mL single dose glass vials, closed with rubber stoppers and

aluminium seals. The amount per vial will depend on the dose level.

9.1.2 Supply and Packaging

Betalutin is shipped as a Type A radioactive package according to international transportation guidelines for radioactive materials.

Each vial will be labelled with a unique vial number, identifying the specific vial as well as the batch number. The content of the labels will be according to national requirements.

Each vial should be used for one patient only.

9.1.3 Handling and Storage of Betalutin

A dedicated person, who has the responsibility delegated from the Principal Investigator, will be responsible for handling and storage of Betalutin. The dedicated person has the overall responsibility for handling and storage of Betalutin at the study centre; i.e. that the vials containing Betalutin are correctly received and recorded, handled and stored safely and properly, and used in accordance with this protocol. Betalutin is a radiopharmaceutical and should be handled by individuals who are qualified by training and experience in the safe handling of radionuclides. A deputy person should also be nominated.

The vials must be stored in a secure facility. Betalutin should be stored in the lead container in a refrigerator, 2˚C to 8˚C. Storage must be in accordance with local requirements for radioactive materials. Betalutin must reach room temperature before patient administration.

See the Drug Handling Plan for further details.

9.1.4 Preparation and Administration of Betalutin

The total activity to be injected will be calculated volumetrically using the patient's body weight on the day of injection (kg), the dose level, and decay correction factor (DC) to correct for physical decay of ^{177}Lu. A table with correction factors is provided in the Drug Handling Plan. The measured Betalutin dose must be +/-10% of the intended prescribed dose. The dose will be capped for patients who weigh more than 130 kg (patients heavier than 130 kg will receive the dose for a 130 kg patient).

The total amount (volume to be drawn into the syringe) to be administered to a patient should be calculated as follows:

$$\frac{\text{Body weight (kg)} \times \text{Betalutin Dose MBq/kg b.w.}}{\text{DC} \times \text{radioactive concentration at the reference (calibration) date MBq/mL}} = \underline{\text{Volume to be injected (mL)}}$$

Filling of the syringe should take place at a dedicated area for working with radioactive solutions. Personnel should wear medical gloves and eye protection during syringe filling to prevent contamination of the radioactive solution of skin and eyes. The individual responsible for Betalutin preparation will draw the correct volume of the study drug into a syringe, and control the correct activity for administration in a dose calibrator. Data regarding activity and volume to be injected for the various patients should be recorded on the study drug administration eCRF page.

To maintain traceability, there are four labels for syringe shield and forms per patient, with identification of batch, vial, and patient. One (1) sticker with the identification number should

be attached to the study medication preparation page, the other on the syringe shield and the third to the study medication administration page.

The syringe should be shielded from β radiation during preparation and administration of the patient doses. Aseptic technique should be used in the administration of Betalutin. Each patient will receive one dose in accordance with the treatment schedule. Betalutin will be given as a slow bolus injection using a shielded syringe driver. After administration, the syringe and line must be flushed with a minimum of 10 mL of sterile normal saline (0.9% NaCl) after injection, as detailed in the Drug Handling Plan. The equipment used in connection with the preparation and administration of the study medication, are to be treated as radioactive waste and should be disposed in accordance with hospital procedure for handling of radioactive material.

9.1.5 Patient Protection

The patient will receive verbal and written instructions in accordance with the hospital radiation safety policies and procedures regarding precautions, as necessary, after receiving the radioactive drug. Betalutin can be administered on an outpatient basis.

9.1.6 Rituximab Infusion

Rituximab will be ordered through the standard procedure at the study centre. The product should be administered according to the approved product information (prescribing information) for rituximab. Pre-medication consisting of an antipyretic and an antihistamine, e.g. paracetamol and Dexchlorpheniramine or cetirizine, should always be administered before each infusion of rituximab. The types of pre-medication used prior to rituximab infusion will follow each hospital's routine, including any use of corticosteroids. The prepared rituximab solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus. The standard hospital procedure for infusion of rituximab will be followed. If an AE occurs, the infusion will be stopped. When the symptoms have disappeared, the infusion will be re-started with 50% decreased infusion rate.

9.1.7 Lilotomab Infusion

Lilotomab will be delivered in vials of approximately 5 mg/mL lilotomab. Lilotomab for infusion will be prepared aseptically at the hospital and made ready for infusion as detailed in the Lilotomab Drug Handling Plan. Pre-medication consisting of an antipyretic and antihistamine medication should be administered before infusion of lilotomab.

Lilotomab will be infused within 4 hours prior to the Betalutin administration. The infusion rate will be 100 mL/hour. For doses of lilotomab given on a BSA basis, this should be calculated using the duBois calculation. The infusion rate may be adjusted depending on how well it is tolerated. If the patient experiences an AE such as a drop in blood pressure, chills, fever, or dyspnoea the infusion will be stopped. When the symptoms disappear, the infusion will start again with 50% reduced infusion rate.

9.1.7.1 Part A (phase I and phase IIa):

Lilotomab will be given by intravenous infusion over 60 minutes.

- In Arm 1, a total of 40 mg lilotomab will be given.

- In Arm 4, the dose of lilotomab will be 100 mg/m^2 up to a maximum body surface area of 2.7 m^2.
- In Arm 5, the patients will receive 60 mg/m^2 lilotomab up to a maximum body surface area of 2.7m^2.

9.1.7.2 Part B (FL phase IIb):

In Part B, the patients will be randomised 1:1 (stratified for double-refractory patients) to receive either 40 mg or 100 mg/m^2 lilotomab up to a maximum body surface area of 2.7 m^2 (that is, maximum of lilotomab 270 mg).

Following the interim analysis performed on the first 47 patients with FL, patients will receive the regimen lilotomab 40mg and Betalutin 15MBq/kg ("40/15").

All patients must be observed closely during the infusion and in the first hour after the infusion. Blood pressure and heart rate are measured before infusion and subsequently every 15 minutes until the patient seems clinically stable. The blood pressure and heart rate must be measured at 30 minutes and at 1 hour after the infusion has ended. Temperature is measured before, and 1 hour after, the lilotomab infusion. If the patient experiences any reactions, vital signs must be recorded frequently until the patient is stable. Any AEs will be recorded in the eCRF.

9.1.7.3 Part C (Pharmacokinetic Cohort, phase IIa)

In Part C, patients will receive the "40/15" regimen and will therefore receive 40 mg lilotomab.

9.1.8 Drug Accountability

The study medications, rituximab, Betalutin and lilotomab, should be kept in a secure place and must be administered only to patients in the study. For all 3 drugs, an appointed individual is responsible for maintaining accurate records of the study medication. A list of study medication (received, administered to patients, destroyed) must be prepared and signed by the dedicated person responsible for drug handling.

When the drug accountability has been monitored by the Sponsor representative, the vials can be destroyed in accordance with hospital procedure. Betalutin should be stored for a minimum of 3 months (>10 half-lives) before disposal.

See the Drug Handling Plans for further details.

9.2 Methods of Assigning Patients to Treatment

9.2.1 Part A (phase I and phase IIa)

A screening number will be assigned when a patient signs the informed consent form and is evaluated for inclusion into the study. The patients will then undergo screening procedures and those who meet the inclusion and not the exclusion criteria will be assigned a unique identification number. This number will be assigned sequentially by the hospital personnel. Once assigned, this number must not be used again for a different patient.

When an eligible patient has consented to be included in the study, a "Drug Order Form" will be sent from site to the Sponsor. The Sponsor's dedicated person who is responsible for ordering of the IMP will send the IMP order to the manufacturer and the IMP will be shipped to the study centre.

Cohort enrolment was closely monitored to ensure that patients were only enrolled following the appropriate review of the data from previous patients (see Section 6.2.2). Arms 1 and 2 were enrolled sequentially. Enrolment into either Arms 3 or 4 was based on the investigator/site preference.

9.2.2 Part B (FL phase IIb)

At the time of evaluation of the patient for enrolment, a patient number will be assigned via an Interactive Web Response system (IWRS). In the randomised period, patients will be enrolled to receive one of the two dosing regimens: "40/15" or "100/20". There will be central stratification for double refractory patients. After the interim analysis performed on the first 47 patients entered to Part B, the study will proceed with a single regimen, and all patients will be assigned to "40/15" treatment regimen. Patients with a prior autologous SCT and/or platelet count$\geq 100\times10^9$/L but $<150\times10^9$/L will receive a reduced dose of Betalutin as follows:

- Patients with a prior autologous-SCT and platelet count $\geq 150\times10^9$/L will receive Betalutin at the reduced dose of 12.5 MBq/kg.
- Patients with a prior autologous-SCT and platelet count $\geq 100\times10^9$/L but $<150\times10^9$/L will receive Betalutin at the reduced dose of 10 MBq/kg.
- Patients without a prior autologous-SCT and platelet count $\geq 100\times10^9$/L but $<150\times10^9$/L) will receive Betalutin at the reduced dose of 12.5 MBq/kg.

A patient is double-refractory if they are refractory to both an anti-CD20 therapy and an alkylating agent therapy. The definitions of refractory to each treatment are as follows:

i. Anti-CD20 therapy:
    i. No response (no CR or PR) during rituximab or anti-CD20 containing therapy, or
    ii. A response (CR/PR) lasting less than 6 months after the completion of a regimen of rituximab or other anti-CD20 therapy (including occurrence of progressive disease (PD) during rituximab/anti-CD20 maintenance therapy, or within 6 months of completion of maintenance therapy).

ii. Alkylating agent:
    i. No response (no CR or PR) during alkylating agent therapy comprising at least 2 cycles of treatment, or
    ii. The occurrence of progressive disease (PD) within 6 months of the completion of alkylating agent therapy comprising at least 2 cycles of treatment.

The purpose of stratification is to balance the number of double refractory patients between treatment regimens. No analysis within strata are planned. Randomisation records are selected by finding the next available minimum patient randomisation number, within the stratum, in the central randomisation list.

Site users will confirm in the IWRS system when all screening procedures have been completed and the patient is considered eligible for enrolment. A medical monitor will review the patient and confirm that the patient is eligible in the IWRS system before the patient is enrolled.

9.2.3 Part C (Pharmacokinetic Cohort, phase IIa)

At the time of evaluation of the patient for enrolment, a patient number will be assigned via an

IWRS system. All patients will receive the "40/15" treatment regimen

Site users will confirm in the IWRS system when all screening procedures have been completed and the patient is considered eligible for enrolment. A Sponsor medical monitor will review the patient and confirm that the patient is eligible in the IWRS system before the patient is entered.

9.3 Prior and Concomitant Therapy

Information about previous cancer-related treatment will be collected in the eCRFs.

All concomitant therapies, including any pre-medication given before rituximab injection have to be recorded in the eCRF from the screening visit until 12 weeks after Betalutin administration on Day 0 of the study. The generic or trade name, indication, dose, and when applicable the start and stop date will be recorded.

Haematology parameters should be carefully checked prior to administration of any other myelosuppressive therapy.

Warfarin should be changed to low-molecular heparin. The dose of low-molecular heparin should be temporarily reduced if platelets are below 50×10^9/L, and be temporarily stopped if platelets are below 25×10^9/L.

Prophylaxis with allopurinol for tumour lysis will be permitted at the discretion of the investigator.

9.4 Supportive Care Guidelines

Persistent neutropenia (neutrophils/granulocytes < 0.5×10^9/L) without fever

Patients with persistent neutropenia will be started on G-CSF 5 µg/kg/daily given subcutaneous until the neutrophil count has reached the local hospital's reference range.

Neutropenia with fever (Neutrophils/granulocytes <1×10^9/L; fever >38°C)

Blood cultures will be obtained from the patient. The patient should start on empiric antibiotics as long as clinically indicated. Provision of G-CSF to such patients is highly recommended.

Severe thrombocytopenia (platelets <5×10^9/L) or bleeding with platelets <50×10^9/L

Patients will be transfused with platelets to maintain a platelet count >20×10^9/L or higher if clinically indicated to control bleeding. Epsilon aminocaproic acid may be given to patients with mucosal bleeding and platelet count <50 x 10^9/L.

Severe anaemia (haemoglobin <8.0 g/dL)

Patients will be transfused with packed red cells to maintain haemoglobin level >8.0 g/dL.

9.5 Treatment Compliance

Patients will receive Betalutin treatment under supervision of a nuclear medicine specialist (or any other specialist physician authorised to administer radiopharmaceuticals per local regulations). Study centre personnel will check the administration volume and total radioactivity injected and will record the activity dose and volume injected in the patient's source documents and eCRF.

Patients will receive infusions of lilotomab and rituximab under surveillance by trained

personnel used to handle infusions with rituximab. The volume to be given will be prepared by the pharmacy following instructions of the drug handling manual and the infusion bags will be delivered as ready to use solutions.

9.6 Study Procedures

Safety and efficacy measurements obtained during the course of the study are summarised in the Schedule of Assessments, Section 6.

9.6.1 Screening

Assessment or Procedure	Explanation
Informed Consent	The patient must be fully informed about the study and sign the Informed consent form. The ICF needs to be signed before any treatment or study-related procedures are initiated.
SAE	Any SAEs occurring after Informed Consent has been signed should be recorded
AE	**Part B and Part C only:** Any AEs occurring after Informed Consent has been signed should be recorded
Demographic information and body measurements	Date of birth, sex, ethnic origin, race should be recorded
Medical History	Record details of all previous or concomitant conditions or surgical procedures excluding NHL
Disease stage at study entry	Record date of NHL diagnosis and subtype at diagnosis and last time of relapse. Ann Arbor staging and presence of B symptoms.
Concomitant medication and procedure	If the patient is receiving any medication for conditions mentioned on the Medical history page, details need to be recorded on the Concomitant therapies record
Previous treatment of NHL	Previous treatment component of regimen, regimen number and response to treatment should be recorded.
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Any abnormalities should be recorded on Medical history record
Electrocardiogram (ECG)	**Part B and Part C only**: 12 Lead ECG. Date and time of ECG and interpretation need to be recorded
Performance status	WHO (ECOG) performance status (WHO PS)
Vital signs	Weight, height, pulse rate, blood pressure, body temperature
Pregnancy test	For women of childbearing potential: serum β-HCG pregnancy test
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, lactate dehydrogenase (LDH), gamma glutamyl transferase, glucose, total bilirubin, albumin
Coagulation Parameters	**Part B and Part C only:** Prothrombin Time (PT) or International Normalised Rate (INR), Partial Thromboplastin Time (PTT)

Lymphocyte subset	CD3 T-Cell Count, $CD3^+CD4^+$ T-Cell count, $CD3^+CD8^+$ T-Cell count, $CD19^+$ B-Cell count
Immunoglobulin levels	Protein electrophoresis – gamma-globulin (IgG, IgA, IgM)
HAMA / ADA testing	• To screen for pre-existing HAMA. Eligibility can be assessed using a commercially available test (such as the Milenia Quickline® HAMA test or any commercially available HAMA-ELISA test) • A serum sample for the IFMA test performed at a central laboratory is mandatory.
Tumour tissue biopsy (if no suitable archival sample available, a new tumour tissue biopsy will be performed	• Measure CD37 expression (formalin-fixed paraffin embedded [FFPE] blocks or 5 µM slides). **Part B and Part C only**: • Genomic biomarkers – gene expression analysis (DNA, ribonucleic acid (RNA), proteins) to evaluate the relationship between the anti-tumour activity and NHL-related genes. This is subject to separate patient informed consent. • FFPE tumour biopsy sample will be sent to Covance Central Laboratory Services (CCLS) for biobanking.
Blood sample for human leucocyte antigen (HLA) typing	• **Part B and Part C only**: Genomic biomarkers - HLA class I/II haplotyping. Subject to separate patient informed consent. • Peripheral blood sample to be sent to CCLS for biobanking.
Viral Serology	**Part A:** HBsAg and anti-HBc. **Part B and Part C:** Hepatitis B (HBsAg and anti-HBc), Hepatitis C and HIV
Bone marrow biopsy	To verify <25% tumour cells in bone marrow, Biopsy taken from a site not previously irradiated. It is allowed to use results from bone marrow biopsy that have been done within 8 weeks before rituximab dosing if no clinical transformation is suspected.
CT scans with contrast or MRI scan	CT of neck, thorax, abdomen and pelvis. Information about contrast medium, target lesion location and measurements and non-measurable lesions will be recorded. The same camera should preferably be used throughout the study. MRI scan for patients allergic to X-ray contrast.
(^{18}F) Fluorodeoxyglucose (FDG) PET/CT	Using standard institutional guidelines. Patient needs to be fasting for 6 hours prior to PET/CT examination. Information about FDG administration and uptake (maximum standardised uptake value [SUV_{max}]) will be recorded. The same camera should preferably be used throughout the study.
QoL	**Part A phase IIa and Part B only:** FACT-Lym to be completed by the patient

9.6.2 Treatment Period

9.6.2.1 Pre-treatment, Pre-dosing and Dosing (Day -14 to Day 0): All Patients

Assessment or Procedure	**Explanation**
Day -14 Pre-dose procedures and assessments (Parts B and C only)	
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils) **Haematology parameters need to be reviewed prior to**

	rituximab administration and it must be verified that ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L (Part B) or ≥ 150 x 10^9/L (Part C)
Day – 14 Rituximab administration	
Rituximab administration	Weight, body surface area, dose administered, start and end time of infusion and pre-medication needs to be recorded
Concomitant Medication	Recording of concomitant medication since screening visit
(S)AE	Any (S)AE after rituximab infusion should be recorded
Day -1/0 - Pre-dose procedures and assessments (can be done one day before administration of lilotomab)	
(S)AE	Recording of (S)AEs occurring since D-14 visit
Concomitant medication	Recording of concomitant medication since D-14 visit
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils) **Haematology parameters need to be evaluated prior to lilotomab administration**
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin. **Biochemistry parameters need to be evaluated prior to lilotomab administration and to continue to meet eligibility criteria**
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms.
ECG	Part A (phase I and phase IIa) only: 12 Lead ECG. Date and time of ECG and interpretation need to be recorded
Vital signs	Weight, pulse rate, blood pressure, body temperature
Performance status	WHO PS
Pregnancy Test (if applicable)	Urine dip stick
Immunogenicity	• **Part B and Part C only**: To monitor the ADA response. • Serum samples to be sent to CCLS for biobanking
Day 0 - Lilotomab administration	
Lilotomab infusion within 4 hours before Betalutin administration	Dose (assigned and actual), start and end time of infusion, batch number and pre-medication needs to be recorded. Record pulse rate, blood pressure and body temperature pre-infusion, 15 min, 30 min, 45 min, 1 hour after infusion start and 30 minutes and 1 hour post-infusion
(S)AE	Any (S)AE after lilotomab infusion should be recorded
Day 0 – Betalutin administration	
Betalutin injection	Patient weight, assigned dose level, volume injected, batch number, time of injection and radioactivity in syringe prior and after injection need to be recorded
Day 0 - Post dose procedures and assessments	
Vital signs	2 hours post-dose: blood pressure, body temperature
(S)AE	Any (S)AE after Betalutin administration should be recorded
Concomitant medication	Any medication given post-Betalutin should be recorded

9.6.2.2 Pharmacokinetics and Biodistribution: Applicable Patients

Assessment or Procedure	Explanation
Betalutin pharmacokinetics, total lilotomab antibodies pharmacokinetics and dosimetry assessments post Betalutin - only at selected sites in Part A, phase I and selected sites in Part B and Part C	
Betalutin PK (blood) – only for selected sites and patients	• To measure the total radioactivity in blood. • These are approximate timepoints. The exact clock time that samples are taken need to be recorded in eCRF. **Part A**: • Pre-dose blood sample to be taken before Betalutin dosing • Post-dose blood samples to be taken at the following timepoints after Betalutin dosing: 5 min, 1 hour, 2 hours, 1 day, 2 days, 3 days (optional), 4 days, 7 days (±1 day), 14 days (±2 day) and 21 days (±2 days). **Part B and Part C**: • Pre-dose blood sample to be taken before lilotomab dosing Post-dose blood samples to be taken at the following timepoints after Betalutin dosing: 5 min, 60 min, 2 hours, 24 hours, 2 days, 4 days, 7 days, 21 days, 28 days, 35 days.
Total lilotomab antibodies pharmacokinetics	• To assess drug clearance in serum (lilotomab, lilotomab satetraxetan, Betalutin). • These are approximate timepoints. The exact clock time that samples are taken need to be recorded in eCRF. **Part B and Part C only**: • Pre-dose blood sample to be taken before lilotomab dosing • Post-dose blood samples to be taken at the following timepoints after lilotomab dosing: 5 min, 30 min, 60 min, and 2 hours. • Post-dose blood samples to be taken at the following time points after Betalutin dosing: 5 min, 60 min, 2 hours, 24 hours, 2 days, 4 days, 7 days, 21 days, 28 days, 35 days.
Urine Collection	**Part A only**: Urine collection should only be done at specific sites and only if feasible. Timepoints: first-void (before Betalutin injection), 0 - 2-4 hours post dose, 2-4 - 24 hours post Betalutin
Serial whole body scans (gamma camera images) and SPEC/CT. Dosimetry (SPECT/CT) scans.	**Part A:** • Whole body scan at 2 hours, 24 hours, Day 4 and Day 7 Some patients that do not participate in the serial whole-body study may take a SPECT/CT at Day 4 **Part B and Part C**: SPECT/CT scans will be acquired 2 hours after Betalutin dosing, at 24 hours and Days 4 and 7 from patients in sites in Germany and in other agreed sites only.

9.6.2.3 Part A Day 1 to Week 12

Assessment or Procedure	Explanation
Day 1 - Only for Part A, phase 1	
(S)AE	Any (S)AE since day 0 should be recorded
Concomitant medication	Recording of concomitant medication used since Day 0
Physical examination	Check and describe heart, lung and other significant findings

Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Day 2 - Only for Part A, phase 1	
(S)AE	Any (S)AE since day 1 should be recorded
Concomitant medication	Recording of concomitant medication used since Day 0
Physical examination	Check and describe heart, lung and other significant findings
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Day 4 - Only for Part A, phase 1	
(S)AE	Any (S)AE since day 2 should be recorded
Concomitant medication	Recording of concomitant medication used since day 0
Physical examination	Check and describe heart, lung and other significant findings
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, ASAT, ALAT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Day 7 - Only for Part A, phase 1	
(S)AE	Any (S)AE since day4 should be recorded
Concomitant medication	Recording of concomitant medication used since Day 0
Physical examination	Check and describe heart, lung and other significant findings
Performance status	WHO PS
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, ASAT, ALAT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Immunogenicity	HAMA positive or negative

Day 7 (Part A phase IIa), Week 2 (only Part A phase I patients) and Weeks 3, 5, 6, 7, 9, 10, 11 (all patients)

The purpose of these visits was to take additional weekly blood samples after Betalutin administration (until platelet and ANC recovered to $\geq 100\times10^9$/L and $\geq 1.5\times10^9$/L, respectively after nadir values. These samples could be taken remotely, except for patients having whole body studies and/or pharmacokinetic sampling (see Section 9.6.2.2) when a hospital visit was required on Days 7, 14 and 21.

(S)AE	Any (S)AE since last visit should be recorded

Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Month 1 and 2	
(S)AE	Any (S)AE since last visit should be recorded.
Concomitant medication	Recording of concomitant medication used since last visit.
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any abnormalities should be recorded on AE record.
Vital signs	Pulse rate, blood pressure, body temperature.
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, ASAT, ALAT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Performance status	WHO PS
Immunogenicity	**Month 1 only:** HAMA positive or negative.
Month 3	
(S)AE	Any (S)AE since last visit should be recorded.
Concomitant medication	Recording of concomitant medication used since last visit.
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature.
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Performance status	WHO PS
Immunogenicity	HAMA positive or negative.
Lymphocyte subset	CD3 T-Cell Count, $CD3^+CD4^+$ T-Cell count, $CD3^+CD8^+$ T-Cell count, $CD19^+$ B-Cell count.
Immunoglobulin levels	Protein electrophoresis – gamma-globulin (IgG, IgA, IgM).
CT scans with contrast	CT of neck, thorax, abdomen and pelvis. Information about contrast medium, target lesion location, tumour measurements, non-measurable lesions and any new lesions will be recorded. Response assessment following CT examination (CR, complete response unconfirmed [Cru], PR, stable disease (SD), PD).
FDG PET/CT	Using standard institutional guidelines. Patient need to be fasting 6 hours prior to PET/CT examination. PET response evaluation according to Deauville score.

Overall tumour response	Assessment of tumour response following CT, PET/CT and bone marrow examinations (CR, PR, SD, PD).
Tumour tissue biopsy (new tumour tissue biopsy at relapse and/or disease progression	• To assess CD37 expression in tumour. Tissue slide to be sent to central lab if relapse. This is optional
Bone marrow biopsy	Bone marrow biopsy required for confirmation of CR if patient had BM infiltration at baseline
QoL	**Part A Phase IIa only:** FACT-Lym to be completed by the patient

9.6.2.4 Part B and Part C Day 7 to Month 3

Assessment or Procedure	**Explanation**
Week 1	
(S)AE	Any (S)AE since last visit should be recorded
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, ASAT, ALAT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Immunogenicity	• To monitor the ADA response. • Serum samples to be sent to CCLS for biobanking.
Week 3, 5, 6, 7, 9, 10, 11 The purpose of these visits is to take additional weekly blood samples after Betalutin administration (until platelet and ANC recovered to $\geq 100\times10^9$/L and $\geq 1.5\times10^9$/L, respectively after nadir values. These samples can be taken remotely, except for patients having SPECT/CT and/or pharmacokinetic sampling (see Section 9.6.2.2) when a hospital visit is required on Day 21.	
(S)AE	Any (S)AE since last visit should be recorded
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Week 4	
(S)AE	Any (S)AE since last visit should be recorded
Concomitant medication	Recording of concomitant medication used since last visit
Physical examination	Check and describe heart, lung and other significant findings
Vital signs	Pulse rate, blood pressure, body temperature
Pregnancy test (if applicable)	Urine dip stick
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, ASAT, ALAT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Performance status	WHO PS
Immunogenicity	• To monitor ADA response. • Serum samples to be sent to CCLS for biobanking.
Month 2	

Assessment or Procedure	Explanation
(S)AE	Any (S)AE since last visit should be recorded
Concomitant medication	Recording of concomitant medication used since last visit
Physical examination	Check and describe heart, lung and other significant findings
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Performance status	WHO PS
Month 3	
(S)AE	Any (S)AE since last visit should be recorded.
Concomitant medication	Recording of concomitant medication used since last visit.
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature.
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Coagulation parameters	PT/INR and PTT
Pregnancy test (if applicable)	Urine dipstick
Performance status	WHO PS
Immunogenicity	• To monitor ADA response. • Serum samples to be sent to CCLS for biobanking.
Lymphocyte subset	CD3 T-Cell Count, $CD3^+CD4^+$ T-Cell count, $CD3^+CD8^+$ T-Cell count, $CD19^+$ B-Cell count.
Immunoglobulin levels	Protein electrophoresis – gamma-globulin (IgG, IgA, IgM).
CT scans with contrast or MRI scan	CT of neck, thorax, abdomen and pelvis. Information about contrast medium, target lesion location, tumour measurements, non-measurable lesions and any new lesions will be recorded. Response assessment following CT examination (CR, complete response unconfirmed [Cru], PR, stable disease (SD), PD).
FDG PET/CT	Using standard institutional guidelines. Patient needs to be fasting 6 hours prior to PET/CT examination. PET response evaluation according to Deauville score.
Overall tumour response	Assessment of tumour response following CT, PET/CT and bone marrow examinations (CR, PR, SD, PD).
Tumour tissue biopsy (new tumour tissue biopsy at relapse and/or disease progression	• To assess CD37 expression in tumour. • Genomic biomarkers. Gene expression analysis (DNA, RNA, proteins) to evaluate the relationship between the anti-tumour activity and NHL-related genes. This is subject to separate patient informed consent.

Assessment or Procedure	Explanation
	FFPE tumour tissue biopsy to be sent to CCLS for biobanking
Bone marrow biopsy	Bone marrow biopsy required for confirmation of CR if patient had BM infiltration at baseline
QoL	**Part B only:** FACT-Lym to be completed by the patient

9.6.3 Follow-up Period

9.6.3.1 Part A

Assessment or Procedure	Explanation
Month 6	
(Serious) ADR	Any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) since last visit should be recorded
Adverse events of special interest	Adverse events of special interest should be recorded on the SAE record.
Cancer related treatment	Record if the patient has received any cancer-related treatment since last visit
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest). Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin.
Performance status	WHO PS
Immunogenicity	HAMA positive or negative
Lymphocyte subset	CD3 T-Cell Count, $CD3^+CD4^+$ T-Cell count, $CD3^+CD8^+$ T-Cell count, $CD19^+$ B-Cell count
Immunoglobulin levels	Protein electrophoresis – gamma-globulin (IgG, IgA, IgM)
CT scans with contrast	CT of neck, thorax, abdomen and pelvis. Information about contrast medium, target lesion location, tumour measurements, non-measurable lesions and any new lesions will be recorded. Response assessment following CT examination (CR, Cru, PR, SD, PD)
Overall tumour response	Assessment of tumour response following CT, PET/CT and bone marrow examinations (CR, PR, SD, PD)
CD37 expression	Tissue slide to be sent to central lab if relapse. This is optional
Bone marrow biopsy	Bone marrow biopsy required for confirmation of CR if patient had bone marrow infiltration at baseline
Month 9	
(Serious) ADR	Any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) since last visit should be recorded
Adverse events of special interest	Adverse events of special interest should be recorded on the SAE record.
Cancer related treatment	Record if the patient has received any cancer-related treatment since last visit

Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Performance status	WHO PS
Lymphocyte subset	CD3 T-Cell Count, $CD3^+CD4^+$ T-Cell count, $CD3^+CD8^+$ T-Cell count, $CD19^+$ B-Cell count
Immunoglobulin levels	Protein electrophoresis – gamma-globulin (IgG, IgA, IgM)
CT scans with contrast	CT of neck, thorax, abdomen and pelvis. Information about contrast medium, target lesion location, tumour measurements, non-measurable lesions and any new lesions will be recorded. Response assessment following CT examination (CR, CRu, PR, SD, PD)
CD37 expression	Tissue slide to be sent to central lab if relapse. This is optional
Month 12	
(Serious) ADR	Any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) since last visit should be recorded
Adverse events of special interest	Adverse events of special interest should be recorded on the SAE record.
Cancer related treatment	Record if the patient has received any cancer-related treatment since last visit
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Performance status	WHO PS
Immunogenicity	HAMA positive or negative
Lymphocyte subset	CD3 T-Cell Count, $CD3^+CD4^+$ T-Cell count, $CD3^+CD8^+$ T-Cell count, $CD19^+$ B-Cell count
Immunoglobulin levels	Protein electrophoresis – gamma-globulin (IgG, IgA, IgM)
CT scans with contrast	CT of neck, thorax, abdomen and pelvis. Information about contrast medium, target lesion location, tumour measurements, non-measurable lesions and any new lesions will be recorded. Response assessment following CT examination (CR, CRu, PR, SD, PD)

CD37 expression	Tissue slide to be sent to central lab if relapse. This is optional
QoL	**Phase IIa only:** FACT-Lym to be completed by the patient (phase IIa)
Month 18, 24, 36, 48, 60	
(Serious) ADR	Any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) since last visit should be recorded
Adverse events of special interest	Adverse events of special interest should be recorded on the SAE record.
Cancer related treatment	Record if the patient has received any cancer-related treatment since last visit
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Performance status	WHO PS
CT scans with contrast	CT of neck, thorax, abdomen and pelvis. Information about contrast medium, target lesion location, tumour measurements, non-measurable lesions and any new lesions will be recorded. Response assessment following CT examination (CR, CRu, PR, SD, PD)
CD37 expression	Tissue slide to be sent to central lab if relapse. This is optional
Month 30, 42, 54	
(Serious) ADR	Any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) since last visit should be recorded
Adverse events of special interest	Adverse events of special interest should be recorded on the SAE record.
Cancer related treatment	Record if the patient has received any cancer-related treatment since last visit
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Performance status	WHO PS

CD37 expression	Tissue slide to be sent to central lab if relapse. This is optional

9.6.3.2 Part B and Part C

9.6.3.2.1 Follow-up – Months 6, 9 and 12 (all patients)

Extensive follow-up (hospital visits) should be performed for all patients at Months 6, 9 and 12.

Assessment or Procedure	**Explanation**
Month 6	
(Serious) ADR	Any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) since last visit should be recorded
Adverse events of special interest	Adverse events of special interest should be recorded on the SAE record.
Cancer related treatment	Record if the patient has received any cancer-related treatment excl. analgesics since last visit
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature
Pregnancy test (if applicable)	Urine dip stick
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Lymphocyte subset	CD3 T-Cell Count, $CD3^+CD4^+$ T-Cell count, $CD3^+CD8^+$ T-Cell count, $CD19^+$ B-Cell count
Immunoglobulin levels	Protein electrophoresis – gamma-globulin (IgG, IgA, IgM)
Performance status	WHO PS
Immunogenicity	• To monitor the ADA response. • Serum samples to be sent at CCLS for biobanking.
CT scans with contrast or MRI scan	CT of neck, thorax, abdomen and pelvis. Information about contrast medium, target lesion location, tumour measurements, non-measurable lesions and any new lesions will be recorded. Response assessment following CT examination (CR, PR, SD, PD). MRI scan for patients allergic to x-ray contrast.
FDG PET/CT	Using standard institutional guidelines. Patient needs to be fasting 6 hours prior to PET/CT examination. PET response evaluation according to Deauville score.
Overall tumour response Only for patients without disease progression (per central review) or further anticancer treatment	Assessment of tumour response following CT, PET/CT and BM examinations (CR, PR, SD, PD)
Tumour tissue biopsy (new tumour tissue biopsy at	• To assess CD37 expression in tumour. • Genomic biomarkers. Gene expression analysis (DNA, RNA, proteins) to evaluate the relationship between the anti-tumour

relapse and/or disease progression	activity and NHL-related genes. This is subject to separate patient informed consent. • FFPE tumour tissue biopsy to be sent to CCLS for biobanking
Bone marrow biopsy	BM biopsy required for confirmation of CR if patient had BM infiltration at baseline
Performance status	WHO (ECOG) performance status (WHO PS)
Survival status	Survival status if patient has already relapsed.
Month 9	
(Serious) ADR	Any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) since last visit should be recorded
Adverse events of special interest	Adverse events of special interest should be recorded on the SAE record.
Cancer related treatment	Record if the patient has received any cancer-related treatment excl. analgesics since last visit
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Lymphocyte subset	CD3 T-Cell Count, $CD3^+CD4^+$ T-Cell count, $CD3^+CD8^+$ T-Cell count, $CD19^+$ B-Cell count
Immunoglobulin levels	Protein electrophoresis – gamma-globulin (IgG, IgA, IgM)
Performance status	WHO (ECOG) performance status (WHO PS)
CT scans with contrast or MRI scan Only for patients without disease progression (per central review) or further anticancer treatment	CT of neck, thorax, abdomen and pelvis. Information about contrast medium, target lesion location, tumour measurements, non-measurable lesions and any new lesions will be recorded. Response assessment following CT examination (CR, PR, SD, PD). MRI scan for patients allergic to x-ray contrast.
Tumour tissue biopsy (new tumour tissue biopsy at relapse and/or disease progression	• To assess CD37 expression in tumour. • Genomic biomarkers. Gene expression analysis (DNA, RNA, proteins) to evaluate the relationship between the anti-tumour activity and NHL-related genes. This is subject to separate patient informed consent. • FFPE tumour tissue biopsy to be sent to CCLS for biobanking
Survival status	Survival status if patient has already relapsed.
Month 12	
(Serious) ADR	Any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) since last visit should be recorded
Adverse events of special interest	Adverse events of special interest should be recorded on the SAE record.

Cancer related treatment	Record if the patient has received any cancer-related treatment excl. analgesics since last visit
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature
Pregnancy test (if applicable)	Urine dip stick
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Lymphocyte subset	CD3 T-Cell Count, $CD3^+CD4^+$ T-Cell count, $CD3^+CD8^+$ T-Cell count, $CD19^+$ B-Cell count
Immunoglobulin levels	Protein electrophoresis – gamma-globulin (IgG, IgA, IgM)
Performance status	WHO (ECOG) performance status (WHO PS)
Immunogenicity	• To monitor the ADA response. • Serum samples to be sent to CCLS for biobanking
CT scans with contrast or MRI Only for patients without disease progression (per central review) or further anticancer treatment	CT of neck, thorax, abdomen and pelvis. Information about contrast medium, target lesion location, tumour measurements, non-measurable lesions and any new lesions will be recorded. Response assessment following CT examination (CR, PR, SD, PD). MRI scan for patients allergic to x-ray contrast.
QoL	**Part B only:** • FACT-Lym to be completed by the patient
Tumour tissue biopsy (new tumour tissue biopsy at relapse and/or disease progression	• To assess CD37 expression in tumour. • Genomic biomarkers. Gene expression analysis (DNA, RNA, proteins) to evaluate the relationship between the anti-tumour activity and NHL-related genes. This is subject to separate patient informed consent. • FFPE tumour tissue biopsy to be sent to CCLS for biobanking
Survival status	Survival status if patient has already relapsed.

9.6.3.2.2 Follow-up – after 12 months

Until disease progression or further anticancer treatment

For patients without disease progression or further anticancer treatment at Month 12, extensive follow-up (hospital visits) will continue every 6 months for up to 5 years after the Betalutin dose.

Assessment or Procedure	**Explanation**
Month 18, 24, 36, 48, 60	
(Serious) ADR	Any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) since last visit should be recorded
Adverse events of special interest	Adverse events of special interest should be recorded on the SAE record.

Cancer related treatment	Record if the patient has received any cancer-related treatment excl. analgesics since last visit
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest, lymph nodes). Presence of B-symptoms. Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE
Vital signs	Pulse rate, blood pressure, body temperature
Haematology	Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Biochemistry	Including sodium, potassium, calcium, creatinine, uric acid, BUN, ALP, AST, ALT, LDH, gamma glutamyl transferase, glucose, total bilirubin, albumin
Performance status	WHO Performance Status
Immunogenicity	• To monitor the ADA response. • Only to be done if positive ADA test at Month 12 visit. • Should continue to do immunogenicity sampling every 6 months until negative ADA test result is obtained.
CT scans with contrast or MRI scan	CT of neck, thorax, abdomen and pelvis. Response assessment following CT examination (CR, PR, SD, PD). MRI scan for patients allergic to x-ray contrast.
Tumour tissue biopsy (new tumour tissue biopsy at relapse and/or disease progression	• To assess CD37 expression in tumour. • Genomic biomarkers. Gene expression analysis (DNA, RNA, proteins) to evaluate the relationship between the anti-tumour activity and NHL-related genes. This is subject to separate patient informed consent. • FFPE tumour tissue biopsy to be sent to CCLS for biobanking

After disease progression or start of further anticancer treatment

After disease progression has occurred or other anticancer treatment has started (whichever comes first), limited follow-up only will be performed every 6 months for up to 5 years after the Betalutin dose.

Unless blood sampling is required for ADA, these visits can be performed by telephone.

Months 18, 24, 36, 48, 60	
(Serious) ADR Adverse events of special interest (AESI)	Any AESI and any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) ongoing at last visit or occurring since last visit should be recorded
Cancer related treatment	Record if the patient has received any cancer-related treatment excluding analgesics since last visit
Immunogenicity	• To be done if positive ADA test at Month 12 visit • Should continue to do immunogenicity sampling every 6 months until negative ADA test result is obtained.
Survival status	Survival status

10 PHARMACOKINETICS AND BIODISTRIBUTION

Pharmacokinetics *in vitro* assessments and biodistribution using SPECT/CT scans (if feasible)

will be performed in all arms in Part A phase I for 3 patients in each dose level. Dosimetry measurements by use of whole-body and SPECT/CT scans will be performed on up to 3 patients in each dose level in phase I, if feasible. Patient fixation will be done before the first gamma scan.

In Part A (phase IIa), Part B (FL phase IIb) and Part C (Pharmacokinetic Cohort), pharmacokinetic and SPECT/CT assessments will be performed at a subset of sites.

The Schedules of Assessments are shown in Table 6-6 (Part A) and Table 6-9 (Part B and Part C).

10.1 Pharmacokinetics

10.1.1 Blood Clearance

10.1.1.1 Schedule

Part A (phase I and phase IIa)

The number of samples for assessment of blood clearance will depend on whether the patient is going to be included in the serial whole body study or not. The patients not participating in the serial whole body study are allowed to leave the hospital about 2 hours after Betalutin injection, and therefore the number of samples will be reduced. The sampling for these patients will be at the following time points after Betalutin administration: 0, 5, 60 and 120 minutes, 24 hours, and 2, 3, 4, 7 (±1), 14 (±2) and 21 (±2) days. Blood samples will be assessed for the presence of lilotomab, Betalutin, ^{177}Lu and ^{177}Lu-satetraxetan. The time points mentioned are approximate time points. The exact time point the sample is taken need to be recorded in the eCRF. The sampling at day 3 will be optional, since it is the only test to be taken that day. The blood for analysis at Day 14 and 21, will be taken from the blood used for the biochemistry/haematology analyses, when feasible. These blood samples will be taken and might be analysed at the local hospitals, and can therefore be difficult to obtain.

Each 3-patient group will be analysed continuously and adaptation of the sampling times may became necessary depending on the results.

Whole blood samples will be shipped to the laboratory at Nordic Nanovector ASA (Oslo), for analyses. The radioactivity in whole blood will be determined from each sample.

Part B (FL phase IIb) and Part C (Pharmacokinetic Cohort phase IIa)

Pharmacokinetics *in vitro* assessments will be performed only **at selected sites only**, for a subset of patients (see Table 6-9).

Sampling of peripheral blood samples will be performed at selected time points (see below).

The time points mentioned are approximate time points, with time windows show in Table 6-9. The exact time point when the sample is taken needs to be recorded in the eCRF. Each patient group will be monitored continuously and adaptation of the sampling times may become necessary depending on the results.

10.1.1.2 In Vitro Assessments

Betalutin Pharmacokinetics - Total radioactivity or Total payload in blood

The total radioactivity per mL of peripheral blood will be measured to assess the presence of Betalutin^{177}Lu-satetraxetan chelate, ^{177}Lu-DTPA chelate and ^{177}Lu in the blood. It is not

expected to observe free ^{177}Lu in blood samples due to its high binding affinity to satetraxetan and diethylenetriaminepentaacetic acid (DTPA). DTPA is included in the Betalutin formulation in order to chelate the ^{177}Lu not radiolabelled to satetraxetan lilotomab. ^{177}Lu-DTPA chelate has a fast renal clearance [30], [57], [58].

In **Part A** of the study, a volume of at least 1.5 mL will be collected on ethylenediaminetetra-acetic acid (EDTA) or heparin at each agreed time point (see Table 6-5 and Table 6-6). An exact volume of 1 mL of peripheral blood will be transferred on-site into a radio-immune assay (RIA) tube and shipped to Nordic Nanovector ASA (Oslo, Norway) for radioactivity measurement. At Day 14 and 21, the peripheral blood sample of 1 mL used for the radioactivity measurement will be collected from the biochemistry or haematology collection tube when feasible.

In **Part B and Part C** of the study, a volume of approximately 2 mL of peripheral blood will be collected on EDTA in a dedicated collection tube at each agreed time point (see Table 6-9 and below). An exact volume of 1 mL of peripheral blood will be transferred on-site into a RIA tube. Radioactivity measurement will be performed at Nordic Nanovector ASA (Oslo, Norway).

Sampling of peripheral blood for Betalutin PK (radioactivity) will be performed at the following time points:

- Before lilotomab administration (baseline)
- After Betalutin administration:
  - 5 (±2), and 60 (±10) minutes.
  - Hours: 2 (±15 minutes), 24 (±4 hours), 48 (±24 hours) and 96 (±24 hours).
  - Days: 7 (±1 day), 21 ±2 days), 28 days (±2 days) and 35 (±2 days).

The time points mentioned are approximate time points. The exact time point when the sample is taken needs to be recorded in the eCRF. Each patient group will be monitored continuously, and adaptation of the sampling times may become necessary depending on the results.

Instructions for handling procedures, preparation, storage and shipping of the peripheral blood samples will be provided in the Betalutin pharmacokinetics laboratory manual prepared by Nordic Nanovector ASA (Oslo, Norway) for this study.

The total radioactivity per mL of blood will be determined from each sample.

Total lilotomab antibodies in serum (Total antibodies PK, Part B and Part C)

In Part B and Part C of the study, a volume of approximately 4 mL of peripheral blood will be collected in a dedicated serum tube at each agreed time point (see Table 6-9 and below). Serum samples will be isolated, aliquoted and frozen in cryovials at -20°C on-site until shipment on dry ice the day after collection to the Covance Central Laboratories (Geneva, Switzerland for non-United States (US) patients and Indianapolis, Indiana for US patients), where they will be biobanked for future use. Measurement of total circulating antibodies in serum (lilotomab, lilotomab satetraxetan, and Betalutin) will be performed by ELISA.

Sampling of peripheral blood for measurement of circulating antibodies in serum (concentration) will be performed at the following approximate time points:

- Before lilotomab administration (baseline)

- After lilotomab administration:
  - Minutes: 5 (±2), 30 (±5), and 60 (±10) minutes
  - Hours: 2 (±15 minutes).
- After Betalutin administration:
  - Minutes: 5 (±2), and 60 (±10) minutes
  - Hours: 2 (±15 minutes), 24 (±4 hours), 48 (±24 hours) and 96 (±24 hours).
  - Days: 7 (±1 day), 21 ±2 days), 28 days (±2 days) and 35 (±2 days).

The time points mentioned are approximate time points. The exact time point when the sample is taken needs to be recorded in the eCRF. Each patient group will be monitored continuously, and adaptation of the sampling times may become necessary depending on the results.

Instructions for handling procedures, preparation, storage and shipping of the serum samples will be provided in the Covance laboratory manual for this study.

10.1.2 Urine Clearance (Part A)

In **Part A**, phase I, Arm 1, spot samples of urine will be measured for total radioactivity after Betalutin injection at Days 1, 4, 7, and 28 for 3 patients in each dose level, if feasible (see Table 6-6).

In **Part A**, phase I, Arms 2, 3, 4, 5 and phase IIa (optional), urine collection will be performed when feasible during the first 24 hours after Betalutin injection. The first void will be collected separately. Spot samples of urine will be collected after the first whole-body scan e.g. 2 to 4 hours after Betalutin injection, and to the next whole-body scan 24 hours after Betalutin injection (see Table 6-6). The time points for urine collection are approximate time points. The exact time point the sample is taken need to be recorded in the eCRF.

An exact volume of 1 mL of urine will be transferred on-site into a RIA tube and shipped to Nordic Nanovector ASA (Oslo, Norway) for radioactivity measurement. The total radioactivity per mL of urine will be determined from each sample.

Assessment of total radioactivity in urine is not included in the Part B or Part C.

10.2 Biodistribution (dosimetry) Measurements Part A (phase I and phase IIa) and Part B (sites in Germany and in other agreed sites only)

The procedure such as measurements and scanner may differ at study centres. A separate biodistribution and dosimetry manual will be made. The text in this section is provided as a guidance.

The purpose of this part of the study is to provide estimates for the absorbed radiation dose to normal body structures as well as to tumours that can be identified in the images. In order to perform such estimates, it is necessary to measure, in absolute terms, the (radio-) activity in the actual organs at different times after injection. Such time series enable one to estimate the cumulative activity in each organ and by measurements/estimates of organ weight the absorbed dose.

The measurements will be performed on a SPECT/CT scanner containing 2 gamma camera heads (Siemens SYMBIA –T16) equipped with medium energy collimators. This equipment will be used for CT, SPECT, and whole-body scanning. Two (2) separate energy windows positioned over the photon energy peaks at 113 keV and 208 keV with 15% window widths will be used. Since the upper (photon energy) peak is the most intense (11% of disintegrations) one may end up with using only one energy window at 208 keV. This will enable simultaneous acquisition in 2 energy windows, one above and one below the highest photon energy peak. The corresponding images will then be used to estimate and correct for the influence of scattered radiation. These settings will be used both for whole-body scans and for SPECT. Quantification will be carried out partially by use of the software of the vendor and partially by the use of computer programs (IDL, ITT visual solutions) that are available in the hospital. A small plastic flask containing <70 MBq of ^{177}Lu will be used as radioactivity standard in the biodistribution study.

The sensitivity (counts/MBq min) obtained with the planned whole-body scanning speed and with the actual collimator, energy window etc., will be established by the use of a source of known activity (^{177}Lu) in a petri-dish.

In order to cover the entire length of the patient, whole-body scan is the only feasible way. An anterior and a posterior camera will acquire images simultaneously, and the attenuation corrected conjugated view technique reported earlier will be applied (34).

There are 2 sources for acquiring attenuation data for whole-body scans: scanning with a ^{99m}Tc line source before administration of activity to the patient or by calculating the necessary attenuation from CT images (34). In the present series of measurements both of these methods will supplement each other – using CT data were available in the main trunk. The collimated line source is positioned on the posterior gamma camera head and moves together with the scanning camera head.

Patient fixation is important, and a thin vacuum mattress will be used to ensure reproducible patient pose on the examination table. Nevertheless, based on earlier experience, the computer program (in-house development, IDL, ITT visual solutions) performs an image correlation to determine any shift and correct the images accordingly. The computer program performs the conjugated view calculation and attenuation correction and is designed such that regions may be drawn into a (conjugated view) whole-body image and be automatically reproduced in all the other conjugated view whole-body images.

In designing the quantification scheme, it is assumed that a whole-body scan has the advantages of producing a good overview of the activity distribution with less noise than is associated with a SPECT study. A SPECT study that should always be performed together with a CT to allow for attenuation correction will lead to increased patient radiation dose. It is therefore the intention in this study to use whole-body scans as the basis means for following the activity as a function of time for selected organs and if possible for tumours, and SPECT studies where a 3D delineation of an organ or a tumour is needed

SPECT/CT examination of the (thorax or abdominal) region will be performed to obtain the cross-sectional data needed to estimate organ volumes. The CT part will also be used to correct for photon attenuation (refer to paragraph on attenuation correction above). Especially the SPECT examination may be influenced by photons scattered to different energies and directions inside the patient. A triple energy window technique (if feasible) will be used to reduce the influences on quantification.

For Arm 1 (phase I); 3 patients at the first dose level (10 MBq/kg) as well as one patient in the 20 MBq/kg dose level, serial planar whole-body scans were acquired at 2, 4, 8, and 20 hours, and on Days 4 and 7, including SPECT/CT images at Days 4 and 7. For Arm 2 (phase I); serial planar whole-body scans were acquired at 2 hours, 20 hours, and on Days 4 and 7, including SPECT/CT images at Days 1, 4 and 7. For Arms 3, 4 (phase I) and 5, serial whole-body scans will be acquired ~2 hours after dosing, at 24 hours and Days 4 and 7. A window of ±1 day is permitted for Day 4 SPECT/CT scans.

Three (3) patients at the different dose levels for different pre-treatment regimes will be included in the biodistribution study if feasible.

For patients enrolled in **Part A** phase IIa, if the study site has the equipment and intends to conduct dosimetry, serial planar whole-body scans will be obtained on Days 0, 1, 4, and 7, including SPECT/CT images at Days 1, 4, and 7. Conducting a SPECT/CT scan is preferable on Day 0 as well. SPECT/CT examination of the thorax and abdominal region will be performed. If the study site does not intend to conduct dosimetry assessments only SPECT/CT images at Day 4 will be conducted.

For patients enrolled in **Part B** (FL phase IIb) **via sites in Germany** and in other agreed sites, SPECT/CT images will be made on Days 0, 1, 4 and 7.

Full details of the scans required are provided in the dosimetry protocol.

Together these images will enable characterisation of the biodynamics and on that basis the calculation of the cumulative activity in each organ. Dose estimates will be obtained by the use of the OLINDA program which is available at the hospital.

More specifically the conjugated whole-body studies and the quantification in regions drawn around each organ together with assay of activity in blood will be done. It includes 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 time point after injection.
- Estimate retention of administered radioactivity in blood.
- Calculation of estimated absorbed radiation dose to target organs and possibly to tumours.

11 BIOMARKERS

11.1 CD37 Expression in Tumour Biopsies

Expression of CD37 will be assessed using tumour tissue biopsy immunohistochemistry (IHC). A patient may be enrolled without waiting for confirmation of histological diagnosis on the condition that pathological materials are known to be available for review. Either an archival FFPE tumour tissue block if the tissue biopsy is <2 years old or a new tumour biopsy will be requested to be collected at screening. In specific cases, tumour tissue biopsies collected within a 2-5 year time frame could be accepted pending Sponsor approval. Alternatively, a new tumour biopsy will be taken for CD37 expression after the patient's informed consent to participate in the study. The result of the analysis is not required for enrolment into the study.

A new tumour tissue biopsy is to be collected at relapse and/or disease progression (this is dependent on the availability of a suitable lesion and the patient's willingness to have a further biopsy).

In **Part A**, the FFPE blocks or 5 µM slides will be sent to the pathology department of the Radium Hospital (Oslo, Norway) for IHC analysis. There will be no biobanking of dedicated FFPE block for future use.

In **Part B and Part C**, the FFPE blocks (or 5 µM slides – see below) will be sent to Covance Central Laboratories, where they will be biobanked for future use. If a tumour block is provided, it will be returned to the hospital upon request. If the site can only provide 5 µM FFPE slides, preparation of such slides should occur only upon sponsor request to ensure integrity of the biomaterial for the relevant assessments.

Instructions for handling procedures, preparation, storage and shipping of the biological material will be provided in the laboratory manual for this study.

The results of these analyses will be reported to the clinical study database.

11.2 Genomic biomarkers (Part B only)

Subject to separate patient informed consent, tumour tissue biopsies (archival tumour tissue biopsies or newly tumour tissue biopsies collected at screening and subsequently at relapse or progression) will be collected for the purpose of cancer related gene expression. The biopsies will be used to identify predictive biomarkers for Betalutin treatment (48, 49).

Additionally, at screening visit and subject to separate patient informed consent, an approximate volume of 2 mL of peripheral blood sample will be collected to perform HLA class I and II haplotype, to further understand the anti-tumour T-cell response and why a patient may develop an ADA response towards lilotomab/Betalutin (41, 42), respectively.

The results of these analyses are not required for enrolment into the study and will not have impact on patient management - but could be published in scientific journals.

Instructions for handling procedures, preparation, storage and shipping of the biological material will be provided in the laboratory manual for this study.

11.3 Biobanking

The patient will be asked to contribute samples in accordance with this clinical trial and allow part of the available tumour biopsy samples (archived or newly obtained) and peripheral blood sample to be biobanked for future use including but not exclusive to genomic biomarkers expression analysis (DNA, RNA, protein) and other biomarkers.

Biobanking of the biological samples for future use will be performed at Covance Central Laboratories in Indianapolis, Indiana for US patients; in Singapore for patients in Asia/Australia) and in Geneva, Switzerland for all other patients. Analysis of samples will be undertaken by an accredited laboratory either in the EU or USA. Any samples remaining after the end of the clinical trial will be destroyed. If a tumour block is provided, it will be returned to the hospital upon request.

12 EFFICACY ASSESSMENTS

Contrast enhanced CT and PET/CT scans will be evaluated at the study centre(s).

For **Part A (phase I and phase IIa)**, tumour response will be determined by investigator assessment. Cheson criteria Versions 1999 and 2007 will be applied (35, 36).

For **Part B (FL phase IIb) and Part C (Pharmacokinetic Cohort)**, investigator assessment will initially be applied as a measure for assessment of tumour response and any urgent patient management decisions. Tumour response will also be determined by independent central review and this assessment used as a basis for all protocol guidelines for management of the patient related to disease progression status. In presence of disease progression per investigator assessment, tumour assessments should continue until disease progression is documented by independent central review, unless an urgent patient management decision is required. All urgent patient management decisions will be documented. Cheson criteria Version 2014 will be applied (40).

12.1 Timing of Assessments and Imaging Modalities

12.1.1 Contrast Enhanced CT Examination

A baseline contrast-enhanced CT scan must be performed within 4 weeks prior to first rituximab infusion. Table 6-5, Table 6-7 and Table 6-8, shows the frequency of subsequent contrast-enhanced CT scans per patient for follow-up.

A CT volume scan re-constructed **in up to 5 mm slides** with use of intravenously injected contrast agent will be performed per examination. The target lesions will be selected and measured at baseline, and followed at each efficacy assessment. The longest perpendicular diameters (major and minor axis) will be recorded in the eCRF.

12.1.2 MRI Examination

For patients unable to receive a contrast-enhanced CT scan due to allergy, a MRI examination is permitted.

12.1.3 PET/CT Examination

The term ‘PET/CT imaging’ refers to PET imaging - which is typically undertaken on a combined PET/CT scanner.

PET/CT imaging will be done at baseline, 3 (Week 12) and 6 months after Betalutin administration for all patients. Baseline imaging must be performed within 4 weeks prior to administration of rituximab infusion. At these timepoints, both a PET scan and a separate contrast-enhanced CT scan (or MRI for those patients allergic to contrast) are to be undertaken. The same combined machine can be used if the CT scanner is a diagnostic quality CT scanner. At subsequent timepoints (Month 9 onwards), only a contrast-enhanced CT scan (or MRI) is required.

Standard institutional guidelines will be followed. The patient must have fasted for 6 hours prior to PET/CT imaging, water is allowed. For patients with known hyperglycaemia or diabetes, the blood glucose level must be < 11 mmol/L before injection of ^{18}Fluorodoxyglucose (FDG). Anti-diabetic drugs cannot be taken on the day of PET/CT examination.

PET/CT examination will be performed by a commercial combined PET/CT scanner. All scans should be performed on the same camera. PET/CT imaging will be performed about 60 to 70 minutes after intravenous administration of 5 to 10 mCi (185 to 370 MBq) of FDG. Same activity +/- 20% and time window must be used in the subsequent PET scans.

PET/CT scans will be done before contrast enhanced CT (or MRI for patients unable to receive contrast) when both modalities are to be done on the same day.

All measurements of uptake will be based on standardised uptake (SUV) values. Lesions <15 mm in short axis with abnormal activity: focal, above the surrounding background, above average liver SUV.

Guidelines for baseline CT examination:

1) Target lesions on the CT scans do not need to match those evaluated on the PET scan.
2) Target nodes should be chosen according to applicable Cheson criteria, see Section 12.2.
3) Approximately 6 target nodes should be selected; there must be at least one target node.
4) The largest target nodes should be selected.
5) Nodes should be from different body regions if possible.
6) Mediastinal and retroperitoneal nodes should be included as target nodes if involved.
7) A measurable node must have a longest diameter (Ldi) greater than 1.5 cm.
8) A measurable extranodal lesion should have an Ldi greater than 1.0 cm.

Guidelines for baseline PET examination:

1) Target lesions on the CT scans do not need to match those evaluated on the PET scan.
2) The lesions with the highest activity level should be chosen for the PET scan.

Part A: Selection of lesions for follow-up PET.

"Modified ECOG criteria":

1) Only sites of abnormality at baseline are evaluated.
2) All positive nodal sites must have an anatomic correlate.
3) Activity in lung, bone/bone marrow, liver and spleen is considered abnormal only if focal and clearly discernible.
4) New foci are considered positive only if they are associated with a lesion on CT.

12.2 Definitions of Tumour Response Criteria: Part A (phase I and phase IIa)

For **Part A**, tumour response will be determined by investigator assessment. Cheson criteria Versions 1999 and 2007 will be applied (36).

For the 3 month evaluation, the PET is used for the response assessment.

In case of CR, repeat a bone marrow biopsy if the patient had a positive bone marrow biopsy at screening.

For the 6 month assessment, the PET is NOT used for evaluation of (possible) progressive disease; only the CT scan should be used for PD.

12.2.1 Part A Response Criteria I; using CT only per Cheson 1999

The response criteria used is defined in Cheson et. Al. 1999 (35) were used for all CT examinations.

- Complete remission (CR)

  Disappearance of all disease-related symptoms and measurable lesions, including normalisation of other abnormal initial parameters (if any) such as biochemical abnormalities definitely assignable to lymphoma (e.g. S-LDH), X-rays and bone marrow. All lymph nodes must have regressed to ≤1.5 cm in their largest transverse diameter and to ≤1.0 cm for those nodes which were 1.1 to 1.5 cm before treatment.

- Complete remission unconfirmed (Cru*)*

  The criteria of a CR are fulfilled, except that residual lymph node(s) mass greater than 1.5 cm have regressed by more than 75% in the SPD in all measurable and evaluable lesions. A Cru should when possible be assigned to a CR or PR by histological examination.

- Partial remission (PR)

  Decrease of at least 50% in the SPD of the six largest dominant nodes or nodal masses (should be clearly measurable in at least 2 perpendicular dimensions, be from disparate body regions and include mediastinal and retroperitoneal areas of disease whenever these sites are involved). There should be no increase in the size of the other nodes, liver, or spleen. Splenic and hepatic nodules must regress by at least 50% in the SPD. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease. No new lesions appearing.

- No Change/Stable disease (SD)

  The patient does not qualify for complete (CR) or partial remission (PR) or progressive disease (PD).

- Progressive disease (PD)

  ≥50% increase from nadir in the SPD of any previously identified abnormal node or the occurrence of new lesions.

12.2.2 PET/CT Score

PET is scored on a 5-point scale, and follow-up will be assessed as described below. In addition, SUV_{max} will be recorded, and lean body mass $(SUL)_{max}$ is optional. In case of discrepancy between the criteria below and SUV_{max}/SUL_{max} the investigators will be involved in decision making.

Images will be evaluated and scored according to a 5-point scale (5PS). The PET/CT scans will be scored with reference to sites of presumed lymphomatous involvement on the PET/CT staging scan (Deauville criteria).

Negative

1 no uptake

2 uptake ≤ mediastinum*

3 uptake > mediastinum but ≤ liver*

NOTE if mediastinal blood pool activity is equal or greater than liver then the uptake within the lesion should be compared with liver (lesion uptake less than liver=score 2; lesion uptake equal to liver=score 3)

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

Mediastinal and liver uptake is defined as SUV_{max} +/-10%

Consider binary response scale for lung, bone/bone marrow, liver and spleen involvement.

12.2.3 Part A: Response Criteria II including PET/CT Imaging

Responses will be categorised as complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD) according to Cheson 2007 (36).

- Complete remission (CR)

  Disappearance of all evidence of disease

  - Nodal Masses:
    (a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative.
    (b) Variably FDG-avid or PET negative; regression to normal size on CT.
  - Bone marrow: Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative.

- Partial remission (PR)

  Regression of measurable disease and no new sites

  - Nodal Masses: 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes.
  - FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site.
  - Variably FDG-avid or PET negative; regression on CT.
  - Bone marrow: Irrelevant if positive prior to therapy; cell type should be specified.

- Stable disease (SD)

  Failure to attain CR/PR or PD

  - Nodal Masses:
    (a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET.
    (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT.

- Progressive disease (PD)
  - Any new lesion or increase by 50% of previously involved sites from nadir.

- Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node >1 cm in short axis.
- Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy.

12.3 Definitions of Tumour Response Criteria: Part B and Part C

For **Part B and Part C**, investigator assessment will initially be applied as a measure for assessment of tumour response and any urgent patient management decisions. Tumour response will also be determined by independent central review and this assessment used as a basis for all protocol guidelines for management of the patient related to disease progression status, wherever possible. In presence of disease progression per investigator assessment, tumour assessments should continue until disease progression is documented by independent central review, unless an urgent patient management decision is required. All urgent patient management decisions will be documented. Cheson criteria Version 2014 (40) will be applied (see Table 12-1).

Table 12-1 Criteria for Tumour Response Evaluation

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	**Complete metabolic response**	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS (**Section 12.2.2**). It is recognised that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤1.5 cm in Ldi No extralymphatic sites of disease.
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	Partial remission (all of the following):
Lymph nodes and extralymphatic sites	Score 4 or 5 (**Section 12.2.2**) with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease At end-of-treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm×5 mm, but smaller than normal, use actual measurement for calculation

Response and Site	PET-CT-Based Response	CT-Based Response
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or stable disease	**No metabolic response**	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 (**Section 12.2.2**) with no significant change in FDG uptake from baseline at interim or end-of-treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	Progressive disease requires at least 1 of the following PPD (individual product of the perpendicular diameters) progression:
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 (**Section 12.2.2**) with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: Ldi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in Ldi or Sdi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g. a 15-cm spleen, must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions

Response and Site	PET-CT-Based Response	CT-Based Response
New lesions	**New FDG-avid foci** consistent with lymphoma rather than another aetiology (e.g. infection, inflammation). If uncertain regarding aetiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis, if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

13 SAFETY ASSESSMENTS

The time points for all assessments are shown in the Schedule of Assessments tables (Section 6.3). AEs will be graded and recorded throughout the study according to the National Cancer Institute CTCAE Version 4.0 or later, as applicable. Safety endpoints will include all types of AEs in addition to laboratory safety assessments and vital signs.

13.1 Adverse Events: Definitions

13.1.1 Definition of Adverse Event

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical condition(s) that occur after the patient's signed informed consent has been obtained.

An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they:

- induce clinical signs or symptoms, or
- are considered clinically significant, or
- require therapy (e.g. transfusion) or
- require changes in medications.

Laboratory abnormalities that meet the criteria for AE should be followed until they have returned to normal. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring, and should not be reported as adverse events.

Progression of underlying malignancy should not be reported as an AE, unless the investigator considers that the study drugs contributed to lymphoma progression (by a means other than lack of effect). AEs separate from the progression of malignancy (e.g. deep venous thrombosis

at the time of progression) should be reported as per usual guidelines with proper attribution regarding relatedness to study treatment.

Each event will be evaluated by the investigator for clinical significance, severity and CTCAE grading, and should be recorded in the eCRF. AEs will be assessed according to the CTCAE Version 4.0 or later as applicable. The following information should be recorded:

- Whether the event is serious or non-serious
- Relationship to study drug
- Severity of the event
- Onset date and time
- Resolution date and time, or date and time of death
- Action taken
- Outcome of the event

13.1.2 Definition of Adverse Drug Reaction

An ADR is all untoward and unintended responses to IMP related to any dose administered.

All AEs judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to an IMP qualify as ADRs. The expression 'reasonable causal relationship' means to convey in general that there is evidence or argument to suggest a causal relationship.

13.1.3 Definition of Serious Adverse Event

A **serious adverse event (SAE)** is defined as one of the following:

- Results in death (excluding deaths due to disease progression). The reported AE should be the AE that caused the death..
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing inpatients' hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is medically important, i.e. defined as an event that jeopardises the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.
- Constitutes a congenital anomaly/birth defect.

Life-threatening in the definition of a SAE refers to an event in which the patient was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe. Medical judgment should be exercised in deciding whether an AE/ADR is serious in other situations.

Hospitalisation for elective surgery or surgery which takes place during the reporting period but was planned prior to enrolment is not to be reported as an SAE (unless the reason for surgery or any complications during or after surgery fulfil any other of the seriousness criteria).

13.1.4 Definition of Unexpected Adverse Drug Reaction

An unexpected ADR is an ADR of which the nature or severity is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an authorised product i.e. the Investigator's Brochure for Betalutin or the approved product information (prescribing information) for rituximab). When the outcome of the ADR is not consistent with the applicable product information this ADR should be considered as unexpected. Reports must also be considered as unexpected if they add significant information on the specificity or severity of an expected ADR.

The expectedness of an AE/ADR will be determined by the Sponsor.

13.1.5 Suspected Unexpected Serious Adverse Reaction

All suspected ADRs that are considered related to any of the study medication and are both unexpected and serious (meeting the definition of a suspected, unexpected serious adverse reaction [SUSAR]) are subject to expedited reporting. It is the Sponsor who reports the SUSARs, based on information from the investigator, see Section 13.3.1.

13.1.6 Definition of Treatment-Emergent Adverse Event

Treatment-emergent adverse events (TEAEs) are defined as events which occur following the first injection of study treatment, or that started prior to the first injection and worsened during treatment.

13.1.7 Definition of Adverse Events of Special Interest

AESI are defined as events (serious or non-serious) which are of medical concern specific to Betalutin, for which ongoing monitoring and rapid communication by the investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterise them. One potential risk for Betalutin is that as an antibody-radionuclide-conjugate, it may over long-term induce secondary malignancies, including MDS, acute leukaemia and others.

During the protocol-mandated follow-up visits, the development of secondary malignancies, myelodysplastic syndrome, acute leukaemia or aplastic anaemia will be assessed by the investigator. These events will be recorded as SAEs.

AESIs are defined on the basis of an ongoing review of the safety data, and are reflected in the Investigators Brochure.

13.1.8 Assessments of Adverse Events; Seriousness, Causality, and Severity

Each individual AE should be evaluated by the investigator with regard to date of onset, its seriousness, severity, and duration, causal relationship to the IMP and/or concomitant therapy and outcome.

Seriousness will be determined according to the definitions in Section 13.1.3.

Causality will be determined for all AEs. All AEs judged as having a reasonable suspected causal relationship to an IMP qualify as ADRs (as defined in Section 13.1.2).

In the eCRF the investigator's opinion of the relationship of the AE(s) to the IMP, will be categorised as unrelated, possibly or probably related, as defined below.

Unrelated: An AE which after careful examination at the time of evaluation, is judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under possible or probable.

Possible: An AE which after careful examination at the time of evaluation, the connection with the IMP administration cannot be ruled out.

Probable: An AE which after careful examination at the time of evaluation, the connection to the IMP administration appears, with a high degree of certainty, to be related to the IMP

In addition to the investigator's own description of the AE, each AE will be encoded by Sponsor's representative, according to the Medical Dictionary for Regulatory Activities (MedDRA).

Severity: The term "severe" is used to describe the intensity (severity) of a specific event. Note that it is not the same as "serious", which is based on patient/event outcome or action criteria.

The severity of all events will be graded according to the CTCAE Version 4.0 (or later, as applicable) by the investigator. For events not listed in the toxicity table, severity should be recorded as:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.2 Reporting of Adverse Events

Any AEs that occur after a patient has signed the Informed Consent Form and up to 12 weeks after Day 0, must be reported, whether or not it is considered related to any of the study medications.

After 12 weeks post last administration of study treatment, only new onset AESIs, and study treatment-related AEs and SAEs must be reported when they come to the investigator's attention.

All AEs will be reported in the patient eCRFs. If more than one AE occurs, each event should be recorded separately. AEs and/or laboratory abnormalities shall be reported to the Sponsor

according to the reporting requirements and within the time periods specified in the protocol. All AEs will be followed up until resolved or as clinically required.

Specific information about secondary malignancies such as leukaemia, MDS and aplastic anaemia or any other malignancy, will be collected up to 5 years after study medication administration or relapse of disease, including information about treatment given to the patient due to NHL. See also paragraph on Adverse Events of Special Interest in Section 13.1.7.

Death is not defined as an AE but as an outcome of an AE. It is important that the event leading to the death is reported. If death is the outcome of an AE, it will be reported as such for (i) all AEs regardless of relationship to study treatment up to 12 weeks after the last administration of study treatment and (ii) AESI, and study treatment related AEs and SAEs with onset >12 weeks after the last administration of study treatment.

Progression of disease:

- **Part A:** Progression of disease will be reported as an AE until Week 12. Thereafter progression of disease will be recorded in the eCRF and still used as an efficacy endpoint. It will be the SRC who will decide if a fatal outcome of disease progression should be considered as an expected AE. This will depend on the information received and medical consideration.
- **Part B and C:** Disease progression is not reported as an AE if it is clearly consistent with the suspected progression as determined by the protocol. Hospitalisation due solely to disease progression should NOT be reported as a SAE. Any associated symptoms may be reported as adverse events if there is any uncertainty about the symptom being exclusively due to disease progression, or if it does not fit the expected pattern of progression of the disease.

AEs due to rituximab injection: Rituximab infusion is given once prior to Betalutin injection, and AEs due to rituximab could happen. The expected AEs with rituximab are described in the package insert for rituximab. This should be taken into consideration when reporting an AE.

AEs may be reported spontaneously by the patient or elicited through open (nonleading) questioning during each visit to the study centre and at the end of the AE follow-up.

As far as possible, all AEs must be described by their duration (start and stop date), severity (graded according to the CTCAE Version 4.0, or later as applicable), relationship to treatment (unrelated, possible, probable), according to the need of other specific therapy, and outcome. All information will be recorded in the AE eCRF page.

A baseline recording of any symptoms of illness will be performed prior to start of study treatment. Only symptoms that increase in severity throughout the treatment period or new symptoms of illness will be recorded as AEs in the eCRF.

13.3 Reporting of Serious Adverse Events

13.3.1 Investigator's Responsibilities

The investigator shall report all SAEs, regardless of suspected causality, immediately (within

24 hours of the investigator becoming aware of the event) to the Sponsor or assigned designee. The immediate report shall be followed by detailed written report(s).

SAEs will be reported in the following time periods:

- SAEs will be collected from signing informed consent to ensure that any protocol-related SAEs are collected.
- Up to 12 weeks after the last administration of study treatment, whether or not considered related to IMP.
- At any time after 12 weeks after the last administration of study treatment when it comes to the investigator's attention and is judged to be related to the patient's participation in the study or related to IMP.

Any SAEs experienced after this 12 week period should only be reported to the Sponsor or assigned designee if the investigator suspects a causal relationship to the study treatment, or if it is an AESI (see Section 13.1.7). Recurrent episodes, complications or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

All SAEs must be reported to Sponsor or assigned designee as follows:

1. Immediately (within 24 hours of discovery of the event) report the event by email, telephone or fax.
2. Complete the SAE report form and send within 3 working days of the discovery of the event.
3. Follow-up the SAE until resolved or as clinically required, all follow-up evaluations must be reported.
4. Record the SAE in the patient eCRFs provided.
5. Document the SAE in the hospital records.

It is important to send "as complete as possible" a report within the timelines. Incomplete information must NOT delay reporting of SAEs. Additional information must be reported once it is available; in follow-up reports using the same SAE forms, but marked as a follow-up report. In Part A, SAEs/SUSARs will be reviewed by both the SRC and the Sponsor.

Where applicable as per local requirements, the investigator will inform the Ethics Committee (EC)/Institutional Review Board (IRB) of the SAE. For reporting death of a patient, the investigator shall supply the Sponsor and the EC with any additional information requested.

Contact address for reporting SAEs:

PharmaLex Norway AS	Karoline Kristiansens vei 1, 0661 Oslo, Norway
Phone:	+47 22 23 88 80
Fax:	+47 21 01 80 19
Email:	PV-nordic@pharmalex.com

The Investigator is also responsible for reporting the occurrence of a new pregnancy (see Section 16.3.7) and IMP dosing errors (see Section 16.3.6) to the Sponsor or assigned designee within 24 hours.

13.3.2 Sponsor's Responsibilities

The Sponsor or assigned designee is responsible for the ongoing safety evaluation of the IMP.

The Sponsor or assigned designee is responsible for the prompt notification to all concerned investigators, the ECs/IRBs and Competent Authorities where Betalutin studies are ongoing, of all the relevant safety information, including findings that affect the health of the patients, impact on the conduct of the study or alter the Competent Authority's authorisation to continue the study in accordance with Directive 2001/20/EC.

The Sponsor has to keep detailed records of all AEs reported to him by the investigators and to perform an evaluation with respect to seriousness, causality and expectedness. These records shall be submitted to the Competent Authorities in the countries where the clinical study is being conducted, if they so request.

Each individual AE should be evaluated by the Sponsor or assigned designee, with regard to its seriousness and causal relationship to the IMP and/or concomitant therapy. The Sponsor will not overrule the causality assessment given by the investigator. If the Sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the Sponsor will be provided with the report.

The Sponsor will assess whether or not the AE is unexpected.

The Sponsor or assigned designee will inform all investigators of relevant information about SUSARs.

13.4 Other Safety Parameters Including Demographics

13.4.1 Diagnosis and Medical History

A histological diagnosis of relapsed incurable NHL of following subtypes; follicular grade I-IIIA, marginal zone, small lymphocytic, lymphoplasmacytic, or mantle cell is established by the pathologist at the study site for Part A and Part C of the study OR follicular grade I-IIIA for Part B. The proficiency of anti-CD37-antibodies at detecting have been tested against FL samples and shown to be suitable for identifying CD37 positive cells.

In **Part A** of the study, the CD37 detection could be set up locally or the study centres could send slides to Radiumhospitalet, Oslo, Norway for centralised reading. If the staining has been verified using samples of FL, the pathology slides and tissue samples must be stored after reading, and may at a later stage be requested to be sent to Radiumhospitalet, Oslo, Norway for centralised reading.

The anti-CD37-antibodies have been tested against FL samples and shown to be suitable for identifying CD37 positive cells.

In **Part A** of the study, the study centres sent slides to Radiumhospitalet, Oslo, Norway for centralised reading.

For patients enrolling in **Part B and Part C**, tumour tissue will be obtained to assess CD37 expression by the tumour cells. The tumour tissue samples will be sent to an accredited laboratory in the European Union (EU) or US for CD37 testing. The results of the analysis are not necessary for inclusion in the study (with the exception of patients entering in Germany), but will be captured in the eCRF.

A summary of the patient's relevant medical history prior to study inclusion should be recorded on the appropriate eCRF page.

CT with contrast agent will be performed at baseline for identifying the tumour lesions. MRI scans for patients with contrast allergy are acceptable.

A bone marrow biopsy will be taken from a site not previously irradiated to ensure that there are less than 25% tumour cells (this may be taken up to 8 weeks before the rituximab administration).

13.4.2 Physical Examination

Physical examination of the lymph nodes is assessed and an abbreviated physical examination consisting of the heart, lungs, and other physical findings will be done at each hospital visit where the patient meets with the treating physician.

Any physical examination finding that is classified by the investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE/SAE, documented on the patient's eCRF, and followed until the outcome is known. Clinical assessments of lymph nodes are included in the physical examination at all visits, at time points given in Schedule of assessments Table 6-5, Table 6-7 and Table 6-8.

The investigator will also assess the WHO/ECOG performance status at time points given in Schedule of assessments tables in Section 6.3.

Table 13-1 Definition of WHO Performance Status

Grade	WHO*
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982*

Performance status response and progression will be evaluated as:

- Improvement or worsening by 1-point or more on the WHO scale from the baseline value.

13.4.3 Vital Signs

Vital signs (systolic/diastolic blood pressure, heart rate, and body temperature) will be measured as described in the Schedule of Assessments, Section 6.3. Additional vital signs assessments will be done under the investigator's judgment.

Measurement of blood pressure will be done on the arm contralateral to the site of IMP administration.

Both "new" and "worsening" vital sign abnormalities are anticipated in patients over the course of a clinical study. A "new" abnormality is defined as one that occurs when a patient's normal baseline vital signs develop clinically significant values ("notable") post-baseline. A "worsening" abnormality is defined as one that occurs when a patient's "notable" baseline vital signs become worse post-baseline by 25%.

Notable vital signs results should be interpreted in conjunction with the clinical situation of the patient. Once AE/SAE notification is decided upon, the investigator is required to follow the procedure described for AE notification and document the clinically notable abnormality on the AE eCRF page. Any notable abnormal vital signs finding or related AE must be followed until outcome is known.

13.4.4 12-lead Electrocardiogram

A standard 12-lead ECG will be performed as per Schedule of Assessments (Table 6-5 and Table 6-8). Results will be recorded as normal or abnormal; abnormal findings will be described in the eCRF. The ECG will be evaluated by the investigator Additional vital signs assessments will be done under the investigator's judgment.

A copy of the ECG page, signed, dated and interpreted should be stored in the patient file.

13.4.5 Clinical Laboratory Parameters

Blood samples for the determination of biochemistry and haematology parameters will be drawn at pre-specified time points, see Schedule of Assessments, Table 6-5, Table 6-7 and Table 6-8 (Section 6.3).

The following laboratory tests will be performed:

Table 13-2 Clinical Laboratory Parameters

Serum Biochemistry	**Haematology**
Sodium	Haematocrit
Potassium	Haemoglobin
Calcium	Platelets
Creatinine	Red blood cell count
Uric acid	White blood cell count
Urea	Differential
Alkaline Phosphatase (total ALP)	Neutrophils
Aspartate aminotransferase (AST)	Lymphocytes
Alanine aminotransferase (ALT)	Monocytes
Lactate Dehydrogenase (LDH)	Eosinophils
Gamma glutamyl transferase	Basophils
Glucose	Lymphocyte subsets
Bilirubin, total	HAMA test
Albumin	Coagulation – PT/INR and PTT (only Part B and Part C)
Protein electrophoresis (gamma globulin g/L)*	
Quantitative serum immunoglobulins (IgG, IgA and IgM)	

Serum Biochemistry	Haematology
HIV test (only Part B and Part C)*	
Hepatitis C (only Part B and Part C)*	
β-HCG (pregnancy test)**	
Hepatitis B test (HBsAg and anti-HBc)*	

*At screening only
**At screening only; post-dose urine pregnancy tests will also be performed in Parts B and C

Reference ranges from the laboratory will be provided to the Sponsor. If during the study, ranges should be changed, the investigator is requested to provide updated laboratory normal values.

The investigator will interpret all clinical laboratory test results outside the reference range.

Laboratory values outside reference range recorded in the CTCAE, will be graded 1 to 4 according to the CTCAE criteria. The laboratory CTCAE grade will be derived programmatically for the purpose of reporting in the Clinical Study Report.

Investigators will assess abnormal laboratory values or test results occurring after informed consent. Abnormal laboratory results constitute AEs only if they:

- induce clinical signs or symptoms, or
- are considered clinically significant, or
- require therapy (e.g. transfusion) or
- require changes in medications.

Laboratory abnormalities that meet the criteria for AE should be followed until they have returned to normal. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring, and should not be reported as AEs.

The laboratory values might be an SAE if meeting any of the seriousness criteria defined in Section 13.1.3. During the follow-up period only changes in laboratory values judged to be related to IMP will be reported as AEs.

Once AE notification is decided upon, investigators are required to follow the procedure described for AE notification and document the notable laboratory results on the AE eCRF page. Any notable laboratory abnormality or related AE must be followed until the outcome is known.

The signed and interpreted laboratory results will be kept together with the patient's eCRF as supplemental pages at the study centre.

13.4.6 Immunogenicity Assessment

Immunogenicity assessment to monitor the potential development of an anti-drug antibody (ADA) response will be performed before the lilotomab administration and at subsequent timepoints (see Section 13.4.6.2).

13.4.6.1 Part A, Phase I and IIa

In Part A, patients will be monitored locally for the development of ADA after treatment up to 12 months. The sampling for these patients will be at the following time points at screening

visit, and after Betalutin administration: 1, 3, 6, and 12 months (see Table 6-5 and Table 6-7). The exact date point when the sample is taken needs to be recorded in the eCRF.

A volume of approximately 9 mL of peripheral blood will be collected in a serum tube at patient screening. The serum will be collected at each study centre and used to assess the presence of pre-existing ADA (HAMA) locally using the Milenia® QuickLine HAMA test (Milenia Biotec), except for patients screened at the Radium Hospital (Oslo, Norway). In this specific case, the IFMA test will be used. When a positive result is obtained with the Milenia QuickLine HAMA test, a serum sample could be sent to the Radium Hospital for confirmation of the positive result with the IFMA test. Centres in Norway and Sweden may also ship serum samples to the Radium Hospital for further ADA testing, when feasible.

13.4.6.2 Part B FL Phase IIb and Part C Pharmacokinetic Cohort phase IIa

All patients included in Part B and Part C of the LYMRIT 37-01 study will be monitored for the development of ADA after treatment up to 12 months.

The blood sampling for these patients will be at the following time points:

- before lilotomab dose (Day-1/0, baseline), and
- after Betalutin administration: 7 days, and 1, 3, 6, and 12 months (see Table 6-8).
- Additional sampling will be required if a test is found ADA positive at 12 months. Persistence of the ADA response will then be assessed every 6 months until the ADA test is negative [46].

The exact time point when the sample is taken need to be recorded in the eCRF.

A volume of approximately 6 mL of peripheral blood will be collected by venipuncture in a dedicated serum tube at each time point (see above) to monitor the development of an ADA response post lilotomab/Betalutin treatment. Serum samples will be isolated, aliquoted and frozen in cryovials at -20^{0}C at each study centre until shipment on dry ice the day after collection to the central biobanking laboratory at Covance Central Laboratories (Indianapolis, Indiana for US patients and Geneva, Switzerland for non-US patients), where they will be biobanked for future use.

Instructions for handling procedures, preparation, storage and shipping of the serum samples will be provided in the study Covance laboratory manual.

13.4.7 Volume of Blood to be Drawn from each Patient

The total volume of blood that will be drawn from each patient in this study will vary depending on how long the patient stays on study. Table 13-3 and Table 13-4 indicates the range for patients during the treatment period (16 weeks).

Table 13-3 Volume of Blood to be drawn from Each Patient in the Treatment Period – Part A (phase I and phase IIa)

Assessment	Sample Volume (mL)	No. of Samples	Total Volume (mL)
Serum biochemistry/haematology/lymphocytes subset	7 mL	Max 14	98 mL
Pharmacokinetic – Total radioactivity (phase I; optional for phase IIa)	1 mL	Max 17	17 mL
Immunogenicity assessments	9 mL	4	36 mL
Immunoglobulin levels/	5 mL	1	5 mL
Total (maximum volume to be drawn)			156 mL

Max = maximum number of samples to be taken

Table 13-4 Volume of Blood to be drawn from Each Patient in the Treatment Period – Part B and Part C

Assessment	Sample Volume (mL)	No. of Samples	Total Volume (mL)
Serum biochemistry/haematology/ lymphocytes subset	7 mL	Max 14	98 mL
Coagulation parameters	6 mL	2	12 mL
ß-HCG pregnancy test	6 mL	1	6 mL
HAMA test	4 mL	1	4 mL
Pharmacokinetic – Total radioactivity in blood	2 mL (1 mL exactly in assay)	Max 11	22 mL
Pharmacokinetics – Total lilotomab antibodies in serum	4 mL	Max 15	60 mL
Immunogenicity	6 mL	4*	24 mL
HLA haplotyping	2 mL	Max 1	2 mL
Immunoglobulin levels/	5 mL	2	10 mL
Total (approximate maximum volume to be drawn for patient not participating in the PK portion of Part B)			158mL
Total (approximate maximum volume for the patients participating in the pharmacokinetic portion of Part B and all patients in Part C)			240mL

Max = maximum number of samples to be taken; *immunogenicity samples continue at months 6 and 12 – and if ADA positive at month 12, further samples will be required.

13.4.8 Potential Long-term Toxicity

At the follow-up visits the investigator will observe for indications of potential late-toxicity, such as secondary cancers, acute myelogenous leukaemia, myelodysplastic syndrome, and aplastic anaemia. In addition, physical examination will be performed and blood samples for biochemistry and haematology taken. Potential long-term toxicity (new onset AESIs, and study treatment-related AEs and SAEs only with onset >12 weeks after the last administration of study treatment) must be reported according to Section 13.2.

13.4.9 Quality of Life (Part A and Part B)

QoL will be assessed using FACT-Lym (Version 4), which will be completed by the patient. The form will only be used in the countries where they are translated and validated. It is essential to explain to the patient that all parts of the questionnaire should be completed as fully as possible. In order to administer these consistently, the questionnaire will be completed by the patient at the hospital visit.

QoL is not collected from patients entered to Part C.

14 STATISTICAL METHODS AND PLANNED ANALYSES

14.1 Statistical Hypotheses and Tests

14.1.1 Sample Size Calculation – Part A (phase I and phase IIa)

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

For Arm 1: Due to the limited number of patients treated in phase I (six), an interim analysis of the safety and efficacy of lilotomab 40 mg/ Betalutin 15 MBq/kg was performed after 9 additional patients had been treated in phase IIa (total: 15 patients).

The following guide was used for the Arm 1 interim analysis, and the final decision was taken by the SRC:

- If ≥4 DLT in 15 patients -> lower the dose
- If ≤3 DLT in 15 patients -> continue on same dose (or see below)

In addition, response rate will be evaluated for futility:

- If ≥4 responses in 15 patients -> continue on same dose
- If ≤3 responses in 15 patients -> stop for futility (or see below)

It will be opened up for a combined evaluation:

- If ≥4 DLT and ≥7 responses -> lower the dose
- If ≤3 DLT and ≤10 responses -> increase the dose to 20 MBq/kg Betalutin based on the recommendation of the SRC analysis of the observed toxicities.

The decision to continue the dose was made by the SRC. Thirty more patients were planned in Part A, phase IIa for a total of 36 patients at that dose level.

Following a review of the Arm 4 phase I patient safety data by the SRC, approximately 10 to 15 additional patients will be enrolled into a Part A, phase IIa expansion arm and be treated with 20 MBq/kg Betalutin and 100 mg/m^2 lilotomab.

14.1.2 Sample Size and Statistical Hypotheses – Part B (phase IIb) Follicular Lymphoma

14.1.2.1 Randomised Part B - Choice of RP2D

Note - Part B of the study was initiated as a randomised, 2-arm, open-label study to further differentiate the risk/benefit of 2 promising dose regimens of lilotomab and Betalutin. (Protocol Version 11)

In total, up to 130 patients (65 patients per candidate regimen) with FL will be enrolled.

Based on data available at time of Protocol Version 11, a difference of 27% in ORR is expected to emerge between the dose regimens with similar low toxicity profiles. The ORR's assumed

for each group are: 69% for the 40 mg lilotomab+15 MBq/kg Betalutin arm, and 42% for the 100 mg/m^2 lilotomab+20 MBq/kg Betalutin arm.

A sample size of 65 patients per arm should be sufficient to detect this difference, using a two-sided significance level 0.05 with at least 80% statistical power. Sample size estimation was performed using nQuery Advisor V7 (Statsol.com). The method was a 2 group continuity corrected chi-square test for equal proportions (55).

14.1.2.2 Interim Analysis – Part B Randomised

Note - The interim analysis was introduced in Protocol Version 11 and amended in protocol Version 13.

Once approximately 50 patients have been treated (approximately 25 per dose regimen), an interim analysis will be performed on the ORR based on IRC assessment for the study. There is no statistical test of hypothesis in the interim analysis.

In line with its charter, the SRC will review the results of the interim analysis and provide a recommendation to the Sponsor to continue or terminate treatment arms or to perform other modifications based on the totality of safety, efficacy, and other available data (e.g. immunogenicity data). The final decision lies with the sponsor.

The SRC will take into account the following guidelines: if ORR ≥40% in each treatment regimen, the study may complete its targeted enrolment of up to 130 patients, around 65 per arm. If ORR < 40% in either regimen then the regimen with ORR <40% may be terminated. If both regimens have ORR <40%, the study may be terminated for futility or modified. There regimen(s) with ORR ≥40% will proceed to enrol the remaining patients, up to 130 total.

To facilitate decision to keep or drop treatment arms based on ORR rates, the boundary of 40% ORR is non-binding and for guidance only.

The primary efficacy endpoint is overall tumour response rate according to the IRC. Scans will be performed at baseline, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months after Betalutin injection for all patients to assess tumour response (see Section 14.1.7).

Response rates will be presented as a percentage of the Intent-to-Treat (ITT) population with the exact 95% confidence interval (Clopper-Pearson).

14.1.2.3 Part B – Population treated with "40/15" Regimen

Note - At the interim analysis, the SRC decided to discontinue the "100/20" treatment regimen, and continue with further recruitment in the "40/15" treatment regimen only.

A total of 87 patients, including the those from the interim analysis, will be recruited and treated with the "40/15" regimen.

With 87 patients, there will be more than 90% power to detect a difference of 18% in response rates using a two-sided exact test with a target significance level of 0.05, assuming the response rate under the null hypothesis is 30% and the response rate under the alternative hypothesis is 48%. If there are at least 36 responders in 87 patients, then there will be at least 97.5% chance that the true response rate will be at least 30%.

Moreover, with 87 patients, there will also be more than 90% power to detect a difference in complete response rate of 8% under the null hypothesis versus 20% under the alternative hypothesis.

14.1.3 Part C (phase IIa) Pharmacokinetic Cohort

At least 10 patients (up to a maximum of 20 patients, all treated with the "40/15" treatment regimen) will be entered into Part C. This number is based on feasibility and the minimum number of patients evaluable for pharmacokinetic analyses (profiles and pharmacokinetic parameter summaries).

For the purpose of pharmacokinetic parameter evaluation and analysis, patients with FL entered into Part B who have also provided PK samples, and who are treated with "40/15" treatment regimen may be combined with patients entered into Part C.

14.1.4 Analysis Populations

Definition of populations

The following 4 populations are defined:

- Safety: All patients who received Betalutin or lilotomab or rituximab.
- Intent-to-treat (ITT): All patients who received Betalutin.
- Per Protocol (PP): The Per Protocol population will consist of a subset of patients from the ITT population 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.
- Pharmacokinetic (PK): The PK Population will be defined as all subjects who received at least a dose of Betalutin and have evaluable PK data, and a complete or agreed sparse scheduled post-dose PK measurements without protocol deviations, ~~violations~~, or events thought to significantly affect the PK of the drug.

Part A (phase I and phase IIa)

The primary efficacy analysis population is PP because in early phase study we are interested in demonstrating in principle whether the treatment is efficacious. Efficacy endpoints will also be evaluated in the ITT population.

Part B (FL Phase IIb)

The primary efficacy analyses will be conducted on the ITT population.

Part C (Pharmacokinetic Cohort, phase IIa)

The primary pharmacokinetic analyses will be conducted on the PK population.

14.1.5 Statistical Methods

Results from Part A (Phase I and Phase IIa), Part B and Part C will be summarised separately due to differences in study design, dose regimens and patient populations. However, analyses in specific populations and for specific dose regimens may be performed in the overall study population.

The results from this study will be presented mostly using descriptive statistical methods. Details of planned analyses for Parts A, B and C will be provided in separate statistical analysis plans.

All statistical programming and analyses will be performed using SAS® software.

Data will generally be presented by time of measurement. In general, continuous variables will be described using standard summary statistics such as number of observations, mean value, standard deviation, minimum value, maximum value, median, and first and third quartiles. Categorical variables will be summarised in frequency tables as count and percentages.

All individual data collected in the eCRF will be presented in data listings. Patients screened but not included in the study will not be presented in any tables or listings.

Prior to database lock and analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be prepared and approved, describing all the analyses to be performed. The SAP will document any changes to the analyses described in this protocol.

14.1.6 Analysis of Demographic and Pre-treatment Characteristics

Demographic data and other pre-treatment characteristics (including medical and disease history) will be summarised by dosing cohort (Part A) or dosing regimen (Part B) or Part C.

For all demographic and baseline characteristics, the analysis population will be the safety population.

Administration of the IMP will be listed provided in listings, by cohort and patient.

14.1.7 Analysis of Efficacy Data

Tumour response will be reported as follows in individual patients:

- CR
- PR
- SD
- PD
- NE

In Part A and Part C: Response rate will be presented as a point estimate of the proportion of responders along with the 95 % exact confidence interval of response rate.

In Part B randomised period: The ORR will be compared between dosing regimens using the Fisher's Exact test, and the difference in response rates and the corresponding 95% exact CI will be presented. ORR estimates and 95% exact CI for each dosing regimen will also be presented.

In Part B Single-arm 40/15 part: – The primary efficacy analysis on ORR (based on independent assessment) will be performed by testing whether the ORR is less than or equal to 30% against the alternative hypothesis that ORR is greater than 20% at overall two-sided 5% level of significance, i.e.,

H0: $p = 0.3$ vs. Ha: $p \neq 0.3$

In addition, the secondary efficacy analysis on CRR (based on independent assessment) will be performed by testing whether the CRR is less than or equal to 8% against the alternative hypothesis that ORR is greater than 8% at overall two-sided 5% level of significance, i.e.,

H0: p = 0.08 vs. Ha: p ≠ 0.08

Responders are defined as having CR and PR according to definition in Section 12.3.

Time to event endpoints will be analysed using standard Kaplan-Meier techniques. The estimate of the median survival curve will be calculated along with the associated 95% confidence intervals (when applicable). The efficacy endpoints are:

Overall Response Rate (ORR)

ORR, defined as the proportion of patients who achieve a CR or PR assessed with the use of standard criteria for lymphoma (1). The ORR will be assessed at 3 months image evaluation.

Best ORR will also be evaluated, taking the best response

achieved independent of time point for image evaluation.

Complete Response Rate (CRR)

CRR, defined as the proportion of patients who achieve a CR assessed with the use of standard criteria for lymphoma (1). The CRR will be calculated based on complete responses achieved at any timepoint.

Progression-free survival (PFS)

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.

If none of the above events are observed, PFS will be censored at the date of the last adequate tumour assessment

Duration of response (DoR)

DoR is the time from when criteria for response (CR or PR) is first met to the time of relapse or progression. Patients who have not relapsed/progressed will be censored at the last adequate tumour assessment.

Duration of Complete Response (DoCR)

DoCR is the time from when the complete response is first observed to the time of relapse. Patients who have not relapsed will be censored at the last adequate tumour assessment.

Overall survival (OS)

OS is defined as the time from administration of Betalutin to the date of death from any cause. Patients still alive or lost to follow-up are censored at the last date they were known to be alive. Patients still alive are censored at the last known date alive.

14.1.8 Biodistribution and Pharmacokinetics

These data, which are obtained from a subset of patients in Part A and B, and from all patients in Part C, as described in Section 10, will be listed by patient by time point.

Individual pharmacokinetic data will be tabulated and total radioactivity in blood (Betalutin PK) and total lilotomab antibodies in serum concentration(s) (total lilotomab antibodies

pharmacokinetics) vs. time curves presented. Pharmacokinetic results will also be summarised by cohort (Part A) or dosing regimen (Part B and Part C). Pharmacokinetic parameters will be determined using non-compartments analyses including activity-corrected area under the blood radioactivity vs. time curve, dose-corrected area under the serum concentration vs. time curve clearance, apparent volume of distribution and half-life.

14.1.9 Analysis of Pharmacokinetic Data

The study population displays will be based on the PK population, unless otherwise specified.

Betalutin pharmacokinetic parameters to be determined include: Maximum total radioactivity in blood (C_{max}), time to reach maximum blood concentration (t_{max}), area under the total radioactivity-time curve ($AUC_{0-\infty}$, AUC_{0-last}), mean residence time (MRT), terminal elimination half-life ($t_{1/2, z}$), biological half-life (Tb), effective half-life (te) total body clearance (CL), renal clearance (CL_R), and volume of distribution (V_d). Activity-adjusted C_{max} and AUC will also be calculated using the actual activity injected (Bq).

Total lilotomab antibodies pharmacokinetic parameters to be determined include: Maximum total drug concentration in serum (C_{max}), time to reach maximum drug concentration (t_{max}), area under the drug concentration-time curve ($AUC_{0-\infty}$, AUC_{0-last}), mean residence time (MRT), terminal elimination half-life ($t_{1/2, z}$), total body clearance (CL), renal clearance (CL_R), and volume of distribution (V_d). Dose-adjusted C_{max} and AUC will also be calculated using the actual dose of antibody injected (mg) to investigate the effect of body size on the pharmacokinetics of lilotomab.

Pharmacokinetic analysis will be carried out using actual sampling times. Data will be tabulated by patient by time point. Descriptive statistics (geometric mean, standard deviation, minimum, median, and maximum) and coefficient of variation (%) will be calculated for pharmacokinetic parameters. For each of the parameters, summary statistics will be calculated and tabulated by arm and dose group. Output will be presented separately for Part A and Part B, whilst data obtained from Part B patients (treated with the "40/15" regimen) may be combined with data obtained from Part C patients. Additional analysis such as pharmacokinetic/pharmacodynamic modelling will be considered pending the size of the PK population.

14.1.10 Analysis of Safety Data

Standard safety listings will be provided for treatment exposure, patient disposition, AEs, AEs leading to discontinuation, SAEs, laboratory safety data (serum chemistry and haematology), vital signs, 12-lead ECG, physical examination, ECOG performance status, and long-term toxicity. i.e. all safety parameters mention in Section 13.

The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance. The number of patients reporting AEs, and the number of AEs reported will be presented. AEs will be coded using MedDRA and graded according to CTCAE. The events will be tabulated by system organ class, preferred term, CTCAE grading, severity, and relationship to study medication. Start of AE after study medication injection and duration of AEs will also be tabulated. SAEs will also be presented in separate tabulations.

For laboratory data, the number of abnormal and clinically significant observations will be listed by patient and by time of measurement. The laboratory values will also be graded according to toxicity graded as CTCAE. All patients who receive any amount of the study

medication will be evaluated for toxicity.

14.1.11 Analysis of Immunogenicity Data

The study population displays will be based on the Safety population, unless otherwise specified.

Immunogenicity analysis will be carried out using nominal or actual sampling times. Data will be tabulated by patient by time point. Descriptive statistics (geometric mean, standard deviation, minimum, median, and maximum) and coefficient of variation (%) will be calculated for each relevant immunogenicity parameters. For each of the parameters, summary tables and figures will be generated by arm and dose group. Output will be presented separately for Part A, Part B and Part C.

Immunogenicity parameters to be determined include:

- Incidence, titre, timing of onset and duration of antibody responses for each type of antibody assay used (e.g. IgG by ELISA, neutralisation)
- Relationship of antibody formation to underlying disease, concomitant medication, dose, duration, regimen and formulation when relevant
- Analyses of potential clinically relevant correlates of immunogenicity, for example, to determine the extent to which the presence of antibodies of a particular type or titer appears to correlate with alterations of pharmacokinetics, changes in pharmacodynamics), loss of efficacy, loss of adverse event profile or development of adverse events. Events that might be immunologically mediated (e.g. serum sickness) and events that might result from binding of cross-reactive endogenous substances by antibodies to the administered drug will be explored.

14.1.12 Handling of Drop-outs and/or Missing Data

No missing data will be imputed.

14.1.13 Sub-group Analysis

No sub-group analyses are planned. However, sub-groups may be identified on a data-driven basis.

14.2 Analysis for Patients in Part B with FL

The statistical analysis for Part B (in relation to the current single-arm design) will be performed at the following timepoints after last patient has been dosed with Betalutin:

- After all patients have had at least one post-treatment tumour assessment: This will consist of the baseline data, efficacy data on ORR, CRR and preliminary assessment on the longer-term efficacy outcomes (DoR, DoCR), and selected safety data. No change to the trial conduct nor the statistical analysis plan is envisaged.
- 9 months post Betalutin administration (6-month follow up of response for all patients with PR or CR): This will consist of the baseline data, efficacy data on ORR, CRR and preliminary assessment on the longer-term efficacy outcomes (DoR, DoCR, PFS, OS), and all safety data accumulated to this point.

- 15 months post Betalutin administration (12-months follow up of response for all patients with PR or CR): This will include updated analysis on the longer-term efficacy outcomes (DoR, DoCR, PFS and OS) and updated long-term safety data.
- 5 years: Final analysis will include long-term efficacy outcomes and safety data.

Pharmacokinetics, immunogenicity and biomarker assessments may be analyzed subsequently and reported in individual analytical reports as addendum to the Clinical Study Report(s). Exploratory biomarkers analysis will be published if relevant.

14.3 Timing of Analysis in Part C (Pharmacokinetic Cohort)

Pharmacokinetic parameters will be analyzed and summarized at the same time as the final analysis of patients in Part B (Section 14.2). Pharmacokinetic data from patients with FL entered to Part B (and who have also provided pharmacokinetic samples) may be combined with iNHL patients entered to Part C (assuming a dose regimen of "40/15").

The analysis of pharmacokinetic parameters is described in Section 14.1.8.

15 DATA HANDLING

15.1 Patient Data Protection

Patient number and year of birth will identify the patients in the eCRFs.

The investigator is responsible for keeping a list of all enrolled patients including patient numbers, full names, and dates of birth. In addition, the investigator will prepare a list of patients who were screened for participation of the study but were not enrolled and the reason for non-eligibility. A note will be made in the hospital medical records that the patient is participating in a clinical study. The patients' written informed consent forms will be kept at the hospital in strict confidence.

The patients will be informed in writing that the results will be stored and analysed electronically according to national laws, as applicable, and that patient confidentiality will be maintained.

The patients will also be informed in writing about the need for source data verification (SDV), audits, and inspections. The audit/inspection and SDV will be performed by at least one of the following parties; authorised representatives of the Sponsor, authorised monitors, hospital ECs/IRBs or regulatory authority. In these cases, a relevant part of the patient records will be required and reviewed.

In accordance with the General Data Protection Regulation (GDPR), the patient will be informed of the following:

- Nordic Nanovector ASA is responsible their personal data collected as a participant in this clinical trial or study.
- The personal data collected as part this study may be kept for 25 years in accordance with clinical trial rules.

- The use of their personal data for the purposes described in the informed consent form is based on their consent, legal requirements that cover the conduct of research studies and public interest.
- If the patient previously agreed that his/her personal data may be used for other scientific purposes that are additional to the study, they may have a right to object to the use of their personal data for this additional research for reasons specific to them. If they wish to object to such use, to contact their study doctor or Data Protection Officer at the study site.
- The patient can ask to see the information that has been collected about them or ask that we send their personal data to another person or company. If they think any of the information is incorrect, they can ask their study doctor in writing if it can be changed or removed. If they change their mind about taking part, we will not collect any further personal data from them. However, we are not able remove the personal data that was collected for this research study before they stopped. They can also ask that we restrict the use of your personal data.
- If the patient has questions about how we use their personal data or wish to exercise any of their rights, they will be asked to contact their study doctor or Data Protection Officer at the study site. If they are not happy with the response they receive, the patient may make a complaint to their local data protection authority.

15.2 Electronic Case Report Forms

All data, except from laboratory assays, which should be reported in the study report, will be recorded in the eCRF. Only high-level conclusions based on imaging or biodistribution results will be recorded in the eCRF. Source data and intermediate calculations will be stored at the study centre.

eCRFs will be used to capture study results and data. The study coordinator or other authorised study personnel will transcribe data from source documents to the eCRFs. All eCRFs will be reviewed and source verified by the study monitor, . Once the eCRFs are complete and source-verified, the investigator must electronically sign and date all required pages, verifying the accuracy of all data in the eCRF.

Specific instructions for completing and submitting eCRF will be provided to the study centre.

Because it is extremely important to have proper data collection in a timely manner, the investigator(s) or assigned designee shall complete the eCRFs continuously. The monitor will perform SDV against the entries in the eCRF. When the monitor requests additional data or clarification of data for the eCRF, the request must be answered satisfactorily

Any data recorded directly in the eCRF, for which no other written or electronic record will be maintained in the patient's medical record, will be considered source data.

15.3 Data Management

Data management will be carried out as described in the Standard Operating Procedures (SOPs) for clinical studies of the Sponsor's subcontractor.

All eCRFs will be entered electronically by study centre staff into a validated database. Data

entry will be SDVed by a Sponsor representative. Comprehensive edit checks will be used to clean the data, and data queries will be generated and resolved by the investigator(s) or assigned designee. Patient data will be entered continuously. All changes to the data and the database structure will be recorded in an audit trail.

All changes to the data and the database structure will be fully audit trailed either electronically within the clinical database or via a paper trail.

Data queries will be generated at data entry or if questions arise during the data validation or detected during a manual review (safety data). The queries are entered into the eCRF and resolved according to the electronic data capture manual.

AEs and SAEs will be handled in the same way as the other data reported in the eCRF. However, in addition the initial notification of SUSARs will be coded and medically assessed for reporting to authorities according to national regulatory requirements. Procedures for reconciliation of the clinical and safety databases will be provided in the Data Management Plan. Coding of AEs and medical history will be performed according to MedDRA and coding of concomitant medications will be performed according to WHO-Drug dictionary.

A quality check of a random sample of the data will be performed to ensure that the consistency between the database and the eCRFs are at least on the pre-defined level described in SOPs of the Sponsor's subcontractor and in the data validation plan.

Database lock will be declared when all data have been entered, the data entry verified, the data validated and the database defined as clean by the Clinical Data Manager. After declaration of database lock the data will be exported from the database to SAS-datasets and both the database and the SAS-datasets will be locked and protected from changes. Subsequently then the inclusion of patients into the 4 analysis sets will be done in such a way that it is ensured that all rules have been applied equally on all patients. All statistical analyses will be performed on the locked SAS-datasets.

15.4 Retention of Documents

The following information must be retained for at least 15 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region; or at least 15 years have elapsed since the formal discontinuation of clinical development of the IMP: source data, source documents (including scans/imaging data), eCRFs, protocol and amendments, drug accountability forms, correspondence, patient identification list, informed consent forms, and any other essential documents.

It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained according to ICH Good Clinical Practice (GCP) guidelines. The eCRFs will be archived by the Sponsor for the lifetime of the product. No study document should be destroyed without prior written agreement between the Sponsor and the investigator. In accordance with data protection legislation, the patient identification list should be destroyed when it is no longer needed. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice should be given to the Sponsor.

16 SPECIAL REQUIREMENTS AND PROCEDURES

16.1 Ethics Committee/Institutional Review Board

The study protocol, including the patient information and informed consent to be used, must be approved by the hospital EC, hospital IRB and/or regional EC. Written approval must be obtained before enrolment of any patients into the study. It is the responsibility of the investigator to supply the Sponsor with a copy of the members of the hospital EC/IRB or Regional EC and the Letter of Approval defining the version of each document approved.

The investigator will ensure that this study is conducted in full conformance with the Seoul (2008) amendment to the Declaration of Helsinki 1964, including notes of clarification up to Tokyo (2004), and FDA 21 Code of Federal Regulations (CFR) part 50, and with national laws and regulations for clinical research.

The investigator is responsible for informing the ECs and regulatory authorities of any SAEs and/or major amendments to the protocol as per national requirements. The investigator should file all correspondence and a copy should be sent to Sponsor.

Either the investigator or the Sponsor must submit progress reports to the EC/IRB according to local regulations and guidelines.

16.2 Protocol Amendments and Discontinuation

Any changes to the protocol or discontinuation of the study require a written protocol amendment or statement, respectively. The investigators, EC/IRB in some cases and Sponsor must approve the protocol amendment or statement. The Principal Investigator(s) and the Sponsor's authorised representative will sign the protocol amendment. Any significant deviation from the protocol when no approved amendment exists will be regarded as a protocol violation, and will be addressed as such during the reporting of the study.

National authorities and hospital EC/IRB, or regional EC will be notified about all protocol amendments or discontinuation of the study. If the protocol amendment results in major changes, affecting patient safety, the objective(s) or the scientific integrity of the study, it must be approved by the hospital EC/IRB or regional EC of all participating study centres as per local regulations, as well as by the national regulatory authorities.

The Sponsor will have the right to terminate the study at any time in case of SAEs or if special circumstances concerning the study substance or the company itself should occur, making further patient treatment impossible. The Sponsor will inform the investigators about the reasons for study termination.

16.3 Investigator's Responsibility

16.3.1 Overall Responsibility

This study will be conducted in full accordance with the Seoul (2008) amendment to the Declaration of Helsinki 1964, including notes of clarification up to Tokyo (2004) and FDA 21 CFR part 50, and with national laws and regulations for clinical research. Information regarding any study centres participating in this study that cannot comply with these standards will be documented.

The investigator is responsible for performing the study in accordance with this protocol and the ICH guidelines on GCP, and for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the Sponsor and other forms as required by national authorities in the country where the study centre is located.

The investigator is responsible for giving information and training about the study to all staff members involved in the study or in any element of patient management, both before starting the practical performance of the study and during the course of the study (e.g. when new staff become involved).

The investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study. The investigator must be familiar with the background and requirements of the study and with the properties of the IMP as described in the Investigator's Brochure.

The investigator is responsible for destroying the patient identification list when it no longer needs to be retained according to ICH guidelines.

The investigator at each study centre has the overall responsibility for the conduct and administration of the study at that study centre, and for contacts with study centre management, the EC/IRB, and with local authorities.

16.3.2 Patient Informed Consent

Written and oral information about the study in a language understandable by the patient will be given to all patients. Written informed consent will be obtained from each patient before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

The patient’s willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. The investigator will keep the original consent forms and copies will be given to the patients.

16.3.3 Direct Access to Source Data/Documents

The monitor(s), auditor(s), authorised personnel of the Sponsor, and health authority inspector(s) or their agents will be given direct access to source data and documentation (e.g. medical charts/records, laboratory results, printouts, etc.) for SDV, provided that patient confidentiality is maintained in accordance with local requirements.

16.3.4 Confidentiality Regarding Study Patients

The investigator must assure that the privacy of the patients, including their personal identity and all other personal medical information, will be maintained at all times. In the eCRF and

other documents or image material (including materials from all imaging modalities) submitted to the Sponsor, patients will not be identified by their names, but by an identification code (e.g. study centre and patient number). Personal medical information may be scrutinised for the purpose of verifying data recorded in the eCRF. This may be done by the monitor(s), properly authorised persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

16.3.5 Study Monitoring

Monitoring is a Sponsor's process for tracking a clinical study to ensure its scientific integrity, the data quality, safety, and well-being of the patients and compliance with the Declaration of Helsinki and other regulatory and/or Sponsor regulations.

To ensure compliance with GCP, the monitor or Sponsor's representative is responsible for ensuring that the study is conducted according to the protocol, and other written instructions.

The monitor is the primary association between the Sponsor and the investigator. The main responsibilities of the monitor are to assure adherence to the protocol, accurate and complete data recording and reporting in the eCRFs, and that informed consent is obtained and recorded for all patients before their participation in the study.

The monitor will contact and visit the investigator at regular intervals throughout the study. To assure the accuracy and completeness of the data recorded in the study, the monitor will be allowed to compare eCRFs with medical records and other relevant documentation during the on-site monitoring visits to ensure the completeness, consistency, and accuracy of the data being recorded.

The monitor is responsible for explaining the protocol and study-related procedures to all study staff, including the investigator. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the monitor.

As part of the supervision of the study progress, other Sponsor personnel may, on request, accompany the monitor on visits to the study centre. The investigator and assisting staff must agree to cooperate with the monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits.

16.3.6 Collection of IMP Dosing Errors

A reportable IMP dosing error is defined as:

- Betalutin: greater than +10% of the intended dose.
- Lilotomab 40 mg: a dose <30 mg or a dose >70 mg

The investigator must report an IMP dosing error to the Sponsor or assigned designee within 24 hours of treatment administration or within 24 hours of the error having been identified, following the process for SAE reporting in Section 13.3.

16.3.7 Collection of Pregnancy Information

16.3.7.1 Male Participants with Partners who become Pregnant

The investigator will attempt to collect pregnancy information or any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive Betalutin.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or assigned designee within 24 hours of learning of the partner's pregnancy following the process for SAE reporting in Section 13.3. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be 12 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

16.3.7.2 Female Participants who become Pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy following the process for SAE reporting in Section 13.3. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will be for 12weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will continue to be followed during the course of her pregnancy.

16.4 Safety Review Committee (SRC)

A SRC will periodically review and monitor the safety of patients in this study. The SRC will consist of 3 to 4 relevant experts (haematologists/oncologists) including the coordinating investigator for the study.

The following safety data are examples of data that may be collected and evaluated for the SRC:

- AEs.
- Laboratory variables: serum chemistry and haematology
- Immunogenicity

- Vital signs (systolic/diastolic blood pressure, heart rate, and body temperature).
- 12-lead ECG at baseline.
- Physical examination, including WHO (ECOG) PS.
- Long-term toxicity.

In Part A, the SRC made recommendations for dose escalation and expansion according to Table 6-2.

In Part B, the SRC reviewed the safety and efficacy data from the first 47 patients in the randomised section and recommended the future dose for development to be lilotomab 40 mg and Betalutin 15 MBq/kg.

The SRC will also review the safety data from the first 3 patients in each of the sub populations in Part B (see Section 6.1) and make recommendations according to Table 6-4.

In Part C, the SRC may review emerging data at the same time as data from patients entered to Part B is reviewed.

16.5 Independent Review Committee (IRC) - Parts B and C

For Part B, an IRC will be established to provide an independent review of radiographic data and pertinent clinical data in order to provide expert interpretation of changes in tumour status. The IRC will include 1 independent board-certified radiologist and 1 independent board-certified haematologist/oncologist, and will be managed by a clinical research organisation selected by Nordic Nanovector. The review of radiographic and clinical data by the IRC will be performed on an ongoing basis. Details of the IRC's processes/analysis methods will be described in a charter developed by the contracted imaging facility in conjunction with Nordic Nanovector.

From Part C, the IRC may review the radiological and pertinent clinical data from patients entered to this cohort.

16.6 Audit and Inspection

According to ICH Guidelines on GCP, the Sponsor may audit the study centre to compare raw data, source data, and associated records with the interim or final report of the study to assure that data have been accurately reported. The investigator must accept that regulatory authorities, EC/IRB may conduct an inspection to verify compliance of the study with protocol, ICH GCP guidelines, and any applicable regulatory requirements. If the investigator is contacted with a request for an inspection, the investigator must inform the Sponsor immediately.

16.7 Laboratory Accreditation

Any clinical laboratory facility used for analysis of samples obtained under this protocol must demonstrate adequate licensure and accreditation. Reference ranges of test results must be provided to the Sponsor.

The study centre must have the appropriate license for any procedure involving the administration of radioactive substances supplied by the Sponsor.

16.8 Patient Insurance and Indemnity

This study is covered under the Sponsor's liability insurance policy. A certificate of insurance can be provided upon request.

17 INVESTIGATOR AGREEMENT

17.1 Financial Disclosure

According to the FDA 21 CFR, part 54, the Sponsor is required to completely and accurately disclose or certify information to the FDA concerning the financial interests of a clinical investigator who is not a full-time or part-time employee. Therefore, the investigator must provide the Sponsor with sufficient, accurate financial certification that no financial arrangements (further defined in 21 CFR 54.2) exist with the Sponsor, or fully disclose the nature of the arrangement.

17.2 Study Agreement and Payment of Grant

A separate financial agreement (Clinical Study Agreement) including budget will be signed between the Sponsor and the investigator and/or the institution involved. The budget will be itemised on a per patient basis and the payee name(s) and tax identification number(s). Additionally, the investigator should not begin the study until the Sponsor has confirmed the agreed final budget in writing. The investigator must comply with all the terms, conditions and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, the study agreement shall prevail.

18 CONFIDENTIALITY AND REPORTING AND PUBLICATION OF RESULTS

All information concerning Betalutin and the Sponsor's research and product development including patent applications and manufacturing processes not previously published are considered confidential and shall remain the sole property of the Sponsor.

18.1 Statistical and Clinical Study Reports

The Sponsor is responsible for preparing a clinical study report, in cooperation with the Principal Investigator. The report will be added to the Sponsor's data file and may be used for regulatory purposes and/or in company publications.

If the study is terminated prematurely for any reason an abbreviated clinical study report will be prepared.

End of study' is defined as when the last patient has completed the last study visit or after the last patient last visit for the final analysis of the study if that is sooner.

18.2 Regulatory Use of Data

By signing the protocol, the investigator agrees that the results of this study may be used for submission to national and/or international regulatory and supervising authorities. The

authorities will be informed of the investigator's name, address, qualifications, and extent of involvement.

18.3 Publication of Results

All publications will be prepared and published in collaboration between investigators and the Sponsor.

Manuscripts based on this protocol will be made according to the "Vancouver System": Uniform Requirements for Manuscripts Submitted to Medical Journals (latest updated version 2000: www. Icmj.org). Authorship is based on important contributions to:

- Idea, planning or modifying the protocol, collection, analysis or interpretation of data.
- Writing or critically revising the manuscript.
- Acceptance of the final manuscript.
- All 3 aspects must be covered.

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(61) Robinson SN, Freedman AS, Neuberg DS, et al. Loss of marrow reserve from dose-intensified chemotherapy results in impaired hematopoietic reconstitution after autologous transplantation: CD34+, CD34+ 38−, and week-6 CAFC assays predict poor engraftment. Experimental hematology 2000 28(12),1325-1333.

20 APPENDICES

Appendix I Changes from Version 14

General

- Headings have been updated where applicable; the part of the study the section is applicable to has only been stated in the headings where this not Parts A, B and C.
- Corrections to individual typographical errors and formatting improvements have not been individually listed as these do not alter meaning.
- The clarification relating to relating to subpopulations with prior autologous SCT and/or definition of the lower platelet thresholds (platelet count ≥100×10^9/L but <150×10^9/L) for the subpopulations enrolled in Part B (identified for Section 4.2.3) was made throughout the protocol, also affecting Sections 4.8.7.1 (Section 4.8.6.1 in previous version), Section 4.8.10, Section 6.1, Section 9.2.2.

Changes to each section are identified below; deleted text is shown in strikethrough and new text in bold font.

Cover Page

Change to Sponsor signatory: ~~Dominic Smethurst~~ **Christine Wilkinson Blanc**, MD

Coordinating Investigator Signature Page

Telephone number removed

Sponsor Signature Page

~~**Authorised Representative o**~~**O**n behalf of Nordic Nanovector ASA:

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The corresponding signatures have been updated accordingly.

Section 1 Synopsis

Changes specific to the synopsis only are listed; other changes made in the synopsis reflect those identified for the main text:

Key Dates:

~~Up to 130 patients will be added in a phase IIb randomised arm.~~ Enrolment was opened upon approval of Protocol Version 11.

Part C (Pharmacokinetic Cohort phase IIa):

Enrolment will open at selected sites (capable of collecting pharmacokinetic samples) upon approval of this version of the protocol (Version 15).

~~All~~ Patients **in Part B and Part C** will be followed up for up to 5 years **after the Betalutin dose**~~or until further anticancer therapy is given. Survival and long term safety data will be collected for all patients for a maximum of 5 years from the date of administration of study drug~~. **Extensive follow-up will take place for all patients for at least the first year (Months 6, 9 and 12) (see "Study Evaluations").**

Population

Part B (FL phase IIb):

Adult patients with relapsed FL who have received ≥2 prior anti-neoplastic or immunotherapy-based regimens, and are refractory to any previous anti-CD20 based regimen. Prior therapy must include an anti-CD20 therapy and an alkylating agent. Anti-CD20 refractory disease is defined as lack of a complete remission (CR) or partial remission (PR), or PD within 6 months of last dose **of an anti-CD20 containing regimen**. Prior exposure to idelalisib or other PI3K (Phosphatidylinositol 3-kinase) inhibitors is allowed. **The eligibility criteria were widened under protocol Version 14 to allow enrolment of patients** with a prior autologous stem cell transplant (SCT) ~~are allowed to be entered~~ (if at least two years have elapsed since transplantation) ~~and the patient has been without grade ≥1 Graft vs Host Disease (GvHD) in the 8 weeks before the date of consent~~ **and/or platelet count ≥100×109/L but <150×109/L at study entry**.

Number of Patients Planned

Part A (phase I and phase IIa): **iNHL patients**

Up to 35 phase I patients ~~will be enrolled~~.

In phase IIa, 30 patients have been enrolled in Arm 1 and approximately 10-15 patients ~~will~~ **have** be**en** enrolled in Arm 4.

Part B (FL phase IIb):

Randomised section of Part B

Up to 130 patients with FL were planned to be enrolled and randomised 1:1 (stratified for double-refractory patients, where double-refractory is defined as refractory to both an anti-CD20 therapy and an alkylating agent therapy – see Section 9.1.7.2 for full definition) to receive dose "40/15" or dose "100/20" **until the selection of one of the 2 regimens for further assessment in clinical development.**

Assessment of dose selected for further development

Following the interim analysis and selection of the "40/15" regimen for future development, patient enrolment will be completed when 87 patients have received this regimen (including patients treated with the "40/15" regimen in the randomised section).

~~All patients enrolled after the IA will receive "40/15".~~

~~Note: the Betalutin dose will be lower for patients entered with prior autologous SCT and/or platelets <150x109/L) as follows :~~

- ~~Patients with a prior auto SCT and who have platelets ≥150x109/L will receive Betalutin at the reduced dose of 12.5 MBq/kg.~~
- ~~Patients with a prior auto SCT and who have platelets <150x109/L will receive Betalutin at the reduced dose of 10 MBq/kg~~
- ~~Patients without a prior SCT, but who have the lower platelet threshold (100 to <150 x 109/L) will receive Betalutin at the reduced dose of 12.5 MBq/kg~~

Part C (phase IIa Pharmacokinetic Cohort): iNHL patients

At least 10 patients (up to a maximum of 20 patients) from selected sites willing and able to collect pharmacokinetic samples.

Study Evaluation

Pharmacokinetics is mandatory for all patients enrolled in Part C.

Statistical Methods and Planned Analysis:

Part B (FL phase IIb)

Comparison of "40/15" and "100/20" regimens

The study is a randomised, 2-arm, open-label study to further differentiate the risk/benefit of 2 ~~promising~~ **candidate** dose regimens of lilotomab and Betalutin in patients with relapsed non-Hodgkin B-cell FL.

Once approximately 50 patients have been treated (approximately 25 per dose regimen), an interim analysis ~~will~~ **was** ~~be~~ performed to evaluate the possibility of study modifications or continuation of both regimens.

The intent-to-treat (ITT) population will consist of all patients who were randomised to one of the dose groups. The primary efficacy endpoint is ORR. Scans will be performed at baseline, 3, 6, 9, 12, 18 and 24, 36, 48 and 60 months after Betalutin injection for all patients to assess tumour response as follows:

- CR
- PR
- No change/stable disease (SD)
- PD
- **NE**

Response rates will be presented as percentage of patients in the ITT population with the exact 95% confidence interval (Clopper-Pearson).

Assessment of ORR in the "40/15" treatment regimen.

A total of 87 patients, including the ones in the interim analysis, will be recruited and treated with the "40/15" regimen.

The response rate under the null hypothesis is set at 30%, versus the response rate of 48% under the alternative hypothesis will be compared. A 2-sided exact test with a significance level of 0.05 will be used to compare the observed response rate against the hypothesis. In addition, a complete response rate of 8% under the null hypothesis versus a complete response rate of 20% under the alternative hypothesis will also be tested.

Descriptive and summary statistics will be calculated for each pharmacokinetic parameter. Further analyses may be conducted, as appropriate.

Pharmacokinetic data and/or parameters from patients who received lilotomab 40mg and Betalutin 15MBq/kg in Part B may be combined with data from Part C.

Safety Review Committee:

Part B:

The SRC will periodically monitor the safety data.

In line with its Charter, the Safety Review Committee reviewed the results of the interim analysis and provided a recommendation to the Sponsor to continue or terminate treatment arms or to perform other modifications. The recommendation was based on the totality of safety, efficacy, and other available data (e.g., immunogenicity data) **based on the following guidelines:**

- **If ORR ≥ 40% in each treatment regimen, the study may complete its targeted enrolment of up to 130 patients (around 65 per arm)**
- **If ORR < 40% in either regimen then the regimen with ORR <40% may be terminated.**
- **If both regimens have ORR <40%, the study may be terminated for futility or modified. The regimen(s) with ORR ≥40% will proceed to enrol the remaining patients, up to 65 patients per regimen (including the patients in the interim analysis). The final decision lies with the Sponsor.**

To facilitate decision to keep or drop treatment arms based on ORR rates, the boundary of 40% ORR was non-binding and for guidance only. Following the interim analysis, the SRC recommended to discontinue the "100/20" treatment regimen and continue with further recruitment in the "40/15" treatment regimen.

For patients included with prior autologous- SCT and/or with platelet counts ≥100×10^9/L but <150×10^9/L, the SRC will evaluate the emerging safety data **(in particular, DLTs)** from the ~~following~~ first 3 patients in each of the ~~following~~ **3** sub-~~groups~~**populations (see "Study Design" section)**

- **If no DLT is observed, the dose of Betalutin may be escalated as follows:**
  - **to 15MBq/kg in the subpopulation with prior autologous SCT and platelet count ≥150×10^9/L.**
  - **to 15MBq/kg in the subpopulation without a prior autologous SCT, and platelet count ≥100×10^9/L but <150×10^9/L.**
  - **to 12.5MBq/kg in the subpopulation with a prior autologous SCT and platelet count ≥100×10^9/L but <150×10^9/L.**
- **If 1 DLT is observed in a given subpopulation, a further 3 patients will be treated at the initial dose in this** subpopulation and the SRC will review the overall safety of the cohort prior to establishing the dose to be recommended.

- **If 2 DLTs are observed in any given subpopulation, the SRC may consider a dose reduction to "40/10" for** the 2 subpopulations treated with "40/12.5" or may decide to close enrolment in the subpopulation. There will be no dose reduction of Betalutin below 10 MBq/kg.

The SRC will evaluate the safety data from each set of 3 patients (either 3 or 3+3) in each subpopulation and may request a subsequent review of safety data.

Part C:

The SRC will periodically monitor the safety data in line with Part B review of safety data.

Section 3 List of Abbreviations

Redundant abbreviations have been removed, missing or new abbreviations added and consistency changes made as follows:

ALAT	Alanine transaminase
~~APC~~	~~antigen presenting cells~~
~~AR~~	~~Adverse reaction~~
~~ARC~~	~~Antibody-radionuclide-conjugate~~
ASAT	Aspartate transaminase
AUC	Area under **the** plasma drug concentration-time curve
BSA	**Body surface area**
~~eGMP~~	~~current Good Manufacturing Practice~~
~~CBC~~	~~Complete blood count~~
CD	**Cluster of differentiation**
CFR	**Code of Federal Regulations**
COVID-19	**Coronavirus Disease 19**
CRR	**Complete response rate**
DNA	**Deoxyribonucleic acid**
DoCR	**Duration of complete response**
EC	Ethic**s** Committee
ELISA	**Enzyme-linked immunosorbent assay**
EU	**European Union**
FcγRIIa	**Fc-gamma-Receptor IIa**
FDG	(^{18}F) Fluor**o**deoxyglucose
GDPR	**General Data Protection Regulation**
~~Hf~~	~~Hafnium~~
~~IA~~	~~Interim analysis~~
LDH	**Lactate dehydrogenase**
LDi	**Longest diameter**
MB-1	**Murine monoclonal antibody**
MDS	**Myelodysplastic syndrome**
MRT	**Mean residence time**
RNA	**Ribonucleic acid**
~~SEC~~	~~Size exclusion chromatography~~
SOP	Standard ~~Operation~~ **Operating** Procedure
~~TMF~~	~~Trial Master File~~
US	**United States**

Section 4.2.3 Introduction; Part B – FL Phase IIb

Following a review of the clinical safety, efficacy, dosimetry, and pharmacokinetic data from the treatment regimens used in Part A, the 2 **candidate RP2D** dosing regimens from Arms 1 and 4 ~~have~~ emerged as contenders

for the ~~recommended phase IIb dose~~ selection **of the RP2D for future clinical development**. Therefore, a phase IIb randomised ~~arm~~ **sub-study** (hereafter referred to as **Part B**, or **"PARADIGME"**) ~~is being~~ **was** added to further delineate the risk:benefit profile of these **candidate RP2D** treatment regimens in a population of FL patients with ≥2 prior lines of therapy who are refractory to rituximab/anti-CD20 therapy.

Following an interim analysis of 47 patients with FL, randomised to either 40 mg lilotomab and 15MBq/kg Betalutin ("40/15"), or 100mg/m^2 lilotomab and 20MBq/kg Betalutin ("100/20"), the Safety Review Committee (SRC) recommended that the "40/15" dose be selected for subsequent patients entered to Part B **(which was formalised in Version 14 of the protocol)**.

Version 14 of the protocol also allowed for a relaxation of 2 selection criteria i.e. minimum accepted level of platelets at study entry and restriction on prior autologous stem cell transplantation (SCT) (note: the Betalutin dose will be lower for patients entered with a prior autologous SCT and/or platelets <150×10^9/L - see Section 4.2.4).

Section 4.2.3 Introduction; Part B – Inclusion of Patients with a Prior Auto-SCT and Inclusion of Patients with Lower Platelet Threshold

Patients with a prior autologous-SCT, for whom at least two years have elapsed since transplantation ~~and who have been without grade ≥1 Graft-vs-Host-Disease (GvHD) for at least 8 weeks~~ before the date of consent can be entered to Part B.

Patients with a ~~lower~~ platelet ~~threshold~~ **count ≥100×10^9/L but <150×10^9/L** can be entered to Part B.

Patients with both a prior autologous-SCT and/**or** a ~~lower~~ platelet ~~threshold~~ **count ≥100×10^9/L but <150×10^9/L** can be entered to Part B. **The Betalutin dose is to be adapted for these patients.**

Patients **will be divided into in 3 subpopulations and the first 3 patients in each** will receive the following doses:

- Patients with a prior autologous-SCT and ~~who have platelets~~ **platelet count** ≥150×10^9/L will be followed for at least 6 weeks. These patients will receive Betalutin at the reduced dose of 12.5 MBq/kg **with lilotomab 40 mg**.
- Patients with a prior autologous-SCT and ~~who have platelets~~ **platelet count ≥100×10^9/L but** <150×10^9/L will be followed for at least 6 weeks. These patients will receive Betalutin at the reduced dose of 10 MBq/kg **with lilotomab 40 mg**.
- Patients without a prior autologous-SCT and ~~who have the lower platelet threshold~~ **platelet count ≥**100×**10^9/L** ~~to~~ **but** <150×10^9/L) will be followed for at least 6 weeks. These patients will receive Betalutin at the reduced dose of 12.5 MBq/kg **with lilotomab 40 mg**.

Emerging safety data **(in particular, dose limiting toxicities [DLT])** from the first 3 patients in each subpopulation will be reviewed by the SRC.

The SRC may request a subsequent review of safety data (see Section~~s 13 and~~ 16.4). The SRC can ~~either retain the current reduced dosing level, stop the recruitment of further patients with a prior auto-SCT and/or lower platelet count, or recommend a different dose~~ **recommend the current reduced dosing level be maintained, a dose escalation (including escalation to Betalutin 15 MBq/kg with lilotomab 40 mg), an evaluation of an additional 3 patients, a dose-decrease, a different dose or to stop the recruitment of further patients with a prior autologous-SCT and/or lower platelet count.**

Section 4.2.3 Introduction; Part C - Inclusion of a Cohort Dedicated to Pharmacokinetic Assessments

Although pharmacokinetic assessment is an exploratory objective in Parts A and B, measurement of total lilotomab antibodies was not included in Part A. Part C has therefore been introduced to further measure total lilotomab antibodies and to assess the total radioactivity of Betalutin in the blood to inform future development activities. Part C will be performed at selected sites that are able to perform blood sampling under the restrictions necessary due to the COVID-19 pandemic. Adult patients with relapsed indolent non-Hodgkin B-cell lymphoma (iNHL) (according to the broader Part A entry criteria) who are willing and able to provide pharmacokinetic samples will be enrolled to improve recruitment to this part of the study.

All patients treated in Part C will be treated with the selected RP2D ("40/15" dose regimen).

Section 4.4 Potential Benefits and Risks

Patients included in Part**s** A **and C** of this study are adults with histologically confirmed relapsed iNHL of any of the following subtypes; a) follicular grade I-IIIA, b) marginal zone, c) small lymphocytic, d) lymphoplasmacytic, or e) mantle cell, considered to have experienced treatment failures from prior treatment regimens, including chemotherapy and immunotherapy treatment regimens.

Following a protocol amendment (Protocol Version 7), the inclusion criterion for testing for CD37 positive cells was removed in order to remove the delay in treating patients while the biopsy testing was completed. **This amendment was supported by** Dahle et al. ~~showed~~ **showing** that CD37 was expressed in 216 out of 217 tumour biopsies from patients with B-cell lymphoma (37)~~. Furthermore they suggested~~ **and suggestion** that the ~~exception~~ **one case with no CD37 expression** (a patient with chronic lymphocyte leukaemia) may have been due to technical reasons associated with the assay.

Section 4.5 Immunogenicity Risk Assessment of Lilotomab and Betalutin

In Part A phase I and phase IIa and Part B (FL phase IIb) **and Part C (Pharmacokinetic Cohort phase IIa),** patients will therefore be tested for pre-existing HAMA, with a positive HAMA test being considered as an exclusion criterion (see Section 7.1.1 and Section 7.2.1 respectively).

Two additional immune responses were detected at 12-month follow-up visits. No reported side-effects could be associated with the development of ~~HAMA~~ **an immune response**.

In Part B **and Part C**, ~~all patients will be tested~~ **screening for pre-existing HAMA will be performed using a commercially available test** prior to inclusion **(such as the Milenia® Quickline HAMA kit or a HAMA-ELISA test commercially available)**.

An exploratory HAMA test to assess HAMA specificity vs. lilotomab (IFMA test) will also be performed at baseline for research purposes. ~~using the IFMA test at a central laboratory. This IFMA test is mandatory for all patients. The decision whether a patient is eligible or not can be made on-site using a local test such as the Milenia® Quickline HAMA kit: or if not available, using the result from the central laboratory.~~ **The IFMA test result may be used to verify a negative HAMA test at baseline in cases, where HAMA testing using a commercially available test is not feasible.**

Section 4.7 Clinical Risk-benefit Summary

A phase IIa expansion cohort ~~is currently enrolling up to 15 patients~~ **has completed enrolment**.

The mean platelet and neutrophil nadirs occurred at Day 40 (range **Day** 34 to **Day** 43) **for platelets** and **Day** 49 (range **Day** 43 to **Day** 56) **for neutrophils** ~~respectively~~ after Betalutin administration.

Table 4-2 Potential Risks Factors of Betalutin Treatment and Proposed Risk Minimisation Activities

Anticipated Risk Factors	Proposed risk minimisation treatment activities	Pharmacovigilance
Myelosuppression, transient reduction of haematological parameters.	• A pre-defined minimum value for platelet counts and neutrophil counts are ~~set~~ to be verified prior to inclusion. • Only patients with <25% tumour cells in bone marrow biopsy (biopsy taken from a site not previously irradiated) will be included. • Patients with previous total body irradiation will be excluded. • Patients with a previous haematopoietic allogenic stem cell transplantation will be excluded. • Patients with a previous haematopoietic autologous -SCT ~~(at least 2 years previously) are eligible provided the patient has not had ≥grade 1 GvHD within 8 weeks of the date of consent.~~ will be excluded if <2 years prior to inclusion but eligible if ≥2 years prior to enrolment). These patients will receive Betalutin 12.5MBq/kg until the SRC confirms the dose for this subpopulation. • Patients with platelet count ≥100×10^9/L ~~and~~ but <150×10^9/L are at risk of Grade 3 or 4 thrombocytopenia. These patients will also receive Betalutin 12.5MBq/kg until the SRC confirms the dose for this subpopulation.	• The inclusion and exclusion criteria in this clinical study protocol must be followed. • Haematological parameters will be closely followed as a safety measure. • The SRC will review the safety data from the first 3 patients enrolled with a history of autologous-SCT or with platelets ≥100×10^9/L but <150×10^9/L who have been treated with Betalutin and ~~who~~ after they have been followed for at least 6 weeks. • The SRC will review the safety data from the first 3 patients with platelets that are below 150 x10^9/L who have been treated with Betalutin and who have been followed for at least 6 weeks. • ~~The SRC will review the safety data from the first 3 patients with both a prior auto-SCT and platelets that are below 150 x10^9/L who have been treated with Betalutin and who have been followed for at least 6 weeks.~~

Anticipated Risk Factors	Proposed risk minimisation treatment activities	Pharmacovigilance
	• Patients with both a prior autologous-SCT and ~~a lower~~ platelet count ≥100×10^9/L but <150×10^9/L will receive Betalutin 10MBq/kg until the SRC confirms the dose for this subpopulation.	
Lilotomab is a murine antibody. *In silico* MHC class II-peptide binding prediction analysis identified promiscuous overlapping T-cell neo-epitopes in the sequence of lilotomab e.g. a risk to develop an ADA response in patients after lilotomab and/or Betalutin dosing	The patients are screened for pre-existing HAMA against lilotomab before inclusion in the study with exclusion of patients with a positive test. ~~Screening for pre-existing HAMA with a positive test leading to the exclusion of the patient from the study.~~	Immunogenicity assessment will be performed from pre-dose up to 1 year after dosing. Additional measurements will be implemented to characterise any observed ADA response (tiered approach) and the HLA class II haplotype of the targeted patients.
Radiopharmaceutical agent	Written instructions concerning safety precautions will be given to the patients, (with recommendations for them, their relatives and ~~friends~~ other close contacts) before administration and to the hospital staff before handling.	

Section 4.8.6 Rationale for Part C and Selection of Patients with Indolent NHL in Part C

New section added; subsequent sub sections are therefore renumbered.

Initial pharmacokinetics data were collected in Part A in a broad population of iNHL. Collection of further pharmacokinetics data was included in Part B to better characterise the pharmacokinetics of Betalutin and total lilotomab antibodies. Pharmacokinetic sampling in Part B is to be performed at selected centres and only for patients consenting for pharmacokinetic sample collection. Pharmacokinetic sample collection is not feasible at all sites participating in study 37-01 and ability to perform adequate sample collection is currently further limited due to restrictions related to COVID-19.

As of January 2021, no Part B patient has consented to pharmacokinetic sample collection, which may have been partly due to patients' reluctance to attend additional hospital visits during the COVID-19 pandemic.

Part C is added to specifically assess the pharmacokinetics of Betalutin and total lilotomab antibodies and is to be conducted at selected centres able and willing to perform adequate pharmacokinetic sample collection. In order to recruit enough patients in Part C, the population has been aligned with the population of Part A population, which is broader than Part B population and should allow for a sufficient amount of patients to be included at each participating site. Preliminary results from Part A have shown responses to study treatment in all populations of iNHL included in Part A (53), which allows their further inclusion in Part C.

Section 4.8.7 Rationale for Dose Selection(s) in Parts B and C

Section 4.8.7.1 Part B (FL phase II)

Following commencement of Part B, an interim analysis of the emerging safety and efficacy data from the first 47 patients was assessed by the SRC **who recommended that** all patients enrolled after the interim analysis ~~will~~ receive **the** "40/15" **dosing regimen**. **The Sponsor followed the SRC recommendation and the study protocol was amended (Version 14) to continue with this single dose regimen only.**

Further changes as identified for Section 4.2.3.

Section 4.8.7.2 Part C (Pharmacokinetic Cohort)

New section added

Part C will start enrolment after the interim analysis and decision on the selected RP2D for future development in Part B. Therefore, all patients enrolled to Part C will receive lilotomab 40 mg followed by Betalutin 15 MBq/kg.

Note: Patients with a prior autologous-SCT and/or platelet count ≥100×10^9/L but <150×10^9/L are excluded from Part C.

Section 4.8.10 Outcome of the Interim Analysis on Patients Entered to Part B

Changes as identified for Section 4.2.3.

Section 4.8.11 Rationale for Lower Betalutin Dose for Patients with Prior Autologous-SCT and/or Lower Platelet Level (Part B)

Discussion with ~~Professor Arne Kolstad and Professor Tim Illidge on~~ the SRC ~~for this study~~, **investigators and lymphoma experts (amendment implemented in protocol Version 14)** lead to ~~a~~ recommendation that:

- The ~~new~~ revised inclusion criteria for platelets should not, ~~in the first instance~~ **allow for the acceptable platelet threshold to** be lowered too much on grounds that many of the DLTs in Part A were bleeding related.

  Elderly patients who have cycled through ~~previous rounds of therapy~~ **therapies** for FL and could potentially be treated on this protocol sometimes have platelets that are lower than would be considered 'normal' in younger, healthier reference populations. In order that this protocol includes a more representative population of FL patients there is a desire to include patients with platelets that are $\geq 100 \times 10^9$/L. This threshold represents a compromise between the desire to be more inclusive and the potential threat from radiation induced thrombocytopenia which is a recognised and reproducible AE with this therapy *<this paragraph has been moved from Section 6.2.2. without change>*

- ~~Following discussions with investigators and lymphoma experts~~ ~~the~~ **There was a** desire for inclusion of patients previously treated with ~~stem cell transplantation was noted and~~ **autologous-SCT**. **T**he prevalence of this approach as the mainstay of first line therapy in some countries was ~~also~~ considered. This was offset against the observation that patients with transplanted stem cells typically ~~can~~ demonstrate more limited bone marrow reserves (61). One of the main effects of Betalutin administration, largely because of the attached radioactive lutetium is to compromised bone marrow. To retain sufficient activity to kill cancerous lymphoid tissue whilst avoiding excessive bone marrow toxicity a lower dose of Betalutin was felt ~~worthy of~~ **suggested for** initial assessment **in this population**.

The choice of the lilotomab 40 mg and Betalutin 15 MBq/kg dose ~~arm~~ **regimen** at the interim analysis points to a generally more efficacious and a more easily adhered to regime**n** with acceptable safety profile. The supposition based on interim data is that the lower dose of cold lilotomab **(in the "40/15" regimen as compared to the "100/20" regimen)** provides sufficient shielding of bone marrow without compromising the efficacy in the ~~tumour~~ **on tumour cells**. The combination of a reduced dose of radioactivity for stem cell transplant patients and **the choice of a** regime**n** that is generally looking to be gentler on the bone marrow was considered an adequate compromise.

A further step to ~~informally~~ assess patients progress after the first 3 patients in each of the sub-~~groups~~**populations** of prior autologous-SCT, lower platelet and both prior auto-SCT and lower platelets, who have been on study for at least 6 weeks adds an extra element of supervision in considering the suitability of this new inclusion criterion. The consideration that future patients might be precluded from therapy by having previously received a mainstay approach like stem cell transplantation owing to the hitherto lack of experience dosing such patients and the desire to treat a representative population of NHL patients also factored into the rationale for ~~this~~ **the** amendment **introduced in protocol Version 14.**

Section 5.3.1 Primary Objectives - Part B – FL Phase IIb "PARADIGME"; Synopsis

The primary objective**s** ~~is~~ **are**:

- **Randomised section:**
  - To evaluate the efficacy of the "40/15" dose regimen (40 mg lilotomab/ 15 MBq/kg Betalutin) compared with the "100/20" dose regimen (100 mg/m^2 lilotomab/20 MBq/kg Betalutin) based on the Independent Review Committee (IRC) assessment of tumour response rates in adult patients with relapsed rituximab/anti-CD20-refractory FL.
- **Selected regimen for further development:**
  - **To evaluate the ORR of the 40/15 regimen based on the IRC assessment of tumour response rates in adult patients with relapsed rituximab/anti-CD20 refractory FL.**

Section 5.3.2 Secondary Objectives; Synopsis

To compare the **"40/15" and "100/20"** treatment ~~groups~~ **regimens in the randomised section and to evaluate the treatment regimen selected for further development,** in terms of the following:

Efficacy

- **ORR by investigator assessment**

- **Complete response rate (CRR) by independent review and investigator assessment**
- DoR **by independent review and investigator assessment**
- **Duration of complete response (DoCR) by independent review and investigator assessment**
- PFS **by independent review and investigator assessment**
- OS

Safety

To characterise the safety profile of Betalutin

Section 5.4 Objectives - Part C – Pharmacokinetic Cohort; Synopsis

New section added

5.4.1 Primary Objective

To further characterise the pharmacokinetics of Betalutin (total radioactivity measurements in blood) and total lilotomab antibodies (antibodies measured in serum).

5.4.2 Secondary Objectives

- **To investigate safety and toxicity**
- **To explore efficacy**

Section 5.5 Study Endpoints Part A (phase I and phase IIa); Synopsis

Safety endpoints:

- Incidence and severity of AEs and serious adverse events (SAEs) graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE Version 4.0 or later, as applicable).
- 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.
- Incidence of potential late toxicity, such as new primary cancers and bone marrow changes (acute myelogenous leukaemia, myelodysplastic syndrome, and aplastic anaemia).

Section 5.6 Study Endpoints Part B: FL phase IIb; Synopsis

Efficacy endpoint definitions moved to Section 14.1.7 for consistency and to remove duplication:

Efficacy endpoints definitions are provided in Section 14.1.7.

Primary endpoint:

ORR ~~defined as the proportion of patients who achieve a confirmed CR or PR~~ as assessed by an independent reviewer based on standard criteria [Cheson 2014] **(40)**

Secondary endpoints:

Efficacy endpoints:

- ORR by investigator assessment
- CRR by independent review and investigator assessment
- DoR **and DoCR by independent review and investigator assessment**~~– defined as the interval from the first documentation of CR or PR to the first documentation of disease progression or death from any cause, whichever comes first.~~
- PFS **by independent review and investigator assessment–** defined as the interval from the start of Betalutin treatment to the first documentation of disease progression, up to 5 years follow-up
- OS - defined as the interval from the start of Betalutin treatment to death from any cause, including disease progression, up to 5 years follow-up
- Change from baseline in the sum of the product of the greatest perpendicular diameters (SPD) of target lymph nodes as documented radiographically.

Section 5.7 Study Endpoints Part C: Pharmacokinetic Cohort; Synopsis

New section added

Primary endpoints:

Pharmacokinetic assessments e.g. total lilotomab antibodies measurements in serum (total lilotomab antibodies pharmacokinetics) and total radioactivity measurements in blood (Betalutin pharmacokinetics).

Pharmacokinetic parameters (weight adjusted, as appropriate) including, but not limited to: C_{max}, T_{max}, $AUC_{0-\infty}$, AUC_{0-last} and $T_{1/2}$, will be calculated for Betalutin pharmacokinetics and total lilotomab antibodies PK using actual sampling times. Activity-adjusted and dose-adjusted Cmax and AUC will also be calculated using the actual activity (Bq) or dose of total antibodies (mg) injected.

Secondary endpoints:

Incidence and severity of AEs.

Exploratory endpoints:

- **Tumour response rate.**
- **Tumour response duration.**
- **OS.**

Section 6.1 Description of Study Design; Synopsis

Part B

In Part B of the study, **up to 130** patients with relapsed, rituximab/anti-CD20 refractory FL **and platelet count ≥150×10^9/L** who have received ≥2 prior lines of therapy ~~will be enrolled~~ **were initially randomised** in a 1:1 ~~fashion~~ **ratio** to compare the **2 candidate** RP2Ds: 40 mg lilotomab + 15 MBq/kg Betalutin versus 100 mg/m^2 lilotomab + 20 MBq/kg Betalutin) **(65 per treatment regimen) until the selection of one of the 2 regimens for further assessment in clinical development.**

~~Following the Interim Analysis of efficacy and safety data from the first 47 patients, the SRC recommended that all patients receive lilotomab 40mg and Betalutin 15 MBq/kg, with the exception of the patients described below.~~

An interim analysis of efficacy and safety data was planned after approximately 50 patients (see Section 14.1.2.2). This was performed after the first 47 patient and the SRC recommended that the "40/15" regimen be selected for further development. Randomisation was therefore stopped.

Patient enrolment will be completed when a total of 87 patients have received the "40/15" regimen selected for further development (including patients in the randomised section).

~~In Part B, patients with prior auto-SCT (more than 2 years previously) and who have not experienced any ≥ grade 1 GvHD in at least the 8 weeks or more prior to the date of consent may be included.~~

The eligibility criteria for Part B, were also widened (under protocol Version 14), to allow enrollment of patients with prior auto-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 (see Section 4.8.5). The Betalutin dose is to be adapted for these patients.

Further changes as identified for Section 4.2.3.

Part C

Open label phase IIa expansion cohort to enable the collection of samples for Betalutin pharmacokinetics and total lilotomab antibodies pharmacokinetics in at least 10 patients (up to a maximum of 20 patients) receiving the "40/15" regimen.

Figure 6-1 LYMRIT 37-01 Study Design (Part A ~~and,~~ Part B **and Part C**)

Figure notes added:

Part A is closed to enrolment.

Part B (PARADIGME) is open to enrolment for patients with FL.

Part C (Pharmacokinetic Cohort) is open at selected sites (subject to regulatory and EC/IRB Approvals) to enrolment for patients with iNHL. All patients will receive the "40/15" regimen. Patients entering Part C will follow the same Schedule of Assessments (except QoL) as those in Part B.

Definition of study periods:

The *study treatment period* is defined as from the first administration of rituximab pre-treatment until 12 weeks after Betalutin administration. All patients will be closely monitored during the study treatment period.

The *follow-up period* is:

Part A - up to 5 years or until the first anticancer treatment after Betalutin administration. Survival and potential long-term toxicity information will continue to be collected up to 5 years, even after further anticancer treatment has begun. All patients will be followed closely the first year after treatment, thereafter every 6 months (See Section 6.3 Schedule of Assessments).

Part B and Part C - up to 5 years after Betalutin administration.

Extensive follow-up (hospital visits) will take place for all patients every 3 months for the first year (Months 6, 9 and 12). Tumour imaging assessments are only required until the patient has further anticancer treatment after Betalutin administration or disease progression prior to further anticancer therapy as assessed by central imaging review. All other scheduled assessments should be performed.
After Month 12, follow-up will continue every 6 months up to 5 years after the Betalutin dose. Extensive follow-up (hospital visits) must be performed until the patient has further anticancer treatment after Betalutin administration or disease progression prior to further anticancer therapy as assessed by central imaging review. Thereafter, the patient will continue limited follow up every 6 months for potential long term toxicity (new onset adverse events of special interest [AESIs], ADRs and study treatment-related SAEs), OS, further anticancer treatment and ADA testing (only if ADA test is positive at Month 12; testing to be continued until a negative result is obtained). Unless blood sampling is required for ADA testing, limited follow-up visits can be performed by telephone.

Section 6.2 Dose Escalation in Part A / Dose Definition in Special Populations in Part B

Section has been restructured to present the definition of a DLT first (with a clarification that both dose escalation in Part A and dose decisions in Part B were based on the incidence of DLTs) and then to delineate the process for dose escalation in Part A (Section 6.2.2) and the dose definition in special populations in Part B (Section 6.2.3). The summary of changes here identifies changes to the original text but does not identify where text has been re-ordered without wording changes.

Section 6.2.2 Dose Escalation in Part A

The dose escalation in Part A followed ~~a~~ **the traditional** "3+3" design **scheme shown in Table** 6-2.

Table 6-2 has been moved from Section 6.2 to Section 6.2.2

Table 6-3 and the text summarising the dose escalation already completed in Arms 1 to 5 Part A have been moved from Section 6.2.1 to Section 6.2.2

~~*Patients with a screening platelet count of 100-150 x 10^9/L*~~

~~Following review of Arm 4 safety data, the SRC considered that it would be appropriate to allow patients with a screening platelet count of 100-150 x 10^9/L to receive lilotomab 100 mg/m^2 followed by Betalutin 15 MBq/kg for evaluation.~~

Section 6.2.3 Dose Definition in Special Populations in Part B

Text previously included in Section 6.2.2 has been moved to Section 4.8.1.1 without change.

The dose escalation in each subpopulation of patients with prior autologous SCT and/or platelet count $\geq 100\times10^9$/L but $<150\times10^9$/L in Part B (see Section 6.1) will follow the modified "3 + 3" design scheme shown in Table 6-4.

Table 6-4 Modified "3+3 Design" in Part B

Outcome	Action
0 DLT out of 3 patients	**Escalate dose for next 3 patients in the subpopulation:** • **to 15MBq/kg in the subpopulation with prior autologous-SCT and platelet count ≥150×10^9/L.** • **to 15MBq/kg in the subpopulation without prior autologous-SCT, and with platelet count ≥100×10^9/L but <150×10^9/L.** • **to 12.5MBq/kg in the subpopulation with prior autologous-SCT and platelet count ≥100×10^9/L but <150×10^9/L.**
1 DLT out of 3 patients	**Expand this dose level with 3 more patients in the subpopulation.** **The SRC will review the overall safety of the cohort (6 patients) prior to establishing the dose to be recommended. Dose escalation may still be considered (same as for no DLT)**
2 DLTs in a subpopulation	**The SRC may consider a dose reduction to "40/10" for the 2 subpopulations treated with "40/12.5" or may decide to close enrolment in the subpopulation. There will be no dose reduction of Betalutin below 10 MBq.**

All patients will be followed for 6 weeks. The SRC will review the safety data from each set of 3 patients (either 3 or 3+3) (in particular, the number of DLTs) of each subpopulation and recommend the current reduced dosing level be maintained, a dose escalation (including escalation to Betalutin 15 MBq/kg with lilotomab 40 mg), an evaluation of an additional 3 patients, a dose-decrease, a different dose or to stop the recruitment of further patients with a prior autologous-SCT and/or lower platelet count.

Section 6.3 Schedule of Assessments

Due to the inclusion of new Table 6-4 in Section 6.2.3, schedules of assessments have been renumbered (Table 6-4 to Table 6-5, Table 6-5 to Table 6-6, Table 6-6 to Table 6-7, Table 6-7 to Table 6-8 and Table 6-8 to Table 6-9). Cross references in the document have been updated accordingly.

There are separate tables for Part A phase I (~~Table 6-4~~ **Table 6-5**), Part A phase IIa (~~Table 6-6~~ **Table 6-7**), Part B FL phase IIb **and Part C** (~~Table 6-7~~ **Table 6-8**).

Pharmacokinetic and dosimetry schedule of assessments for Part A are described in ~~Table 6-5~~ **Table 6-6** and for Part**s** B **and C** in ~~Table 6-8~~ **Table 6-9**. In Parts B and C, pharmacokinetic assessments will be performed at selected sites only, whereas dosimetry assessments will be performed at sites in Germany and in other agreed sites.

During the coronavirus disease 19 (COVID-19) pandemic, every effort should be made to continue to perform the study visits and assessments according to the planned schedules. Where this is not possible, any deviations should be clearly documented. Any results of assessments performed remotely must be entered into the eCRF.

Part B FL phase IIb **and Part C (Pharmacokinetic Cohort):**

Added text:

Screening assessments should be performed within 4 weeks prior to administration of rituximab. In case of unforeseen delays in the planned rituximab administration, including but not limited to delay in the availability of Betalutin, or delay in HAMA testing or results availability, the screening period may be extended upon Sponsor's approval and the validity of imaging tests and bone marrow biopsy may be extended accordingly.

Table 6-7 Schedule of Assessments – Part A Phase IIa

Table note added:

Note: during the COVID-19 pandemic, it may be necessary to perform certain study procedures remotely. All assessments must be recorded in the eCRF

Table 6-8 Schedule of Assessments - Part B, FL Phase IIb "PARADIGME" **and Part C, Pharmacokinetic Cohort Phase IIa**

Changes to "test type": FL **(Part B) or iNHL (Part C)** disease stage and previous treatment;

Additional haematology sample at D-14 before dosing.

Clarifications to table notes 5, 6 and 7:

5) **At screening: The Bone Marrow Biopsy taken up to 8 weeks before rituximab administration may be used. At Complete Response:** Bone marrow biopsy required for confirmation of CR if patient had bone marrow infiltration at baseline, otherwise it is optional.
6) Blood samples weekly until platelet counts ≥ 100 x 10^9/L and neutrophil counts (ANC) ≥ 1.5 x 10^9/L after nadir values **(these do not require a hospital visit)**.
7) If the patient receives cancer related treatment~~,~~ **they should continue with limited long term follow-up and** ~~withdrawal from study is required. Only~~, record the first course of cancer related treatment.

Tablenote added:

Note: during the COVID-19 pandemic, it may be necessary to perform certain study procedures remotely. All assessments must be recorded in the eCRF

Table 6-9 Schedule of Assessments – Pharmacokinetic and Dosimetry, Part B - "PARADIGME" **and Part C Pharmacokinetic Cohort**

Section 7 Selection of Study Population

~~The target population is patients with relapsed incurable non-Hodgkin B-cell lymphoma.~~

Section 7.1.1 Inclusion Criteria - Part A (phase I and phase IIa) **and Part C (Pharmacokinetic Cohort, phase IIa);** Synopsis

1 Histologically confirmed (by World Health Organization [WHO] classification) relapsed incurable non-Hodgkin B-cell lymphoma of following subtypes; follicular grade I-IIIA **(for Part C, this excludes patients meeting Part B criteria, who should enter Part B)**, marginal zone, small lymphocytic, lymphoplasmacytic, mantle cell.

3 **Part A:** A pre-study WHO performance status of 0-1; **Part C: A pre-study WHO performance status of 0-2.**

7 Women of childbearing potential must:
   a) understand that the study medication is expected to have teratogenic risk.
   b) have a negative pregnancy test.
   c) agree to use, and be able to comply with, effective contraception without interruption, 4 weeks before starting study ~~drug~~ **medication**, throughout study ~~drug~~ **medication** therapy and for 12 months after end of study ~~drug~~ **medication** therapy, even if she has amenorrhoea <*terminology was made consistent with synopsis*>

Section 7.1.2 Inclusion Criteria - Part B; Synopsis

1 Histologically confirmed (by WHO classification) relapsed non-Hodgkin B-cell FL (~~follicular~~ grade I-IIIA).

3 Received at least 2 prior **systemic** anti-neoplastic or immunotherapy-based regimens (maintenance therapy following a CR/PR is not considered to be a separate line of therapy). **Systemic regimens including agents such as idelalisib or other PI3K inhibitors qualify as a prior line of therapy**.

4 Prior therapy must **have** include**d** a rituximab/anti-CD20 agent and an alkylating agent – **which may have been administered in separate regimens.** ~~Prior exposure to other systemic anti-neoplastic agents (including idelalisib or other PI3K inhibitors, etc.) is also allowed.~~

5 Patients must be refractory to ~~any~~ **at least one** previous regimen **that contained** ~~containing~~ rituximab or an anti-CD20 agent, **with refractoriness** defined as:
   i. no response (no CR or PR) during therapy, or
   ii. a response (CR/PR) lasting less than 6 months after the completion of a regimen including rituximab/anti-CD20 therapy (including occurrence of progressive disease (PD) during rituximab/anti-CD20 maintenance therapy, or within 6 months of completion of maintenance therapy).

9 Measurable disease by CT or MRI: longest diameter (LDi) >1.5 cm for nodal lesion, LDi >1.0 cm for extra nodal lesion ~~within~~ **on an assessment performed during the screening period** ~~28 days prior to the start of treatment~~.

Criteria 10 and 11 must be satisfied within 72 hours of the administration of rituximab:

Criteria 12 to 15 must be verified at time of eligibility review within 2 weeks prior to rituximab administration:

17 Male patients must agree to use condoms during intercourse throughout study ~~medication therapy~~ **treatment administration** and ~~the following~~ **for** 12 months **following the administration of Betalutin**.

Section 7.2.1 Exclusion Criteria - Part A (phase I and phase IIa) **and Part C (Pharmacokinetic Cohort, phase IIa)**; Synopsis

2 Laboratory values within 15 days pre-registration:

a. ANC ≤1.5×10^9/L.

b. **Part A:** Platelet count ≤150×10^9/L; **Part C: Platelet count <150×10^9/L.**

For Part C, criteria 2a and 2b must be satisfied within 72 hours of the administration of rituximab

c. Creatinine ≥115 µmol/L (men), 97 µmol/L (women) **(Part A only).**

~~**Adequate renal function as demonstrated by a**~~ Serum creatinine ≥ ~~<~~1.5×ULN (Part C only).

5. ~~Known history of~~ **Positive test for** HAMA.~~(Part A) Positive for HAMA~~ **at screening**

9. **Part A**: Previous treatment with radioimmunotherapy. **Part C: Not applicable**.

12. **Part A and Part C:** Test positive for hepatitis B (HBsAg and anti-HBc**). Part C only: Test positive for hepatitis C and HIV.**

Section 7.2.2 Exclusion Criteria - Part B (FL phase IIb); Synopsis

2 Patients with a prior autologous-SCT are excluded unless at least two years have elapsed since ~~transplantation and the patient has been without grade ≥1 Graft vs Host Disease (GvHD) in the 8 weeks before the date of consent.~~

3 Evidence of histological transformation from FL to DLBCL at time of screening **(transformation to grade IIIB that was successfully treated with recurrence of grade I-IIIA initial clone is accepted).**

5 Prior anti-lymphoma therapy (chemotherapy, immunotherapy or other **systemic agent including any** investigational agent) within 4 weeks prior to start of study treatment (corticosteroid treatment at doses of ≤20 mg/day, topical or inhaled corticosteroids, granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) are permitted up to 2 weeks prior to start of ~~study treatment~~ **rituximab**). ~~Note: excludes pre-treatment with rituximab as part of this study.~~

8 **History of malignancy other than FL within 5 years prior to screening (i.e. patients with cancer diagnosed within 5 years prior to screening or who were diagnosed prior to 5 years and were not in CR or were on treatment within 5 years prior to screening), with the exception of malignancies with a negligible risk of metastasis or death (e.g. 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localised prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer**

~~8 History of a previous treated cancer except for the following:~~

~~a. adequately treated local basal cell or squamous cell carcinoma of the skin.~~

~~b. cervical carcinoma in situ.~~

~~c. superficial bladder cancer.~~

~~d. localised prostate cancer undergoing surveillance or surgery.~~

~~e. localised breast cancer treated with surgery and radiotherapy but not including systemic chemotherapy.~~

~~f. other adequately treated Stage 1 or 2 cancer currently in CR.~~

Section 8 Withdrawal and Termination Criteria

The following text has been moved from Section 8.2 to Section 8.1 to clearly delineate patient withdrawal and termination, with the modifications shown. The start of further anticancer therapy has been removed as a reason for withdrawal

Single patient **withdrawal** ~~termination~~ is per definition:

- when the patient is withdrawn during the treatment period or extensive follow-up without consent to be followed up for survival, collection of long-term toxicities and anticancer therapies ~~(consented patients will be followed up for survival)~~
- when the patient has died.
- ~~Completed the 5 year follow up visit~~

If **a patient dies,** ~~the reason for withdrawal is death~~, the immediate cause of death should be noted, in addition to death caused by underlying disease, the Investigator's judgement on possible relationship to study drug should be recorded in the CRF.

If **a patient starts further** ~~the reason for withdrawal is start of~~ further anticancer **treatment** ~~therapy~~, details of the new anticancer therapy regimen should be noted and recorded in the CRF. ~~Patients who are withdrawn for reasons such as toxicity, or at the start of further anticancer therapy (after Betalutin) will continue in follow up for survival and any potential long term toxicities. Confirmation of continued consent to follow up is recorded in the eCRF.~~

The following text modifications were made to Section 8.1:

It is advisable to monitor the haematology parameters of the withdrawn patients after Betalutin administration **until recovery to Grade 1 NCI CTCAE.**

Survival information, ~~and~~ potential long-term toxicity information **and further anticancer therapy** will continue to be collected on withdrawn patients unless the patient specifically withdraws their consent ~~(see below).~~ Confirmation of continued consent to survival or collection of long term toxicities follow-up is recorded in the eCRF.

The following text was removed from Section 8.2:

~~As described above, consented patients who terminate for any of the above reasons will continue to be followed for survival and any potential long term toxicities.~~

Section 9.1 Study Treatment

Rituximab, lilotomab and Betalutin can all be administered on an outpatient basis. The patient should be under surveillance at the hospital at least 2 hours after administration **of Betalutin** (unless local regulations require a longer surveillance period).

Section 9.1.1 Investigational Drug Product Betalutin

The product is isotonic and has a pH of 6.4-7.4. The radioactive concentration at the reference date will depend on the dose level and the patient body weight; **however, the dose is capped for patients who weigh more than 130 kg (patients heavier than 130 kg will receive the dose for a 130 kg patient).** When administered on a day other than the reference day, the volume should be corrected according to the physical decay table included in the Drug Handling Plan. The measured Betalutin dose must be +/-10% of the intended prescribed dose.

Section 9.1.7 Lilotomab Infusion

Lilotomab will be infused within 4 hours prior to the Betalutin administration. The infusion rate will be 100 mL/hour**. For doses of lilotomab given on a BSA basis, this** ~~Body surface area~~ should be calculated using the duBois calculation.

Section 9.1.7.2 Part B (FL phase IIb)

The following text was removed as irrelevant to a section on lilotomab infusion:

~~However, the first 3 patients in each of the following sub-groups will be reviewed by the SRC. These patients will receive the following doses:~~

- ~~Patients with a prior auto-SCT and who have platelets ≥150x10^9/L will receive Betalutin at the reduced dose of 12.5 MBq/kg.~~
- ~~Patients with a prior auto-SCT and who have platelets <150x10^9/L will receive Betalutin at the reduced dose of 10 MBq/kg.~~

- ~~Patients without a prior SCT, but who have the lower platelet threshold (100 to <150 x 10^9/L) will receive Betalutin at the reduced dose of 12.5 MBq/kg.~~

Section 9.1.7.3 Part C (Pharmacokinetic Cohort, phase IIb)

New section added

In Part C, patients will receive the "40/15" regimen and will therefore receive 40 mg lilotomab.

Section 9.2.2 Methods of Assigning Patients to Treatment - Part B (FL phase IIb)

At the time of evaluation of the patient for enrolment, a patient number will be assigned via an Interactive Web Response system (IWRS). **In the randomised period**, patients will be enrolled to receive one of the two dosing regimens: "40/15" or "100/20".

Further changes as identified for Section 4.2.3.

The purpose of stratification is to balance the number of double refractory patients between treatment regimens. No analysis within strata are planned. Randomisation records are selected by finding the next available minimum patient randomisation number, within the stratum, in the central randomisation list. ~~After approximately 50 patients have been treated (approximately 25 per arm), there will be an interim analysis (IA) to evaluate future study modifications and continuation of both regimens. Subsequently, one or both arms may continue to enrol patients (see Section 14.3).~~

Site users will confirm in the IWRS system when all screening procedures have been completed and the patient is considered eligible for enrolment. A medical monitor will review the patient and confirm that the patient is eligible in the IWRS system before the patient is ~~randomised~~ **enrolled**.

Section 9.2.3 Methods of Assigning Patients to Treatment - Part C (Pharmacokinetic Cohort, phase IIb)

New section added

At the time of evaluation of the patient for enrolment, a patient number will be assigned via an IWRS system. All patients will receive the "40/15" treatment regimen

Site users will confirm in the IWRS system when all screening procedures have been completed and the patient is considered eligible for enrolment. A Sponsor medical monitor will review the patient and confirm that the patient is eligible in the IWRS system before the patient is entered.

Section 9.5 Treatment Compliance

Patients will receive Betalutin treatment under supervision of a nuclear medicine specialist **(or any other specialist physician authorised to administer radiopharmaceuticals per local regulations)**. Study centre personnel will check the administration volume and total radioactivity injected and will record the activity dose and volume injected in the patient's source documents and eCRF.

Patients will receive infusions of lilotomab and rituximab under surveillance by trained personnel used to handle infusions with rituximab. The volume to be given will be prepared by the pharmacy **following instructions of the drug handling manual** and the infusion bags will be delivered as ready to use solutions.

Section 9.6 Study Procedures

Subsections have been added to assist readability:

Section 9.6.1 Screening

- The following changes were made for AEs, ECG, tumour tissue biopsy, HLA typing and viral serology: Part B **and Part C** only
- The following clarification was added for coagulation: **Part B and Part C only**

Section 9.6.2 Treatment Period

Section 9.6.2.1 Pre-treatment, Pre-dosing and Dosing (Day -14 to Day 0): All Patients

Assessment or Procedure	Explanation
Day -14 Pre-dose procedures and assessments (Parts B and C only)	

Haematology	**Including haematocrit, haemoglobin, platelet count, erythrocyte count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils, basophils) Haematology parameters need to be reviewed prior to rituximab administration and it must be verified that ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L**

- The following change was made for immunogenicity: Part B **and Part C** only
- The following change was made to HAMA/**ADA** test**ing**:
  - To screen for pre-existing HAMA. **Eligibility can be assessed using a commercially available test (such as the Milenia Quickline® HAMA test or any commercially available HAMA-ELISA test)**
  - ~~–~~ A serum sample for the IFMA test performed at a central laboratory is mandatory. ~~Eligibility can be assessed using a local test such as the Milenia Quickline® HAMA test (optional).~~

Section 9.6.2.2 Pharmacokinetics and Biodistribution: Applicable Patients

- Change made throughout: Part B **and Part C** only
- Clarifications to Betalutin pharmacokinetics for Part A:
  - **Pre-dose blood sample to be taken before Betalutin dosing**
  - Post-dose blood samples to be taken at the following timepoints after Betalutin dosing: 5 min, 1 hour, 2 hours, **4 hours (patients in whole body study), 8 hours (patients in whole body study)** 1 day, 2 days, 3 days (optional), 4 days, 7 days (±1 day), 14 days (±2 day) and 21 days (±2 days).
- Clarifications to serial whole body scans for Part A: **Whole body scan at 2 hours, 24 hours, Day 4 and Day 7**

Section 9.6.2.3 Part A Day 1 to Week 12

- Clarification added for Day 7 (Part A phase IIa), Week 2 (only Part A phase I patients) and Weeks 3, 5, 6, 7, 9, 10, 11 (all patients):

  The purpose of these visits was to take additional weekly blood samples after Betalutin administration (until platelet and ANC recovered to ≥100×10^9/L and ≥1.5×10^9/L, respectively after nadir values. These samples could be taken remotely, except for patients having whole body studies and/or pharmacokinetic sampling (see Section 9.6.2.2) when a hospital visit was required on Days 7, 14 and 21.

Section 9.6.2.4 Part B Day 1 to Month 3

- Week 1 and 3 changed to Week 1
- Clarification added for Week **3**, 5, 6, 7, 9, 10, 11:

  The purpose of these visits is to take additional weekly blood samples after Betalutin administration (until platelet and ANC recovered to ≥100×10^9/L and ≥1.5×10^9/L, respectively after nadir values. These samples can be taken remotely, except for patients having SPECT/CT and/or pharmacokinetic sampling (see Section 9.6.2.2) when a hospital visit is required on Day 21.

Section 9.6.3 Follow-up Period

Section 9.6.3.1 Part A

Clarification added that QoL is only for Phase IIa

Section 9.6.3.2 Part B and C

Section 9.6.3.2.1 Follow-up – Months 6, 9 and 12 (all patients)

Extensive follow-up (hospital visits) should be performed for all patients at Months 6, 9 and 12

- Clarification added to overall tumour response: Overall tumour response Only for patients without disease progression (per central review) or further anticancer treatment
- Line removed for CD37 expression (at relapse) as this duplicates the line below on tumour tissue biopsy
- Clarification added that QoL is only for Part B only

Section 9.6.3.2.2 Follow-up – after 12 months

Until disease progression or further anticancer treatment

For patients without disease progression or further anticancer treatment at Month 12, extensive follow-up (hospital visits) will continue every 6 months for up to 5 years after the Betalutin dose.

After disease progression or start of further anti-cancer therapy

After disease progression has occurred or other anticancer treatment has started (whichever comes first), limited follow-up only will be performed every 6 months for up to 5 years after the Betalutin dose.

Unless blood sampling is required for ADA, these visits can be performed by telephone.

Months 18, 24, 36, 48, 60	
(Serious) ADR **Adverse events of special interest (AESI)**	**Any AESI and any (S)AEs judged to be related to any of the IMPs (rituximab, lilotomab and Betalutin) ongoing at last visit or occurring since last visit should be recorded**
Cancer related treatment	**Record if the patient has received any cancer-related treatment excluding analgesics since last visit**
Immunogenicity	• **To be done if positive ADA test at Month 12 visit** • **Should continue to do immunogenicity sampling every 6 months until negative ADA test result is obtained.**
Survival status	**Survival status**

Section 10 Pharmacokinetics and Biodistribution

Pharmacokinetics in vitro assessments and biodistribution using SPECT/CT scans (if feasible) will be performed in all arms in **Part A** phase I for 3 patients in each dose level. ~~In phase IIa (Part A) and in FL phase IIb (Part B) of the study, these assessments may be performed at a subset of sites.~~ Dosimetry measurements by use of whole-body and SPECT/CT scans will be performed on up to 3 patients in each dose level in phase I, if feasible. Patient fixation will be done before the first gamma scan.

In Part A (phase IIa), Part B (FL phase IIb) and Part C (Pharmacokinetic Cohort), pharmacokinetic and SPECT/CT assessments will be performed at a subset of sites.

The Schedules of Assessments are shown in Table 6 6 (Part A) and Table 6 9 (Part B **and Part C**).

Whole blood samples will be shipped to the laboratory at Nordic Nanovector ASA (Oslo), for analyses. The radioactivity in whole blood will be determined from each sample. ~~A certificate of analysis will be saved in the TMF.~~

Section 10.1.1.2 In Vitro Assessments

Betalutin Pharmacokinetics - Total radioactivity or Total payload in blood

In Part B and Part C of the study, a volume of approximately 2 mL of peripheral blood will be collected on EDTA in a dedicated collection tube at each agreed time point (see Table 6 9 and below). An exact volume of 1 mL of peripheral blood will be transferred on-site into a RIA tube. Radioactivity measurement will be performed ~~on site at the study centres that are experienced and equipped to perform these assessments, or~~ at Nordic Nanovector ASA (Oslo, Norway).

Instructions for handling procedures, preparation, storage and shipping of the **peripheral blood** samples will be provided in the ~~Nordic Nanovector specific radioactivity~~ **Betalutin pharmacokinetics** laboratory manual **prepared by Nordic Nanovector ASA (Oslo, Norway)** for this study.

Total lilotomab antibodies in serum (Total antibodies PK, Part B **and Part C**)
In Part B **and Part C** of the study, a volume of approximately 4 mL of peripheral blood will be collected in a dedicated serum tube at each agreed time point (see Table 6 9Table 6-8 and below).

Section 10.1.2 Urine Clearance (Part A)
Assessment of total radioactivity in urine is not included in the Part B **or Part C**.

Section 11.1 CD37 Expression in Tumour Biopsies

A new tumour tissue biopsy is to be collected at relapse and/or disease progression (this is dependent on the availability of a suitable lesion **and the patient's willingness to have a further biopsy)**.

In Part B **and Part C**, the FFPE blocks (or 5 µM slides – see below) will be sent to Covance Central Laboratories, where they will be biobanked for future use.

Section 11.3 Biobanking

Biobanking of the biological samples for future use will be performed at Covance Central Laboratories in Indianapolis, Indiana for US patients; **in Singapore for patients in Asia/Australia** and in Geneva, Switzerland for ~~ex US~~ **all other** patients.

Section 12 Efficacy Assessments

For Part A (phase I and phase IIa), tumour response will be determined by investigator assessment. Cheson criteria Versions 1999 and 2007 will be applied (**35**, 36).

For Part B (FL phase IIb) **and Part C (Pharmacokinetic Cohort)**, investigator assessment will **initially** be applied as a measure for assessment of tumour response and any urgent patient management decisions. ~~and as a basis for all protocol guidelines for management of the patient related to disease status.~~ Tumour response will **also** be determined by independent central review **and this assessment used as a basis for all protocol guidelines for management of the patient related to disease progression status. In presence of disease progression per investigator assessment, tumour assessments should continue until disease progression is documented by independent central review, unless an urgent patient management decision is required. All urgent patient management decisions will be documented.** Cheson criteria Version 2014 will be applied (40)

Section 12.1.3 PET/CT Examination

Standard institutional guidelines will be followed. The patient must have fasted for 6 hours prior to PET/CT imaging, water is allowed. **For patients with known hyperglycaemia or diabetes**, the blood glucose level must be < 11 mmol/L before injection of 18Fluorodoxyglucose (FDG). Anti-diabetic drugs cannot be taken on the day of PET/CT examination.

Guidelines for baseline CT examination:

2 Target nodes should be chosen according to **applicable** Cheson criteria, **see Section 12.2** ~~(Version 2007 (36)~~.

Section 12.3 Definitions of Tumour Response Criteria: Part B **and Part C**

Changes as identified for Section 12

Section 12.4 Efficacy Endpoints

Section removed and integrated with Section 14.1.7

Section 13.1.3 Definition of Serious Adverse Event

- A serious adverse event (SAE) is defined as one of the following:
- Results in death (~~i.e. all deaths within 12 weeks of study drug administration~~ excluding deaths due to disease progression). ~~Deaths occurring later than 12 weeks following study drug administration do not need to be reported as SAEs unless they result from an event that started within 12 weeks following study drug administration~~. The reported AE should be the AE that caused the death~~. Any AE resulting in death that occurs outside the AE reporting period that the investigator assesses as possibly related to the study drug should also be reported as serious.~~
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing inpatients' hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is medically important, i.e. defined as an event that jeopardises the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.
- Constitutes a congenital anomaly/birth defect.

Section 13.1.4 Definition of Unexpected Adverse Drug Reaction

An unexpected ADR is an ADR of which the nature or severity is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an authorised product i.e. the Investigator's Brochure for Betalutin or the approved product information (prescribing information) for rituximab). When the outcome of the ADR is not consistent with the applicable product information this ADR should be considered as unexpected. **Reports must also be considered as unexpected if they add significant information on the specificity or severity of an expected ADR.**

The expectedness of an AE/ADR will be determined by the Sponsor.

Section 13.1.8 Assessments of Adverse Events; Seriousness, Causality, and Severity

Each individual AE should be evaluated by the investigator with regard to date of onset, its seriousness, severity, and duration, causal relationship to the IMP and/or concomitant therapy and outcome.

Seriousness will be determined according to the definition, ~~sees~~ **in** Section 13.1.3.

Causality will be determined **for all AEs**. ~~based on the definition in Section 13.1.2~~. All AEs judged ~~by the investigator or the Sponsor~~ as having a reasonable suspected causal relationship to an IMP qualify as ADRs (**as defined in Section 13.1.2**). ~~The Sponsor will not overrule the causality assessment given by the investigator. If the Sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the Sponsor will be provided with the report.~~

~~All toxicities/AEs will be graded according to CTCAE.~~

Section 13.2 Reporting of Adverse Events

Any AEs that occur after a patient has signed the Informed Consent Form and up to 12 weeks after Day 0, must be reported, whether or not it is considered related to any of the study medications

After 12 weeks post last administration of study treatment, only new onset AESIs, and study treatment-related AEs and SAEs must be reported when they come to the investigator's attention.

All AEs will be reported in the patient eCRFs. If more than one AE occurs, each event should be recorded separately. AEs and/or laboratory abnormalities shall be reported to the Sponsor according to the reporting requirements and within the time periods specified in the protocol. All AEs will be followed up until resolved or as clinically required. ~~AEs that occur from 12 weeks after Day 0 that are judged to be related to any of the study medications will be reported when they come to the investigator's attention.~~

Specific information about secondary malignancies such as leukaemia, MDS and aplastic anaemia or any other malignancy, will be collected up to 5 years after study medication administration or relapse of disease, including information about treatment given to the patient due to NHL. See also paragraph on Adverse Events of Special Interest in Section 13.1.7.

Death is not defined as an AE but as an outcome of an AE. It is important that the event leading to the death is reported. **If death is the outcome of an AE**, it will be reported as ~~an AE~~ **such** for **(i) all AEs regardless of relationship to study treatment** up to 12 weeks after ~~Betalutin injection~~ **the last administration of study treatment and (ii) AESI, and study treatment related AEs and SAEs with onset >12 weeks after the last administration of study treatment**. ~~Thereafter, death it will be collected in the eCRFs as survival information. It will be reported as the outcome of an ADR when it is judged as related to IMP.~~

Progression of disease:

- Part A: Progression of disease will be reported as an AE until Week 12. Thereafter progression of disease will be recorded in the eCRF and still used as an efficacy endpoint. It will be the SRC who will decide if a fatal outcome of disease progression should be considered as an expected AE. This will depend on the information received and medical consideration.
- Part B **and C**: Disease progression is not reported as an AE if it is clearly consistent with the suspected progression as determined by the protocol. Hospitalisation due solely to disease progression should NOT be reported as a SAE. Any associated symptoms may be reported as adverse events if there is any uncertainty about the symptom being exclusively due to disease progression, or if it does not fit the expected pattern of progression of the disease.

Section 13.3.1 Reporting of Serious Adverse Events – Investigator's Responsibilities

The investigator shall report all SAEs, regardless of suspected causality~~, occurring after the patient has provided informed consent and until at least 12 weeks following study drug administration~~, immediately (within 24 hours of

the investigator becoming aware of the event) to the Sponsor~~'s representative~~ **or assigned designee**. The immediate report shall be followed by detailed written report(s).

- SAEs will be reported in the following time periods:
- SAEs will be collected from signing informed consent to ensure that any protocol-related SAEs are collected.
- Up to 12 weeks after **the last administration** ~~end~~ of study treatment, whether or not considered related to IMP.

At any time after 12 weeks after **the last administration** ~~last injection~~ **of study treatment** when it comes to the investigator's attention and is judged to be related to the patient's participation in the study or related to ~~the~~ IMP.

Any SAEs experienced after this 12 week period should only be reported to ~~Nordic Nanovector~~ **the Sponsor or assigned designee** if the investigator suspects a causal relationship to the study treatment, or if it is an AESI (see Section 13.1.7). Recurrent episodes, complications or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

All SAEs must be reported to Sponsor~~'s representative~~ **or assigned designee** as follows:

1. Immediately (within 24 hours of discovery of the event) report the event ~~to representative~~ by email, telephone or fax.
2. Complete the SAE report form and send ~~it to representative~~ within 3 working days of the discovery of the event.
3. Follow-up the SAE until resolved or as clinically required, all follow-up evaluations must be reported ~~to representative.~~
4. Record the SAE in the patient eCRFs provided.
5. Document the SAE in the hospital records.

It is important to send "as complete as possible" a report within the timelines. Incomplete information must NOT delay reporting of SAEs. Additional information must be reported once it is available; in follow-up reports using the same SAE forms, but marked as a follow-up report. In Part A, SAEs/SUSARs will be reviewed by both the SRC and the Sponsor.

~~The Sponsor or assigned designee is responsible for reporting all the relevant safety information to the concerned Competent Authorities and to the Ecs/IRBs concerned.~~ Where applicable as per local requirements, the investigator will inform the Ethics Committee (EC)/Institutional Review Board (IRB) ~~and/or the Competent Authority~~ of the SAE. For reporting death of a patient, the investigator shall supply the Sponsor and the EC with any additional information requested.

The Investigator is also responsible for reporting to the Sponsor within 24 hours the occurrence of a new pregnancy (see Section 16.3.7) and IMP dosing errors (see Section 16.3.6). to the Sponsor or assigned designee within 24 hours.

Section 13.3.2 Reporting of Serious Adverse Events - Sponsor's Responsibilities

The Sponsor **or assigned designee** is responsible for the ongoing safety evaluation of the IMP.

The Sponsor **or assigned designee** is responsible for the prompt notification to all concerned investigators, the ECs/IRBs and Competent Authorities where Betalutin studies are ongoing, **of all the relevant safety information, including** findings that affect the health of the patients, impact on the conduct of the study or alter the Competent Authority's authorisation to continue the study in accordance with Directive 2001/20/EC.

The Sponsor has to keep detailed records of all AeEs reported to him by the investigators and to perform an evaluation with respect to seriousness, causality and expectedness. These records shall be submitted to the Competent Authorities in the countries where the clinical study is being conducted, if they so request.

Each individual AE should be evaluated by the Sponsor **or assigned designee**, with regard to its seriousness and causal relationship to the IMP and/or concomitant therapy. **The Sponsor will not overrule the causality assessment given by the investigator. If the Sponsor disagrees with the investigator's causality assessment,**

both the opinion of the investigator and the Sponsor will be provided with the report <*text moved from Section 13.1.8*>

The Sponsor will assess whether or not the AE is unexpected.

The Sponsor or assigned designee will inform all investigators of relevant information about SUSARs <*text moved from Section 13.3.1*>

Section 13.4.1 Diagnosis and Medical History

A histological diagnosis of relapsed incurable NHL of following subtypes; follicular grade I IIIA, marginal zone, small lymphocytic, lymphoplasmacytic, or mantle cell is established by the pathologist at the study site for Part A **and Part C** of the study OR follicular grade I-IIIA for Part B. The proficiency of anti-CD37-antibodies at detecting have been tested against FL samples and shown to be suitable for identifying CD37 positive cells.

For patients enrolling in Part B **and Part C**, tumour tissue **will be obtained to assess CD37 expression by the tumour cells. The tumour tissue samples will be sent to an accredited laboratory in the European Union (EU) or US for CD37 testing**~~. slides for central laboratory staining for CD37 will be obtained. Tumour blocks for central biobanking may also be obtained, this is optional for the patient. STumour tissue samples will be sent to Covance Central Laboratories in Harrogate, UK for staining~~. The results of the analysis are not necessary for inclusion in the study **(with the exception of patients entering in Germany)**, but will be captured in the eCRF.

A summary of the patient's relevant medical history prior to study inclusion should be recorded on the appropriate eCRF page.

CT with contrast agent will be performed at baseline for identifying the tumour lesions. **MRI scans for patients with contrast allergy are acceptable**.

A bone marrow biopsy will be taken from a site not previously irradiated to ensure that there are less than 25% tumour cells **(this may be taken up to 8 weeks before the rituximab administration).**

Section 13.4.6.2 Immunogenicity Assessments - Part B FL Phase IIb **and Part C Pharmacokinetic Cohort phase IIa**

All patients included in Part B **and Part C** of the LYMRIT 37-01 study will be monitored for the development of ADA after treatment up to 12 months.

Instructions for handling procedures, preparation, storage and shipping of the serum samples will be provided in the study **Covance** laboratory manual.

Table 13-4 Volume of Blood to be drawn from Each Patient in the Treatment Period – Part B **and Part C**

Final row assessment changed to "Total (approximate maximum volume for the patients participating in the pharmacokinetic portion of Part B and all patients **in Part C)**"

Section 13.4.5 Clinical Laboratory Parameters

Clarification added to Table 13-2 that the following were for Part B and Part C only: coagulation, HIV test, hepatitis C

Table note added to Table 13-2: **At screening only; post-dose urine pregnancy tests will also be performed in Parts B and C

The investigator will interpret all clinical laboratory test results outside the reference range. ~~using the following criteria:~~

~~1 = Value out of reference range, but not a clinically significant worsening from previous examination.~~

~~2 = Value out of reference range, and a clinically significant worsening from previous examination.~~

Laboratory values outside reference range recorded in the CTCAE, will be graded 1 to 4 according to the CTCAE criteria. **The laboratory CTCAE grade will be derived programmatically for the purpose of reporting in the Clinical Study Report.**

Section 13.4.8 Potential Long-term Toxicity

At the follow-up visits the investigator will observe for indications of potential late-toxicity, such as secondary cancers, acute myelogenous leukaemia, myelodysplastic syndrome, and aplastic anaemia. In addition, physical examination will be performed and blood samples for biochemistry and haematology taken. **Potential long-term toxicity (new onset AESIs, and study treatment-related AEs and SAEs only with onset >12 weeks after the**

last administration of study treatment) must be reported according to Section 13.2. ~~For recording of ADRs see Section 13.3.1.~~

Section 13.4.9 Quality of Life (Part A and Part B)

QoL is not collected from patients entered to Part C.

Section 14 Statistical Methods and Planned Analyses

Text in this section has been re-ordered to improve understanding. Where text has been moved only changes have been identified.

Section 14.1.2 Sample Size **and Statistical Hypotheses** – Part B (phase IIb) Follicular Lymphoma

Subsections 14.1.2.1, 14.1.2.2 and 14.1.2.3 were added:

14.1.2.1 Randomised Part B - Choice of RP2D

Note - Part B of the study **was initiated as** ~~is~~ a randomised, 2-arm, open-label study to further differentiate the risk/benefit of 2 promising dose regimens of lilotomab and Betalutin. **(Protocol Version 11)** *<text moved from Section 14.2, with modifications shown>*.

In total, up to 130 patients **(65 patients per candidate regimen)** with FL will be enrolled.

Based on ~~response~~ data ~~to date~~ **available at time of Protocol Version 11**, a ~~dose~~ difference of 27% in ORR is expected to emerge between the dose regimens with similar low toxicity profiles. The ORR's assumed for each group are: 69% for the 40 mg lilotomab+15 MBq/kg Betalutin arm, and 42% for the 100 mg/m^2 lilotomab+20 MBq/kg Betalutin arm.

A sample size of 65 patients per ~~group~~ arm should be sufficient to detect this difference, using a two-sided significance level 0.05 with at least 80% statistical power. Sample size estimation was performed using nQuery Advisor V7 (Statsol.com). The method was a 2 group continuity corrected chi-square test for equal proportions (55).

14.1.2.2 Interim Analysis – Part B Randomised

<text moved from Section 14.3>

Note - The interim analysis was introduced in Protocol Version 11 and amended in protocol Version 13.

14.1.2.3 Part B – Population treated with "40/15" Regimen

Note - At the interim analysis, the SRC decided to discontinue the "100/20" treatment regimen, and continue with further recruitment in the "40/15" treatment regimen only.

A total of 87 patients, including the those from the interim analysis, will be recruited and treated with the "40/15" regimen.

With 87 patients, there will be more than 90% power to detect a difference of 18% in response rates using a two-sided exact test with a target significance level of 0.05, assuming the response rate under the null hypothesis is 30% and the response rate under the alternative hypothesis is 48%. If there are at least 36 responders in 87 patients, then there will be at least 97.5% chance that the true response rate will be at least 30%.

Moreover, with 87 patients, there will also be more than 90% power to detect a difference in complete response rate of 8% under the null hypothesis versus 20% under the alternative hypothesis.

Section 14.1.3 Part C (phase IIa) Pharmacokinetic Cohort

New section added

At least 10 patients (up to a maximum of 20 patients, all treated with the "40/15" treatment regimen) will be entered into Part C. This number is based on feasibility and the minimum number of patients evaluable for pharmacokinetic analyses (profiles and pharmacokinetic parameter summaries).

For the purpose of pharmacokinetic parameter evaluation and analysis, patients with FL entered into Part B who have also provided PK samples, and who are treated with "40/15" treatment regimen may be combined with patients entered into Part C.

Section 14.1.4 Analysis Populations

Section renumbered from 14.1.3

Definition of populations

The following ~~3~~ **4** populations are defined:

- Pharmacokinetic **(PK)**: The PK Population will be defined as all subjects who received at least a dose of Betalutin and have evaluable PK data, and a complete or agreed sparse scheduled post-dose PK measurements without protocol deviations, ~~violations,~~ or events thought to significantly affect the PK of the drug.

Part C (Pharmacokinetic Cohort, phase IIa)

The primary pharmacokinetic analyses will be conducted on the PK population.

Section 14.1.5 Statistical Methods

Section renumbered from 14.1.4

Results from Part A (Phase I and Phase IIa), **Part B and Part C** will be summarised **separately due to differences in study design, dose regimens and patient populations. However, analyses in specific populations and for specific dose regimens may be performed in the overall study population** ~~from Part B because patients treated in Part A were treated in 3+3 ascending cohorts.~~

The results from this study will be presented mostly using descriptive statistical methods. Details of planned analyses for Parts A, ~~and~~ B **and C** will be provided in separate statistical analysis plans.

Prior to database lock and analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be prepared and approved, describing all the analyses to be performed. The SAP will document any changes to the analyses described in this protocol.

Section 14.1.6 Analysis of Demographic and Pre-treatment Characteristics

Section renumbered from 14.1.5

Demographic data and other pre-treatment characteristics (including medical and disease history) will be summarised by dosing cohort (Part A) or dosing regimen (Part B) **or Part C**.

Section 14.1.7 Analysis of Efficacy Data

New section added and description of all efficacy analyses moved to one section

Tumour response will be reported as follows in individual patients:

- CR
- PR
- SD
- PD
- **NE**

In Part A and Part C: Response rate will be presented as a point estimate of the proportion of responders along with the 95 % exact confidence interval of response rate.

In Part B **randomised period**: The ORR will be compared between dosing regimens using the Fisher's Exact test, **and the difference in response rates and the corresponding 95% exact CI will be presented**. ORR estimates and 95% exact CI **for each dosing regimen** will also be presented.

In Part B Single-arm 40/15 part: – The primary efficacy analysis on ORR (based on independent assessment) will **be performed by testing whether the ORR is less than or equal to 30% against the alternative hypothesis that ORR is greater than 20% at overall two-sided 5% level of significance, i.e.,**

H0: $p = 0.3$ vs. Ha: $p \neq 0.3$

In addition, the secondary efficacy analysis on CRR (based on independent assessment) will be performed by testing whether the CRR is less than or equal to 8% against the alternative hypothesis that ORR is greater than 8% at overall two-sided 5% level of significance, i.e.,

H0: $p = 0.08$ vs. Ha: $p \neq 0.08$

Responders are defined as having CR and PR according to definition in Section 12.3.

Time to event endpoints will **be analysed using standard Kaplan-Meier techniques. The estimate of the median survival curve will be calculated along with the associated 95% confidence intervals (when applicable).** ~~Time to event data will be presented in cumulative distribution plots along with the Kaplan-Meier estimates of the median time to event, when estimable.~~

The efficacy endpoints are:

Text moved from Section 12.4, with changes shown:

Overall Response Rate (ORR)

ORR, defined as the proportion of patients who achieve a CR or PR assessed with the use of standard criteria for lymphoma (1). The ORR will be assessed at 3 months image evaluation.

Best ORR will also be evaluated, taking the best response achieved independent of time point for image evaluation.

Complete Response Rate (CRR)

CRR, defined as the proportion of patients who achieve a CR assessed with the use of standard criteria for lymphoma (1). The CRR will be calculated based on complete responses achieved at any timepoint.

Progression-free survival (PFS)

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.

If none of the above events are observed, PFS will be censored at the date of the last **adequate tumour** assessment (i.e. last CT scan).

Duration of response (DoR)

DoR is the time from when criteria for response (CR or PR) **is** ~~are~~ **first** met to the time of relapse or progression. **Patients who have not relapsed/progressed will be censored at the last adequate tumour assessment.**

Duration of Complete Response (DoCR)

DoCR is the time from when the complete response is first observed to the time of relapse. Patients who have not relapsed will be censored at the last adequate tumour assessment.

Overall survival (OS)

OS is defined as the time from administration of Betalutin to the date of death from any cause. Patients still alive or lost to follow-up are censored at the last date they were known to be alive. Patients still alive are censored at the last known date alive ~~as captured in the survival follow up~~.

During the study and after its completion the cause of death will be registered.

Section 14.1.8 Biodistribution and Pharmacokinetics

Section renumbered from 14.1.8

These data, which are obtained from a subset of patients **in Part A and B, and from all patients in Part C**, as described in Section 10, will be listed by patient by time point.

Individual pharmacokinetic data will be tabulated and total radioactivity in blood (Betalutin PK) and total lilotomab antibodies in serum concentration(s) (total lilotomab antibodies pharmacokinetics) vs. time curves presented. Pharmacokinetic results will also be summarised by cohort (Part A) or dosing regimen (Part B and Part C). ~~The following p~~**Pharmacokinetic** parameters will be determined using non-compartments analyses **including activity-corrected** area under the blood radioactivity vs. time curve, **dose-corrected** area under the serum concentration vs. time curve clearance, apparent volume of distribution and half-life.

Section 14.1.9 Analysis of Pharmacokinetic Data

Section renumbered from 14.1.7

Output will be presented separately for Part A and Part B, **whilst data obtained from Part B patients (treated with the "40/15" regimen) may be combined with data obtained from Part C patients. Additional analysis**

such as pharmacokinetic/pharmacodynamic modelling will be considered pending the size of the PK population.

Section 14.1.10 Analysis of Safety Data

Section renumbered from 14.1.8

The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance. The number of patients reporting AEs, and the number of AEs reported will be presented. AEs will be coded using MedDRA **and graded according to CTCAE**. The events will be tabulated by system organ class, preferred term, CTCAE grading, severity, and relationship to study medication. Start of AE after study medication injection and duration of AEs will also be tabulated. SAEs will also be presented in separate tabulations.

For laboratory data, the number of abnormal and clinically significant observations will be listed by patient and by time of measurement. The laboratory values will also be graded according to toxicity graded as CTCAE. ~~Toxicity will be graded using CTCAE, and reported for all AEs.~~ All patients who receive any amount of the study medication will be evaluated for toxicity.

Section 14.1.11 Analysis of Immunogenicity Data

Section renumbered from 14.1.9

Immunogenicity analysis will be carried out using nominal or actual sampling times. Data will be tabulated by patient by time point. Descriptive statistics (geometric mean, standard deviation, minimum, median, and maximum) and coefficient of variation (%) will be calculated for each relevant immunogenicity parameters. For each of the parameters, summary tables and figures will be generated by arm and dose group. Output will be presented separately for Part A, ~~and~~ Part B **and Part C**.

Section 14.1.12 Handling of Drop-outs and/or Missing Data

Section renumbered from 14.1.10

No missing data will be imputed. ~~However, tumor response for patients who withdraw or become lost to follow up will be summarized summarised as having disease progression (PD) from the time of last known contact.~~

Section 14.1.13 Sub-group Analysis

No sub-group analyses are planned. However, sub-groups may be identified on a data driven basis~~, and such analyses will be considered exploratory and hypothesis generating only~~.

Section 14.2 Analysis for Patients in Part B with FL

Section renumbered from 14.4

The statistical analysis for Part B (in relation to the current single-arm design) will be performed at the following timepoints after last patient has been dosed with Betalutin:

- **After all patients have had at least one post-treatment tumour assessment: This will consist of the baseline data, efficacy data on ORR, CRR and preliminary assessment on the longer-term efficacy outcomes (DoR, DoCR), and selected safety data. No change to the trial conduct nor the statistical analysis plan is envisaged.**
- **9 months post Betalutin administration (6-month follow up of response for all patients with PR or CR): This will consist of the baseline data, efficacy data on ORR, CRR and preliminary assessment on the longer-term efficacy outcomes (DoR, DoCR, PFS, OS), and all safety data accumulated to this point.**
- **15 months post Betalutin administration (12-months follow up of response for all patients with PR or CR): This will include updated analysis on the longer-term efficacy outcomes (DoR, DoCR, PFS and OS) and updated long-term safety data.**
- **5 years: Final analysis will include long-term efficacy outcomes and safety data.**

~~The final efficacy analysis of patients with FL will occur after the last patient has received Betalutin and all enrolled patients with FL have had the opportunity to be followed up for at least 24 weeks (6 months). Safety and immunogenicity data will be included. All visits from all patients will be included in this analysis.~~

~~Therefore, the timing of the final efficacy analyses from Part B will depend on the time taken to recruit the patients to Part B.~~

Pharmacokinetics, immunogenicity and biomarker assessments ~~will~~ **may** be analyzed subsequently and reported in individual analytical reports as addendum to the Clinical Study Report(s). Exploratory biomarkers analysis will be published if relevant.

Section 14.3 Timing of Analysis in Part C (Pharmacokinetic Cohort)

New section added

Pharmacokinetic parameters will be analyzed and summarized at the same time as the final analysis of patients in Part B (Section 14.2). Pharmacokinetic data from patients with FL entered to Part B (and who have also provided pharmacokinetic samples) may be combined with iNHL patients entered to Part C (assuming a dose regimen of "40/15").

The analysis of pharmacokinetic parameters is described in Section 14.1.8.

Section 15.3 Data Management

AEs and SAEs will be handled in the same way as the other data reported in the eCRF. However, in addition the initial notification of SUSARs will be coded and **medically** assessed for reporting to authorities according to national regulatory requirements.

Section 15.4 Retention of Documents

The following information must be retained for at least 15 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region; or at least 15 years have elapsed since the formal discontinuation of clinical development of the IMP: source data, source documents **(including scans/imaging data),** eCRFs, protocol and amendments, drug accountability forms, correspondence, patient identification list, informed consent forms, and any other essential documents.

Section 16.3.6 Collection of IMP Dosing Errors

New section added

A reportable IMP dosing error is defined as follows:

- **Betalutin: greater than +10% of the intended dose.**
- **Lilotomab 40 mg: a dose <30 mg or a dose >70 mg**

The investigator must report an IMP dosing error to the Sponsor's representative or assigned designee within 24 hours of treatment administration or within 24 hours of the error having been identified, following the process for SAE reporting in Section 13.3.

Section 16.3.7.1 Collection of Pregnancy Information - Male Participants with Partners who become Pregnant

Section renumbered from 16.3.6.1

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor **or assigned designee** within 24 hours of learning of the partner's pregnancy following the process for SAE reporting in Section 13.3.

Section 16.4 Safety Review Committee (SRC)

A SRC will periodically review and monitor the safety of patients in this study~~, .and provide recommendations for dose escalation~~. The SRC will consist of 3 to 4 relevant experts (haematologists/oncologists) including the coordinating investigator for the study.

The following safety data are examples of data that may be collected and evaluated for the SRC:

- AEs.
- Laboratory variables: serum chemistry and haematology (Complete blood count (CBC)).
- Immunogenicity
- Vital signs (systolic/diastolic blood pressure, heart rate, and body temperature).
- 12-lead ECG at baseline.

- Physical examination, including WHO (ECOG) PS.
- Long-term toxicity *<paragraph moved from Section 13 without change>*

In Part A, ~~The SRC (Safety Review Committee) and the Sponsor's representative will review the safety data throughout the course of the study. The~~ the SRC ~~will make~~ **made** recommendations for dose escalation and expansion **according to Table 6-2** ~~in Part A~~.

In Part B, the SRC reviewed the safety and efficacy data from the first 47 patients **in the randomised section** and recommended the future dose **for development** to be lilotomab 40 mg and Betalutin 15 MBq/kg.

The SRC will **also** review the safety data ~~(in particular, DLTs)~~ from the first 3 patients in each of the ~~following~~ sub~~-groups of patients in the special~~ **populations in Part B**. ~~These patients will receive the following doses:~~

~~Patients with a prior autologous SCT and who have platelets ≥150×x109/L will be followed for at least 6 weeks. These patients will receive Betalutin at the reduced dose of 12.5 MBq/kg.~~

~~Patients with a prior autologous SCT and who have platelets <150×x109/L will be followed for at least 6 weeks. These patients will receive Betalutin at the reduced dose of 10 MBq/kg.~~

~~Patients without a prior SCT, but who have the lower platelet threshold (100 to <150× x 109/L) will be followed for at least 6 weeks. These patients will receive Betalutin at the reduced dose of 12.5 MBq/kg.~~

~~The safety data from the first 3 patients in each subgroup were evaluated separately~~ **(see Section 6.1) and make recommendations according to Table 6 4**.

In Part C, the SRC may review emerging data ~~from patients entered to Part C~~ at the same time as data from patients entered to Part B is reviewed.

Section 16.5 Independent Review Committee (IRC) - Part**s** B **and C**

From Part C, the IRC may review the radiological and pertinent clinical data from patients entered to this cohort.