CLINICAL STUDY PROTOCOL

Protocol Title: A phase 1b open-label study of Betalutin in combination with rituximab in patients with relapsed/refractory follicular lymphoma (Archer-1)

Protocol Number: 4.0_ 04 Oct 2021
Amendment Number: 3

Study Number: LYMRIT-37-07

Short Title: Study of safety and efficacy of Betalutin and rituximab in patients with FL

Sponsor Name and Legal Registered Address:

Nordic Nanovector ASA
Kjelsåsveien 168B
N-0884 Oslo
Norway

EudraCT Number: 2017-004506-18

Statement about Proper Study Conduct

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

Confidentiality Statement

SPONSOR SIGNATURE PAGE

Study Number: LYMRIT-37-07

Study Title: A phase 1b open-label study of Betalutin in combination with rituximab in patients with relapsed/refractory follicular lymphoma (Archer-1)

Authorised Representative on behalf of Nordic Nanovector ASA:

Christine Wilkinson Blanc MD
Chief Medical Officer
Nordic Nanovector ASA
Kjelsåsveien 168B
N-0884 Oslo, Norway

Signature:

DocuSigned by:
Christine Wilkinson Blanc
Signer Name: Christine Wilkinson Blanc
Signing Reason: I approve this document
Signing Time: 04-Oct-2021 | 1:51:21 PM BST
E5307C8ACD7246348A785BEC9F78CF9D

Date: 04-Oct-2021

Christine Wilkinson Blanc, MD

Albert Chau
Biostatistician
Datacision Limited
55 Station Road
Beaconsfield, Buckinghamshire
HP9 1QL, United Kingdom

Date: 04-Oct-2021

Signature:

DocuSigned by:
Signer Name: Albert Chau
Signing Reason: I have reviewed this document
Signing Time: 04-Oct-2021 | 1:23:07 PM BST
9E0EEC5DCDE944CCADBF63BA0CE6CA8E

Albert Chau, CStat, CSci

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

CO-ORDINATING INVESTIGATOR SIGNATURE PAGE

Study Number: LYMRIT-37-07

Study Title: A phase 1b open-label study of Betalutin in combination with rituximab in patients with relapsed/refractory follicular lymphoma (Archer-1)

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.

DocuSigned by:
Alexander Fossa
Signer Name: Alexander Fossa
Signing Reason: I have reviewed this document
Signing Time: 04-Oct-2021 | 2:27:49 PM BST
D136ADCF32E54DEA8406F281F25B3D06

Signature: …… Date: 04-Oct-2021

Printed name: Alexander FOSSÅ
Title: Chief Physician, MD

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

Reasons for this Amendment

The primary reasons for this amendment are:

1. To update the design and size of the study to remove the study expansion phase, due to difficulties in recruitment in the study.
2. To restrict individual patient's follow-up to a maximum of 25 months (including clarification of reasons for earlier withdrawal), which is the follow-up required for the study primary endpoint. A longer follow up was envisaged for efficacy assessment but has a limited value considering the reduced sample size.
3. To update the study objectives to formally list the biodistribution of Betalutin in combination with rituximab (RTX) and to establish a recommended dose of Betalutin in combination with RTX for phase 2 studies as objectives and to describe the endpoints for pharmacokinetics, pharmacodynamics and biodistribution studies. This is to rectify an oversight in the initial protocol.

Other reasons for the amendment are:

4. Details of study personal have been updated where appropriate
5. Correction of typographical errors have been made, where relevant. Section headings and formatting were updated, where applicable.
6. A clarification was added that tumour scans must be kept at the study site for potential review by the Sponsor but it is not mandatory to send them for storage.

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

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Version 1.0	6th February 2018
Version 2.0	16th October 2018
Version 3.0	19th December 2018
Version 4.0	04 October 2021 (this document)

The changes are individually listed in Appendix 6.

Contents

List of Tables

List of Figures

1. Protocol Summary

1.1. Synopsis

Investigational drug	Betalutin® **(**lutetium [^{177}Lu] lilotomab satetraxetan) Lilotomab Rituximab
Protocol number	Version 4.0_04 Oct 2021
Sponsor	Nordic Nanovector ASA, Oslo, Norway
Study phase	Phase 1b
Study title	A phase 1b open-label study of Betalutin in combination with rituximab in patients with relapsed/refractory follicular lymphoma (Archer-1)
Short title	Study of safety and efficacy of Betalutin and rituximab in patients with FL
Background/ Rationale	Indolent Non-Hodgkin lymphoma (iNHL) remains largely incurable, despite good response rates to first line therapy, and nearly all patients eventually relapse. As patients relapse, they become resistant or refractory to commonly used therapies, including rituximab (RTX) and alkylating agents, and their prognosis worsens, especially for those who are no longer able to tolerate chemotherapy. New therapies with different mechanisms of action are thus needed to improve outcomes in patients who have recurrent NHL following RTX or other anti-CD20-based therapy. CD37 is highly expressed in B-cell NHL and is an attractive target for treatment. Betalutin is a novel CD37-directed antibody radionuclide conjugate (ARC) that has demonstrated clinical activity and is well-tolerated in patients with relapsed iNHL. Preliminary data from a phase 1/2 clinical study (LYMRIT 37-01) show that Betalutin is active as a single agent, and has a favourable toxicity profile, with reversible neutropenia and thrombocytopenia being the main toxicities reported [Kolstad, 2017]. RTX-based combination regimens are a mainstay of NHL treatment. Recently, preclinical data were reported demonstrating that sequential therapy with Betalutin followed by RTX significantly reduced tumour growth and improved overall survival in a murine model of NHL, suggesting synergism between the 2 agents [Repetto-Llamazares, 2016]. One mechanism may be via increased surface CD20 expression following Betalutin exposure [Repetto-Llamazares, 2015]. These data suggest a potential immunomodulatory role of Betalutin in modulating CD20 expression on NHL cells, which may potentially enhance the efficacy of RTX, and support evaluating the combination of Betalutin followed by RTX in patients with recurrent NHL. This phase 1b study will investigate the dosing of Betalutin in combination with RTX, whereby RTX is given shortly following Betalutin to capitalise on potential enhanced CD20 expression after Betalutin administration. One phase 2 study evaluating short course cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone (CHOP)-RTX chemotherapy followed by 90Y-ibritumomab tiuxetan (Zevalin®) in treatment-naïve

	follicular lymphoma (FL) patients has been reported [Jacobs, 2008]. Fifty-five patients received 3 courses of CHOP-RTX followed by Zevalin® once haematologic recovery was attained. One week following Zevalin administration, four additional weekly doses of RTX were given. The incidences of grade 3/4 neutropenia and thrombocytopenia were 51% and 44% respectively, consistent with previously reported data (prescribing information for RTX), and all patients had full haematologic count recovery by 12 weeks post-Zevalin. The use of RTX six months following Zevalin® administration in previously untreated high tumour burden FL patients was reported to convert all partial responses (PRs) to complete responses (CRs) in one study [Rajguru, 2014], but the optimal duration of rituximab therapy is unknown. Combining Betalutin with RTX may be attractive to patients due to a favourable dosing schedule, and potential for maintaining a good quality of life. We hypothesise that combining Betalutin with RTX could enhance both the response rates and the durability of responses in patients with recurrent FL. This protocol describes a Phase 1b, open-label, single-arm, dose escalation study of Betalutin followed by RTX in patients with previously treated FL. The purpose of this study is to characterise the safety, tolerability, pharmacokinetics, pharmacodynamics and anti-tumour activity of Betalutin in combination with RTX.
Objectives (key primary and secondary)	**Primary** • To evaluate the safety and tolerability of Betalutin in combination with RTX **Secondary** • To establish a recommended dose of Betalutin in combination with RTX for phase 2 studies in NHL patients • To evaluate the preliminary anti-tumour activity of combination treatment based on Investigator assessment of tumour response rates • To evaluate the duration of tumour control in patients receiving Betalutin in combination with RTX • To investigate the immunogenicity of Betalutin in combination with RTX
Endpoints (key primary and secondary)	**Primary** • Frequency and severity of adverse events (AEs), serious adverse events (SAEs) and changes in laboratory values graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 **Secondary** • Responses (overall response rate [ORR], CR, PR, stable disease [SD], progressive disease [PD]) as per Cheson 2014 • Duration of response (DoR) • Progression free survival (PFS) • Time to progression (TTP) • Overall survival (OS) • Monitoring of the anti-drug antibody (ADA) response towards lilotomab, Betalutin and/or RTX
Study design	This protocol describes a Phase 1b open-label, single-arm dose escalation study to investigate the activity and safety and preliminary efficacy of Betalutin combined with RTX in patients with FL who have received one or more prior therapies.

	All patients will receive a single intravenous (i.v.) dose of RTX (375 mg/m^2) on Day -14, and then sequential iv administration of lilotomab (40 mg) followed by Betalutin (10 or 15 MBq/kg) within 4 hours on Day 0. Patients will then be administered RTX (375 mg/m^2) i.v. on Days 7, 14, 21 and 28. Two cohorts of 3-6 patients will be evaluated for dose limiting toxicity, in a 3+3 escalation pattern, to determine the Betalutin dose for future phase 2 studies in NHL. Patients will undergo clinical and laboratory assessments during screening/baseline and periodically during treatment. PET/CT and CT (or MRI) imaging will be performed at baseline and then at 3 and 6 months. CT with contrast (or MRI) will be performed at 12, 18, 24 months or until disease progression or withdrawal from the study for any other reason (whichever comes first) . Patients who achieve SD, CR or PR on their Month 3 imaging scan will be administered maintenance RTX 375 mg/m^2 i.v. or 1400 mg s.c. every 3 months for up to 2 years (8 infusions in total), or until disease progression or withdrawal from the study for any other reason (whichever comes first).
Population	FL patients who have received one or more prior therapies
Inclusion/ exclusion criteria	**Inclusion:** Patients are eligible to be included in the study only if all of the following criteria apply: 1) Patient must be ≥18 years at the time of signing the informed consent 2) A pre-study Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 3) Histologically confirmed diagnosis (by 2008 World Health Organisation [WHO] classification) of iNHL FL (grade 1, 2 or 3a) 4) At least one (but not more than 3) prior regimens with an anti-CD20 antibody (alone or in combination with chemotherapy), with documented relapsed, refractory disease (must not be anti-CD20 antibody-refractory) or PD 5) Presence of at least one bi-dimensionally measurable lesion by CT or MRI: longest diameter (LDi) >1.5 cm for a nodal lesion; LDi >1.0 cm for an extranodal lesion within 28 days prior to start of treatment 6) Normal organ and bone marrow function defined as: a) Absolute neutrophil count ≥1.5 x 10^9/L; b) Platelet count ≥150 x 10^9/L; c) Haemoglobin ≥9 g/dL; d) Total bilirubin ≤1.5 x upper limit of normal (ULN) (except patients with documented Gilbert's syndrome [<3.0 mg/dL]); e) Liver enzymes: Aspartate transaminase (AST); Alanine transaminase (ALT) or Alkaline phosphatase (ALP) ≤2.5 x ULN (or ≤5.0 x ULN if liver involvement by primary disease); f) Adequate renal function as demonstrated by a serum creatinine within the upper limit of normal range 7) Bone marrow involvement by lymphoma <25% 8) Life expectancy >3 months 9) Negative hepatitis B, hepatitis C and human immunodeficiency virus (HIV) screening tests 10) Undetectable human anti-murine antibodies (HAMA) at screening

	11) Women of childbearing potential must: a. have a negative serum pregnancy test at screening b. understand that the study medication is expected to have teratogenic risk c. agree to use, and be able to comply with, highly effective method of birth control with a Pearl-Index ≤1% Contraception is required without interruption, from 4 weeks before starting study drug, throughout study drug therapy and for 12 months after end of study drug therapy, even if she has amenorrhea 12) Male patients must agree to use condoms during intercourse throughout study drug therapy and for 12 months after end of study drug therapy 13) The patient is willing and able to comply with the protocol, and agrees to return to the hospital for follow-up visits and examination 14) Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol **Exclusion:** Patients are excluded from the study if any of the following criteria apply: 1. Previous haematopoietic stem cell transplantation (autologous and allogenic) 2. Evidence of histological transformation from FL to diffuse large B-cell lymphoma (DLBCL) at time of screening 3. Previous total body irradiation 4. Chemotherapy, immunotherapy, or investigational therapy within 28 days before the start of study drug administration (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) or failure to recover from AEs associated with prior treatment 5. Previous treatment with radioimmunotherapy 6. Patients who are receiving any other investigational medicinal products 7. Known or suspected central nervous system (CNS) involvement of lymphoma 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 9. Pregnant or lactating women 10. Exposure to another CD37 targeting drug 11. A known hypersensitivity to RTX, lilotomab, Betalutin or murine proteins or any excipient used in rituximab, lilotomab or Betalutin 12. Receipt of 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, 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) in the past 24 weeks
Sample size	6 to 12 patients will be enrolled
Treatment groups, dose, route of administration, treatment regimen	Single arm study with patients to be treated with the following study drugs: **Rituximab -** 375 mg/m^2 to be administered by i.v. infusion through dedicated line at Days -14, 7, 14, 21 and 28. Patients who achieve SD, CR or PR on their Month 3 imaging scan will be administered maintenance RTX 375 mg/m^2 i.v. or 1400 mg s.c. every 3 months for up to 2 years (8 infusions in total), or until disease progression or withdrawal from the study for any other reason (whichever comes first). **Lilotomab –** 40 mg to be administered by i.v. infusion at Day 0 **Betalutin –** 10 or 15 MBq/kg to be administered by slow bolus i.v. injection within 4 hours following lilotomab on Day 0
Efficacy assessment(s)	PET/CT and CT (or MRI) imaging will be performed at baseline and then at 3 and 6 months. CT with contrast (or MRI) will be performed at 12, 18, 24 months or until disease progression or withdrawal from the study for any other reason (whichever comes first) Tumour response will be determined locally according to Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and non-Hodgkin Lymphoma [Cheson, 2014]
Safety assessment(s)	In the treatment phase vital signs, electrocardiogram (ECG), physical examination, haematology, serum biochemistry and all AEs are collected at specified time points. Two cohorts of 3-6 patients will be initially evaluated for dose limiting toxicity before determining the subsequent Betalutin dose for the remainder of the study. Dose-escalation decisions will be made by the Investigator(s) and Sponsor following review of the safety data once haematologic recovery has occurred. After the last dose of rituximab, vital signs, ECG (final visit only), physical examination, haematology, serum biochemistry, Adverse Drug Reaction (ADR) and Adverse Events of Special Interest (AESI) will be collected at an end of study visit that will occur at least 28 days post last administration of study treatment. Patients in survival follow-up at time of Protocol v4.0 approval can have the EOS visit at their next scheduled visit or an earlier convenient time point.
Pharmacokinetics and biodistribution	Total radioactivity measurements in blood will be performed at certain intervals until Day 28. Mandatory at Radium Hospital (Oslo, Norway) only, otherwise optional. Patients will undergo SPECT imaging at certain time points in order to measure distribution of

	Betalutin in the body and calculate absorbed radiation dose to target organs/tissues and tumours.
Biomarker assessments	Biomarkers assessments including CD20 and CD37 expression in tumour tissue biopsy and immunophenotyping of circulating lymphocyte subsets (absolute cell counts), will be performed at various time points throughout the study
Other biomarker studies on additional samples	Biomarkers including but not exclusive to MRD (blood) and gene expression changes related to disease treatment in tumour tissue (archival or newly collected biopsy at screening, relapse or disease progression), will be assessed at various time points throughout the study. Patient's major histocompatibility complex (MHC) class I/II haplotype will be defined using peripheral blood (DNA) or saliva (DNA). Anti-tumour T-cell responses will be explored by flow cytometry after co-culture of peripheral mononuclear cells (blood) and autologous lymphoma cells (biopsy and/or needle aspirate), and other biomarkers at selected time points throughout the study at Radium Hospital (Oslo, Norway) only.
Statistical methods and data analysis	The safety analysis population will include all patients who received at least one dose of any study drug. The intent-to-treat (ITT) population will consist of all patients who were enrolled and treated with lilotomab/Betalutin, regardless if RTX therapy was initiated. The number and percentage of patients with each response and overall (complete + partial responders) will be presented for each time point for the ITT population. Pharmacokinetic, biodistribution and biomarker exploratory analyses will be described in the statistical analysis plan finalised before database lock.
Key dates	The start date of the study (first patient included) was in October 2018. The expected accrual time is 18 months. Patients will be followed up for up to 25 months (End of study visit) after Betalutin administration. Patients in survival follow at time of Protocol version 4.0 approval can have the EOS visit at their next scheduled visit or an earlier convenient time point

1.2. Schedule of Activities (SoA):

Table 1-1 Treatment, safety and efficacy (Screening to Month 3/Week 12)

Procedure	Protocol Section	Screening	Treatment Period									
		Pre-study (Up to 4 weeks before 1st rituximab dose)	D-14 Dosing Day	D0 Dosing Day	D+7 Week 1 Dosing Day (±2 days)	D+14 Week 2 Dosing Day (±2 days)	D+21 Week 3 Dosing Day (±2 days)	D+28 Week 4 Dosing Day (±2 days)	Week5+ Weeks 5, 6 and 7 (±2 days)	Month 2 Week 8 (±2 days)	Month 2+ Weeks 9, 10 and 11[17] (±2 days)	Month 3 Week 12 (±7 days)
Hospital visit		X	X	X	X	X	X	X		X		X
Obtain informed consent	Appendix 2	X										
Demographics	Section 8.1	X										
Inclusion/exclusion criteria	Section 5	X										
Medical history (includes substance useage)	Section 8.1	X										
Urinalaysis	Section 8.1	X										
Concomitant medication/therapy	Section 6.6	X	X	X[12]	X	X	X	X		X		X
Antineoplastic therapy since discontinuation	Section 8.3											
Physical examination	Section 9.2.6.1	X	X	X				X		X		
Height	Section 8.1 / 8.2	X										
Weight	Section 8.1 / 8.2	X	X	X								X
Vital signs	Section 9.2.6.2	X	X	X[13,14]	X	X	X	X		X		X
12-lead ECG (also to be performed at any other stage if clinically indicated)	Section 9.2.6.3	X		X[13]	X			X				X
ECOG Performance Status	Section 9.2.6.1	X	X	X				X		X		X
Haematology	Section 9.2.6.4	X	X	X	X	X	X	X	X	X	X	X
Serum biochemistry	Section 9.2.6.4	X	X	X	X	X	X	X	X	X	X	X
Immunophenotyping[1]	Section 9.2.6.4	X		X[13]				X				X
Coagulation	Section 9.2.6.4	X										X
HIV test	Section 9.2.6.4	X										
Hepatitis B and C test	Section 9.2.6.4	X										
Pregnancy test (WOCBP only)	Section 8.1	X		X[13]				X				
Immunoglobulin levels	Section 9.2.6.4	X						X				X
HAMA at screening[2]	Section 9.2.6.4	X										
Immunogenicity[3]	Section 9.2.6.5	X						X				X
Immunohistochemistry[4]	Section 9.4	X										
Gene expression analysis in tumour (optional)[5]	Section 9.5	X										
HLA haplotyping (blood or saliva)[6]	Section 9.4	X										
Minimal Residual Disease	Section 9.4	X[10]										X[18]
Bone marrow biopsy	Sections 8.1 / 8.2 / 8.3	X										X[19]
Radiology assessments	Section 9.1	X[11]										X[11]
Anti-tumour T cell response (Optional, Radium Hospital only)												
New tumour tissue biopsy (surgical)[7]	Section 9.4	X										
New tumour tissue biopsy (Fine needle aspiration)[8]				X[13, 15]								X
Additional blood collection[9]		X										X
Study drug administration												
Rituximab administration	Section 6.3.3		X		X	X	X	X				
Lilotomab administration	Section 6.3.4			X[16]								
Betalutin administration	Section 6.3.1			X								
Adverse events	Section 9.2	Continuous										
AESI monitoring	Sections 9.2.1.4 / 9.2.1.7											
Survival status	Section 7.2											

Table 1-2 Treatment, safety and efficacy (Month 3/Week 14 to Month 25/Week 108 - EOS)

Procedure	Protocol Section	Treatment Period										Additional optional tests to be performed at visit following relapse or progressive disease
		Month 3 Week 14 (±7 days)	Month 6 Week 26 (±7 days)	Month 9 Week 39 (±7 days)	Month 12 Week 52 (±7 days)	Month 15 Week 65 (±7 days)	Month 18 Week 78 (±7 days)	Month 21 Week 91 (±7 days)	Month 24 Week 104 (±7 days)	Month 25 End of study [25] Week 108 (±7 days)		
Hospital visit		X	X	X	X	X	X	X	X	X		
Obtain informed consent	Appendix 2											
Demographics	Section 8.1											
Inclusion/exclusion criteria	Section 5											
Medical history (includes substance useage)	Section 8.1											
Urinalaysis	Section 8.1											
Concomitant medication/therapy	Section 6.6	X	X	X	X	X	X	X	X	X		
Antineoplastic therapy since discontinuation	Section 8.3											
Physical examination	Section 9.2.6.1	X		X		X	X	X	X	X		
Height	Section 8.1 / 8.2											
Weight	Section 8.1 / 8.2											
Vital signs	Section 9.2.6.2	X	X	X	X	X	X	X	X	X		
12-lead ECG (also to be performed at any other stage if clinically indicated)	Section 9.2.6.3											
ECOG Performance Status	Section 9.2.6.1		X	X	X	X	X	X	X	X		
Haematology	Section 9.2.6.4		X	X	X	X	X	X	X	X		
Serum biochemistry	Section 9.2.6.4		X	X	X	X	X	X	X	X		
Immunophenotyping [1]	Section 9.2.6.4		X	X	X							
Coagulation	Section 9.2.6.4											
HIV test	Section 9.2.6.4											
Hepatitis B and C test	Section 9.2.6.4											
Pregnancy test (WOCBP only)	Section 8.1											
Immunoglobulin levels	Section 9.2.6.4		X		X							
HAMA at screening [2]	Section 9.2.6.4											
Immunogenicity [3]	Section 9.2.6.5		X		X		X		X			
Immunohistochemistry [4]	Section 9.4											X
Gene expression analysis in tumour (optional) [5]	Section 9.5											X
HLA haplotyping (optional - blood or saliva) [6]	Section 9.4											
Minimal Residual Disease	Section 9.4		X[18]		X[18]				X[18]			X
Bone marrow biopsy	Sections 8.1 / 8.2 / 8.3		X[19]		X[19]		X[19]		X[19]			
Radiology assessments	Section 9.1		X[11]		X[22]		X[22]		X[22]			
Anti-tumour T cell response (Optional, Radium Hospital only)												
New tumour tissue biopsy (surgical) [7]	Section 9.4											
New tumour tissue biopsy (Fine needle aspiration) [8]			X[20, 21]									
Additional blood collection [9]				X[20]								
Study drug administration												
Rituximab administration	Section 6.3.3	X	X	X	X	X	X	X	X			
Lilotomab administration	Section 6.3.4											
Betalutin administration	Section 6.3.1											
Adverse events	Section 9.2	Continuous										
ADR & AESI monitoring	Sections 9.2.1.4 / 9.2.1.7											
Survival status	Section 7.2											

All blood samples at each visit to be taken before study drug administration (unless specified)

1) Define absolute cell counts for peripheral blood T-cells, CD4 T-cells, CD8 T-cells, B-cells and NK cells, respectively identified as CD3+, CD3+CD4+, CD3+CD8+, CD19+ and CD3- CD16+ CD56+ lymphocytes, by flow cytometry.
2) A serum sample will be sent for HAMA screening to a central laboratory (mandatory). Eligibility can be assessed using a local test such as the Milenia Quickline® HAMA test (optional).
3) Assessment of anti-drug antibodies directed against lilotomab, Betalutin and/or RTX.
4) CD37 and CD20 expression in tumour will be assessed by immunohistochemistry. Prior to treatment, an archived tumour tissue biopsy (FFPE block) can be used. If not available, a new tissue biopsy to be collected surgically at screening.
A new tumour tissue biopsy (optional) will be collected surgically at relapse and /or disease progression. Preparation of the 5 µM FFPE slides for the analysis will be performed only when requested by Sponsor.
Note: A sample of the archived or newly collected tumour tissue biopsy will be used to calibrate the blood MRD test (see footnote 10). A biopsy sample may also be used for the optional gene expression analysis in tumour (see footnote 5).
5) Optional, A sample of an archived or new tissue biopsy collected prior to treatment, at relapse and/or disease progression can be used (see footnote 4). Preparation of the 5 µM FFPE slides for the analysis only when requested by Sponsor.
6) Optional, HLA-typing. Blood sample preferred or alternatively a saliva sample either direct or via mouth swab may be taken.
7) Optional, to be performed at Radium Hospital (Oslo, Norway) only. Additional tumour tissue biopsy (surgical) to explore the anti-tumour T-cell response.
8) Optional, to be performed at Radium Hospital (Oslo, Norway) only. Additional tumour tissue biopsy (fine needle aspiration) to explore the anti-tumour T-cell response.
9) Optional, to be performed at Radium Hospital (Oslo, Norway) only. Additional peripheral blood samples to explore the anti-tumour T-cell response.
10) A sample of an archived tumour biopsy collected before treatment or a new tumour tissue biopsy collected at screening will be used to calibrate the blood MRD test (see footnote 4). Preparation of the 5 µM FFPE slides for the analysis only when requested by Sponsor.
11) FDG PET/CT Imaging and Contrast CT or MRI.
12) Before lilotomab and after Betalutin administration.
13) Pre-lilotomab administration.
14) 2-4 hours after Betalutin administration.
15) Sample may be taken at Day -1 or Day 0.
16) On the dosing day, within 4 hours prior to Betalutin administration.
17) Blood samples weekly until platelet counts ?100 x 109/L and neutrophil counts (ANC) ?1.5 x 109/L after nadir values.
18) Mandatory blood sampling, unless relapse or disease progression has been clinically observed since the previous sampling.
19) Bone marrow biopsy required for confirmation of initial CR if patient had bone marrow infiltration at baseline. Otherwise it will be optional.
20) Before RTX dosing.
21) Optional biopsy to be taken only if there is sufficient tumour remaining at this timepoint.
22) Contrast CT/MRI only.
23) *Removed in Version 4.0*
24) To be performed every 6 months during scheduled visit or by telephone.
25) Patients in survival follow up at time of Protocol v4.0 approval can have the EOS visit at their next scheduled visit or an earlier convenient time point. Collection of concomitant medications is not mandated for these patients, but AESIs must be assessed

Table 1-3 Pharmacokinetics and biodistribution

Test Type	Day -14	Day 0 relative to Betalutin dosing					Day 1	Day 4	Day 7	Day 28
	2 weeks prior to dosing	Dosing Day	Pre-dose	5 min	60 min	2 hrs	24 hrs	96 hrs	W1	W4
Visit Window			must be pre-dose	± 2 min	± 10 min	± 15 min	± 4 hrs	± 24hrs	± 2d	± 2 d
Rituximab infusion	X								X	X
Lilotomab infusion		X[1]								
Betalutin administration		X								
Pharmacokinetics[3]			X[2]	X	X	X	X	X	X[4]	X[4]
SPECT/CT[3]						X	X	X[3]	X	

1) Lilotomab infusion within 2-4 hours prior to Betalutin injection.

2) One baseline blood sample **before lilotomab and Betalutin dose.**

3) To be performed at Radium Hospital (Oslo, Norway) only; otherwise optional.

4) Before RTX dosing.

2. Introduction

Betalutin® (^{177}Lu-lilotomab satetraxetan) is a beta-emitting antibody radionuclide conjugate (ARC) composed of a murine anti-CD37 immunoglobulin G_1 (IgG_1) antibody (lilotomab) conjugated via lysine groups to a p-SCN-benzyl-DOTA chelator (satetraxetan). Betalutin is specifically designed to treat non-Hodgkin lymphoma (NHL). The chelator complexes the radionuclide,^{177}Lu, to form the ARC. The CD37 antigen is highly expressed (>90%) on B-cells and on the surface of tumours of B-cell origin, including NHL and chronic lymphocytic leukaemia [1-3]. Betalutin is administered systemically. Lutetium-177 emits beta-radiation, resulting in DNA damage and tumour cell death. ARCs may be a beneficial approach for treating NHL, because this disease is radiosensitive.

Betalutin has been in clinical development for almost 5 years and approximately 65 patients (the majority with indolent NHL [iNHL]) have been dosed. It is currently being investigated as a single agent in clinical studies in iNHL and relapsed/refractory diffuse large B-cell lymphoma (DLBCL). Betalutin is injected after pre-treatment with the anti-CD20 antibody rituximab (RTX) to deplete B-cells (given 2 weeks prior to Betalutin), within 4 hours following pre-dosing with the cold antibody lilotomab. The clinical development is currently most advanced in patients with relapsed iNHL/follicular lymphoma (FL).

2.1. Study Rationale

Indolent NHL remains largely incurable, despite good response rates to first line therapy, and nearly all patients eventually relapse. As patients relapse, they become resistant or refractory to commonly used therapies, including RTX and alkylating agents, and their prognosis worsens, especially for those who are no longer able to tolerate chemotherapy. New therapies with different mechanisms of action are thus needed to improve outcomes in patients who have recurrent NHL following RTX or other anti-CD20-based therapy.

CD37 is highly expressed in B-cell NHL and is an attractive target for treatment. Betalutin is a novel CD37-directed ARC that has demonstrated preliminary efficacy and safety in patients with relapsed iNHL. Preliminary data from a phase 1/2 clinical study (LYMRIT 37-01) show that Betalutin is active as a single agent, and has a favourable toxicity profile, with reversible neutropenia and thrombocytopenia being the main toxicities reported [4].

RTX-based combination regimens are a mainstay of NHL treatment. To be effective, RTX depends on selective expression of sufficient numbers of CD20 antigens per cell. Treatment with RTX alone or in combination with chemotherapy can, however, result in RTX resistance through downregulation or disappearance of CD20 expression [5-8] which can result in significantly reduced clinical effect of subsequent CD20 targeted treatments [5, 9, 10].

Recently, preclinical data were reported demonstrating that sequential therapy with Betalutin followed by RTX significantly reduced tumour growth and improved overall survival in a murine model of NHL, suggesting synergism between the 2 agents [11]. One mechanism may be via increased surface CD20 expression following Betalutin exposure [12]. These data suggest a potential role of Betalutin in modulating CD20 expression on NHL cells, which may potentially enhance the efficacy of RTX, and support evaluating the combination of Betalutin followed by RTX in patients with recurrent FL. Increased in vivo anti-tumour activity of the combination of a ^{177}Lu-labelled anti-CD22 antibody followed by RTX has also been reported [13]. Another mechanism of action for the synergism between ^{177}Lu-ARC therapy and RTX might be the immunomodulatory effect of low dose-rate radiation. Regulatory T-cells (T_{regs})

produce anti-inflammatory cytokines and create an immunosuppressive environment [14] so that the immune cells that are necessary for RTX anti-tumour action are not recruited to the tumour site. The T_{regs} are very radiosensitive and ^{177}Lu-ARC therapy targeted to the tumour site will inactivate them and potentially increase the effect of subsequent RTX therapy [15].

Combination regimens using biologics and immunomodulatory agents are becoming more popular due to both reduced toxicity compared to chemotherapy and the potential for better efficacy due to alternative mechanisms of action. Patients may benefit from higher response rates, a longer duration of response and delayed time to progression.

The combination of lenalidomide/RTX is efficacious in patients with relapsed, non-rituximab-refractory NHL, however prolonged daily administration of lenalidomide is required, and there are associated toxicities of cytopenias, rash and fatigue, some leading to treatment discontinuation, and a risk of thrombosis [16].

This phase 1b study will investigate the dosing of Betalutin in combination with RTX, whereby RTX is given shortly following Betalutin to capitalise on potential enhanced CD20 expression after Betalutin administration. One phase 2 study evaluating short course cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone (CHOP)-rituximab chemotherapy followed by ^{90}Y-ibritumomab tiuxetan (Zevalin®) in treatment-naïve FL patients has been reported [17]. Fifty-five patients received 3 courses of CHOP-RTX followed by Zevalin® once haematologic recovery was attained. One week following Zevalin administration, four additional weekly doses of RTX were given. The incidences of grade 3/4 neutropenia and thrombocytopenia were 51% and 44% respectively, consistent with previously reported data (prescribing information for MabThera), and all patients had full haematologic count recovery by 12 weeks post-Zevalin. The use of RTX 6 months following Zevalin® administration in previously untreated high tumour burden FL patients was reported to convert all partial responses (PRs) to complete responses (CRs) in one study [18], but the optimal duration of RTX therapy is unknown. Combining Betalutin with RTX may be attractive to patients due to a favourable dosing schedule, and potential for maintaining a good quality of life. We hypothesise that combining Betalutin with RTX could enhance both the response rates and the durability of responses in patients with recurrent FL.

This protocol describes a Phase 1b, open-label, single-arm, dose escalation study of Betalutin followed by RTX in patients with previously treated FL. The purpose of this study is to characterise the safety, tolerability, pharmacokinetics (PK), pharmacodynamics and anti-tumour activity of Betalutin in combination with RTX.

2.2. Background

2.2.1. Disease background

NHLs are a heterogeneous group of lymphoproliferative malignancies primarily of B-cell origin that account for approximately 5% of all new cases of cancer in the US per year. The World Health Organization (WHO) classification of lymphoma recognises a variety of NHL subtypes that can be categorised as indolent in nature [19]. The most common of these is FL, which represents approximately 25% of all newly diagnosed cases of NHL and 70% of indolent lymphomas. The incidence of NHL is strongly related to age; approximately 50% of cases are diagnosed in patients age 65 and above, with the peak incidence being between the ages of 75 and 85 [www.seer.gov], thus many patients have co-morbidities, which can complicate or render them ineligible for current treatment options.

An estimated 72,240 new cases of NHL (approximately 15,000 new FL cases) are expected in the US in 2017 (4.3% of all new cancer cases), and an estimated 20,140 people will die of this disease [www.seer.gov]. Patients with recurrent FL who develop resistance to RTX and alkylating agents, particularly the elderly, and those who experience disease progression within 2 years of first-line therapy have the greatest need for new treatment approaches in FL. The 5-year overall survival rates for RTX-refractory FL patients and those with early disease progression are 58% and 50% compared to approximately 90% for all FL patients [19, 20] [www.seer.gov].

The diagnosis and staging of FL are made on the basis of lymph node and bone marrow biopsies, and PET/CT scans. The hallmark t(14;18) translocation is found in 85% of FL, and induces lymphomagenesis. The current grading system evaluates the histological proportion of centrocytes to centroblasts: grade 1-2 FL is defined as ≤15 centroblasts per high-powered field, and grade 3 FL has >15 centroblasts per high-powered field. Grade 3 FL is further subcategorised as 3A or 3B; 3B is a distinct biologic entity characterised by an absence of centrocytes and has a clinical course more similar to DLBCL.

Indolent B-cell NHLs and FL are usually diagnosed in the advanced stage and require systemic therapy. The standard of care for patients with advanced-stage, symptomatic or high tumour-burden grade 1, 2 and 3A FL is immuno-chemotherapy with cyclophosphamide, vincristine and prednisolone (CVP), CHOP or bendamustine in combination with an anti-CD20 monoclonal antibody (mAb) [21-23]. The addition of RTX to chemotherapy has improved response rates, duration of response and overall survival; median survival is now estimated to be greater than 12-15 years [24, 25] Use of maintenance RTX has improved progression free survival (PFS) compared to observation, with no impact on overall survival (OS) as of yet [24].

While immuno-chemotherapy regimens are initially effective in inducing responses in most, the majority of patients inevitably relapse, and the same therapies show decreasing efficacy with repeated administration. Many patients become resistant to RTX or RTX-containing regimens. Treatment options for patients who have failed first-line therapy depend upon factors such as prior treatment used, patient age and co-morbidities, and duration of prior response. Bendamustine or CHOP is commonly given with RTX. For patients who relapsed after, or are refractory to RTX, the combination of bendamustine-obinutuzumab followed by obinutuzumab monotherapy was recently shown to be superior to bendamustine alone for PFS in the phase 3 “GADOLIN” study. This resulted in a full approval by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in 2016 for the treatment of patients with FL who relapsed after, or are refractory to, a RTX-containing regimen.

Fludarabine-based regimens are another option [22] but caution is warranted for use in elderly or heavily pre-treated patients due to toxicity. Radioimmunotherapy targeting CD20 (Yttrium-90 [^{90}Y]-ibritumomab tiuxetan; Zevalin) is approved for patients with relapsed or refractory, low-grade or follicular B-cell NHL, but is underused [26].

Thus, there remains a significant unmet medical need for therapies for patients with recurrent FL, especially for elderly patients who are at risk for developing long-term toxicities such as cumulative myelosuppression, cardiac toxicity and immunosuppression.

2.2.1.1. Non-clinical pharmacodynamics

Betalutin targets and binds the human CD37 antigen, which is abundant on the cell surface of tumours of human B-cell origin, including FL.

Lilotomab does not bind to FcγRIIIA and does not induce antibody dependent cellular cytotoxicity (ADCC). It does not bind to the neonatal Fc receptor either. This is a desirable property as it limits the half-life of lilotomab in the blood and reduces the time for Betalutin to irradiate normal organs which are rich in blood. In addition, lilotomab binds to human C1q at concentrations above 2 μg/mL but does not induce complement dependent *in vitro* cytotoxicity.

In vitro, Betalutin is highly cytotoxic in multiple lymphoma cell lines with high expression of CD37, appearing to be superior in reduction of cell growth when compared with ^{177}Lu-RTX. Betalutin is internalised, which may result in a higher absorbed radiation dose to cells treated with Betalutin than with cells treated with non-internalizing Radioimmunoconjugates (RICs), such as ^{177}Lu-RTX. The effect of the unlabelled lilotomab antibody on the growth of lymphoma cells *in vitro* and *in vivo* has been tested in Daudi and Ramos Burkitt's lymphoma models. No growth inhibition of Daudi cells *in vitro* treated with 100 μg/mL lilotomab for 2 hours or 18 hours was observed.

In vivo, Betalutin was highly active, increasing survival compared with controls in immune-compromised mice (SCID) mice after intravenous (i.v.) injection of CD37-positive Daudi cells, and inhibiting tumour growth and increasing survival in Nude mice with Ramos lymphoma xenografts *in vivo* [27, 28]. The main toxicities were haematological in nature. In an i.v. model of mantle cell lymphoma (Rec-1 cells), Betalutin alone and in combination with RTX resulted in significantly improved survival as compared with no treatment [12]. In a subcutaneous (s.c.) model of Burkitt's lymphoma (Daudi cells), Betalutin showed a strong synergistic effect with RTX [11]. There was no effect on survival of SCID mice i.v. injected Daudi cells treated with a single injection of 50 μg lilotomab or on Ramos s.c. xenografts treated with a single injection with 15 mg/kg lilotomab compared with control.

The cross reactivity of the lilotomab antibody to different human tissues and to other animal species has been evaluated by immunohistochemistry and flow cytometry. Antigen specific binding to B-cells (and not to T-cells or natural killer [NK] cells) was observed and no cross-reactivity was found to any of the other species investigated (rhesus and cynomolgus monkeys, marmoset, rabbit, rat, mouse, dog, mini-pig and guinea-pig).

2.2.1.2. Non-clinical pharmacokinetics and biodistribution

Biodistribution studies with Betalutin in mouse models have been performed to investigate the uptake in tumour and normal tissues, and to compare the biodistribution of Betalutin to that of anti-CD20 antibody RTX (^{177}Lu-RTX).

Betalutin was stable when injected into mice, with no dissociation of the radionuclide detected, and was targeted to tumour xenografts in mice, where it accumulated up to 4 days. Betalutin distribution was similar for mice with Daudi and Ramos tumour xenografts, with the exception of an observation of higher uptake in lymph nodes with Ramos xenografts, and pre-treatment with either rituximab or lilotomab had no significant effect on biodistribution of Betalutin. Biodistribution of Betalutin and ^{177}Lu-RTX was similar in normal organs and Daudi tumour xenografts in nude mice.

2.2.1.3. Toxicology

As no relevant animal model with cross-reactivity to the lilotomab antibody could be identified, the most relevant studies identified for safety evaluation to determine tolerability and target organ toxicity were combined toxicity and therapy studies in immune-compromised SCID and nude mice). The maximum tolerated dose (MTD) of Betalutin in SCID mice with bone marrow lymphoma involvement was between 50 and 100 MBq/kg, and 530 MBq/kg in nude mice. The most common toxicities were reversible leukopenia and thrombocytopenia, occurring 3 weeks after Betalutin administration, and recovering after 7 weeks.

A detailed description of the chemistry, pharmacology, efficacy and safety of Betalutin is provided in the Investigator's Brochure.

2.2.2. Clinical experience with Betalutin

2.2.2.1. Phase 1/2 single, ascending dose study in patients with relapsed indolent NHL (LYMRIT-37-01)

This first-in-human study was performed to evaluate the safety, preliminary efficacy, PK and biodistribution of Betalutin in patients with relapsed iNHL (subtypes mantle cell, follicular grade I-IIIa, marginal zone, small lymphocytic, lymphoplasmacytic lymphoma). Patients were enrolled into 4 dose escalation arms of 3 patients each to receive a single i.v. dose of Betalutin (10, 15, 20 MBq/kg) following pre-treatment with RTX (1 or 2 doses at least 2 weeks prior), and immediate pre-dosing with lilotomab 40 mg (Arm 1) or 100 mg/m^2 (Arm 4), RTX (Arm 3) or no pre-dose (Arm 2) to define the MTD of Betalutin, and to collect additional PK data (n=3; Arm 5). The Phase 1 part of the study utilises a 3+3 dose-escalation study design with the primary objective of defining the MTD of Betalutin. Secondary objectives are to identify a recommended dose of Betalutin for the Phase II part of the study, and investigate the safety, biodistribution, PK and efficacy of Betalutin.

As of 03 July 2017, 62 patients have been enrolled in the study. NHL subtypes were FL (n=47 76%), mantle cell lymphoma (MCL) (n=7; 11%), and marginal zone lymphoma (MZL) (n=8; 13%). The median age of the patients was 69; 46 patients (74%) were ≥65 years old. The median number of prior therapies was 3 (range 1-8); 42 patients (68%) received ≥2 prior therapies, and 34 patients (55%) received ≥2 prior RTX courses.

Three patients were enrolled in Arm 2; the dose-limiting toxicity (DLT) rate exceeded 20% with a Betalutin dose of 15 MBq/kg, and this arm was closed. Three patients were enrolled in Arm 3 and received 15 MBq/kg Betalutin; one developed a DLT. Arm 3 was closed following a review of the first 3 patients as RTX pre-dosing on Day 0 was observed to have a lesser protective effect on neutropenia/thrombocytopenia development than either 40 mg or 100mg/m^2 of lilotomab.

With a lilotomab pre-dose of 40 mg (Arm 1), the recommended dose of Betalutin for phase 2 expansion was 15 MBq/kg. In total, 36 patients have received this regimen (25 with FL); the overall response rate (ORR) is 64% (CR 25%), and 72% (CR 24%) for the FL subset, and the toxicity profile is favourable. The incidence of grade 3/4 neutropenia and thrombocytopenia was 20/36 (56%) for both. Grade 4 neutropenia and thrombocytopenia were reported in 7 patients (19%) and 6 patients (17%) respectively. Of these, there were 2 patients with grade 4 neutropenia lasting >7 days, and 2 with grade 4 thrombocytopenia >7 days.

In Arm 4 (lilotomab pre-dose of 100 mg/m^2), the recommended Betalutin dose for phase 2 expansion was 20 MBq/kg. Eight patients have been enrolled; the ORR is 50%. Two FL patients have had a CR. The incidences of grade 3/4 neutropenia and thrombocytopenia were 3/8 (38%) and 4/8 (50%) respectively (there was one grade 4 thrombocytopenia reported). One patient had a DLT of haematuria with thrombocytopenia (platelet count of 40 x 10^9/L) and received a platelet transfusion. A phase 2 expansion cohort is currently enrolling up to 15 patients.

Overall, Betalutin treatment was well-tolerated, with the most common adverse events (AEs) reported being neutropenia and thrombocytopenia which were transient and generally required no intervention. Bruising/bleeding episodes were reported in 3 and 4 patients respectively; only 2 patients required platelet transfusions for bleeding events in association with thrombocytopenia (one with epistaxis and one with haematuria). Overall, 23 patients (39%) developed infections, with urinary and respiratory tract infections (including nasopharyngitis) being most commonly reported (19 patients [32%]). The majority of infections were low grade in nature. The dosing regimen was generally well tolerated, with only 2 infusion reactions reported; both were related to RTX.

Serious adverse events (SAEs) were reported in 14 patients (23%). Treatment-emergent SAEs occurring in 2 or more patients were thrombocytopenia (n=2), atrial fibrillation (n=2), sepsis (n=2) and lymphoma progression (n=2). Both atrial fibrillation episodes were grade 2 in nature and resolved within 24 hours with oral therapy. One episode was reported 9 months after Betalutin administration. Two patients were reported with sepsis; both episodes occurred in association with neutropenia around Day 40, and both fully resolved within 7-10 days with antibiotic therapy. One patient had an antecedent urinary tract infection. An SAE of myelodysplastic syndrome (MDS)/ Acute myeloid leukaemia (AML) was reported in one patient 24 months after Betalutin administration. This patient had a history of prior alkylating exposure and went on to receive 6 courses of bendamustine/RTX following Betalutin administration. MDS/AML was reported 18 months later; the outcome was fatal, and the SAE was judged to be possibly related to Betalutin and/or prior therapy by the Investigator. There was one on-study death (i.e. within 12 weeks of Betalutin administration) due to disease progression that was not considered related to Betalutin.

The PK profile of Betalutin as assessed by measuring the total radioactivity in blood shows an impact of pre-dosing with lilotomab (40 mg and 100 mg/m^2), with lilotomab increasing the activity-adjusted area under the curve (AUC), and reducing the volume of distribution and rate of clearance of Betalutin, while having little effect on activity-adjusted maximum plasma drug concentration (C_{max}) compared to no lilotomab pre-dosing. These observations could be consistent with blocking of the CD37 antigen sink in the bone marrow by lilotomab and consequently a reduced absorbed radiation dose compared to Arm 2. Preliminary biodistribution data (dosimetry) also indicate that both the 40 mg and the 100 mg/m^2 lilotomab pre-dosing regimens 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 Arm 1 and 4 than for

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 (3 Gy).

For more details, please refer to the Investigator's Brochure.

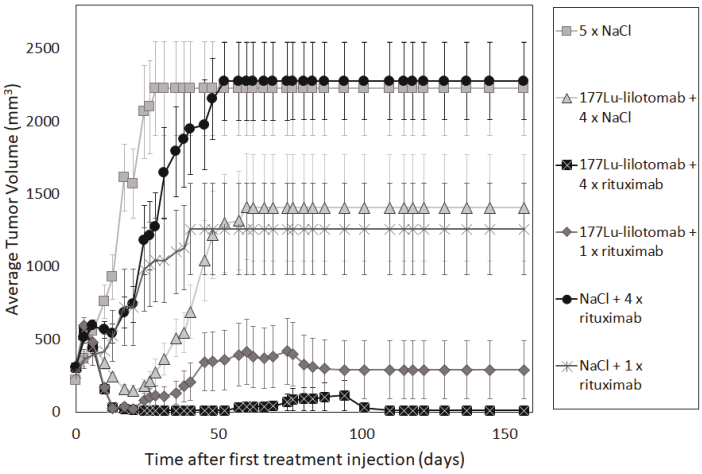
2.3. Overview of combination treatment with Betalutin plus rituximab

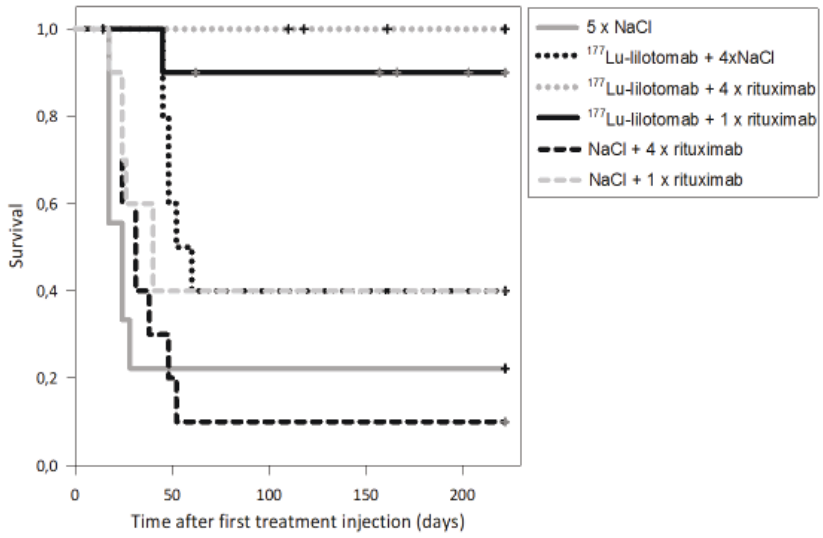
2.3.1. Non-clinical experience

In vitro models of Burkitt's (Ramos cells) and mantle cell lymphoma (Rec-1 cells) demonstrated increased surface CD20 expression following ^{177}Lu-HH1 (Betalutin) treatment compared with cells treated with unlabelled HH1 (lilotomab) [12]. Treatment of nude mice with Ramos xenografts with Betalutin resulted in a 3-fold higher uptake of radiolabelled RTX in tumour xenografts 5 days after start of treatment than in mice treated with unlabelled HH1 ($p < 0.05$). In SCID mice with i.v. injected Rec-1 cells, the combination of Betalutin and RTX resulted in significantly improved survival as compared with saline (NaCl) or RTX alone [12].

The therapeutic effect of the combination of Betalutin and rituximab was also studied in nude mice with s.c. Burkitt's lymphoma (Daudi) xenografts [11]. Sequential therapy with Betalutin followed by RTX substantially reduced tumour growth and improved overall survival compared to either agent alone, suggesting synergism between the 2 agents (Figure 2-1).

Figure 2-1 The effect of combining Betalutin plus RTX on tumour volume and survival in a preclinical NHL model





2.3.2. Clinical experience

There are no clinical data or ongoing studies combining Betalutin with RTX. One phase 2 study has been reported combining Zevalin with RTX in FL patients (summarised in Section 2.3.3).

2.3.3. Potential for overlapping toxicities between Betalutin and rituximab

Although there have been no prior combination studies with Betalutin and RTX, there is one report of a phase 2 study in treatment-naïve FL patients exploring short course CHOP-RTX followed at haematologic count recovery by ^{90}Y-ibritumomab tiuxetan (Zevalin) and 4-weekly RTX doses (375 mg/m^2), starting within 1-2 weeks of receiving radioimmunotherapy (RIT) [17]. For the 55 (out of 60) patients who completed all 3 therapies per protocol, the most frequent toxicities reported following RIT/RTX were grade 3/4 neutropenia and thrombocytopenia in 51% and 44% (grade 4 for both in 20%) of patients respectively, one prolonged episode of grade 3 serum sickness-like toxicity, and one episode of febrile neutropenia. All patients had normal white blood cell and platelet counts by Week 12 post-RIT.

The main toxicities of RTX reported in NHL patients are infusion reactions, fever, lymphopenia, chills, infection and asthenia (MabThera-prescribing information). In patients with NHL receiving RTX monotherapy, grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anaemia (3%) and thrombocytopenia (2%). Grade 3/4 lymphopenia has been reported in approximately 30% of patients receiving Betalutin. Therefore, while combining RTX with Betalutin is not expected to contribute significantly to the development of neutropenia, thrombocytopenia or anaemia, prolonged lymphopenia may increase the incidence of infection. Patients will be monitored frequently by clinical and laboratory assessments for sequelae of myelosuppression (infections, bruising and bleeding, febrile neutropenia).

2.4. Benefit/Risk Assessment

Patients to be included in this study are adults with relapsed, refractory (not anti-CD20 antibody refractory) FL. The patient will have received and be considered to have experienced treatment failures from prior treatment regimens, including chemotherapy and immunotherapy treatment regimens. Treatment options for patients with relapsed/refractory FL are dependent upon the prior regimens that the patient received, and whether the patient is elderly or able to tolerate chemotherapy (due to presence of comorbidities). Generally, chemoimmunotherapy + rituximab maintenance therapy is recommended per ESMO Clinical Practice Guidelines for relapsed FL [29] For example, if a patient received prior chemoimmunotherapy with CHOP-rituximab (CHOP-R) previously, then bendamustine-rituximab (BR) may be tried, or vice versa. Another option, particularly for elderly patients with comorbidities prohibiting chemotherapy, is rituximab monotherapy, however this is associated with an ORR of approximately 50% and a median time to progression of around 7-10 months [30, 31]. Radioimmunotherapy is another option but is underused. The safety profile of Betalutin is well-characterised. The most common grade 3/4 toxicities for Betalutin are thrombocytopenia and neutropenia which resolve by 3 months for the majority of patients. The incidence of bruising/bleeding episodes (7 patients), which were mostly mild in nature, and grade 3/4 infections (5 patients) was low. Infections occurred in association with neutropenia. Lilotomab pre-dosing was shown to mitigate the severity of cytopenia; evaluation of efficacy with a higher lilotomab pre-dose is on-going.

Betalutin has demonstrated clinical activity as a single agent and preliminary evidence of durable responses and is well-tolerated in patients with relapsed/refractory iNHL and FL. Preliminary efficacy data show an ORR of at least 70% for FL patients pre-treated with 40 mg lilotomab followed by 15 MBq/kg of Betalutin (Arm 1), which is the dosing regimen to be used in this study. Eighty-four per cent of patients in the LYMRIT 37-01 study have experienced some degree of decrease in tumour size [4]. Early duration of response data from Arm 1 (n=28) also suggests clinical benefit with a median duration of response of over 12 months. These are promising results in a population of primarily older, heavily pre-treated relapsed iNHL patients with advanced-stage disease.

Patients will be closely monitored for evidence of any overlapping toxicities due to combining Betalutin with RTX, such as infections, febrile neutropenia, bruising or bleeding episodes.

Taken together, the data provided demonstrate a positive benefit:risk balance for Betalutin for the treatment of patients with recurrent FL, a primarily elderly population with a high unmet medical need.

3. Objectives and Endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Study objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of Betalutin in combination with RTX	• Frequency and severity of adverse events (AEs), serious adverse events (SAEs) and changes in laboratory values graded according to CTCAE version 4.03
Secondary	
• To establish a recommended dose of Betalutin in combination with RTX for phase 2 studies in NHL patients	• Frequency and severity of AEs, SAEs and changes in laboratory values graded according to CTCAE version 4.03
• To evaluate the preliminary anti-tumour activity of combination treatment based on Investigator assessment of tumour response rates	• Responses (overall response rate [ORR], complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD]) per Cheson 2014 [30]
• To evaluate the duration of tumour control in patients receiving Betalutin in combination with RTX	• Duration of response (DoR) • Progression free survival (PFS) • Time to progression (TTP) • Overall survival (OS)
• To investigate the immunogenicity of Betalutin in combination with RTX	• Monitoring of the anti-drug antibodies (ADA) response towards lilotomab, Betalutin and/or RTX
Exploratory	
• To characterise the pharmacokinetics (PK) of Betalutin in combination with RTX	• Estimation of the levels of remnant administered radioactivity in blood over time (Betalutin PK)
• To assess the pharmacodynamic effects of Betalutin in combination with RTX	• Change from baseline in peripheral blood B-cell, T-cell and NK cell counts, tumour CD20 and CD37 expression • Biomarker assessments
• To investigate the biodistribution of Betalutin in combination with RTX	• 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. • Calculation of estimated absorbed radiation dose to target organ.
• To evaluate minimal residual disease in patients with a CR	• Monitoring of detectable disease to assess early treatment response and detect relapse using next generation sequencing (NGS) (molecular Minimal Residual Disease (MRD))

• To evaluate the relationship between anti-tumour activity and NHL-related genes in tumour samples	• Gene expression analysis using a panel of cancer-related genes
• To assess anti-tumour T-cell responses	• Anti-tumour response measured by flow cytometry after co-culture of peripheral mononuclear cells and autologous lymphoma cells and other biomarkers

4. Study Design

4.1. Overall Design

This protocol describes a Phase 1b open-label, single-arm, dose escalation study to investigate the activity and safety and preliminary efficacy of Betalutin combined with RTX in patients with FL who have received one or more prior therapies. It is planned that 6-12 evaluable patients will be enrolled in the study.

All patients will receive a single i.v. dose of RTX (375 mg/m^2) on Day -14, and then sequential i.v. administrations of lilotomab (40 mg) followed by Betalutin (10 or 15 MBq/kg) within 4 hours on Day 0. Patients will then be administered RTX (375 mg/m^2) i.v. on Days 7, 14, 21 and 28.

Patients will undergo clinical and laboratory assessments during screening/baseline and periodically during treatment as outlined in the Schedule of activities (Section 1.2). Two cohorts of 3-6 patients will be initially evaluated for DLT, in a 3+3 escalation pattern, before determining the subsequent Betalutin dose for the remainder of the study (Section 6.1).

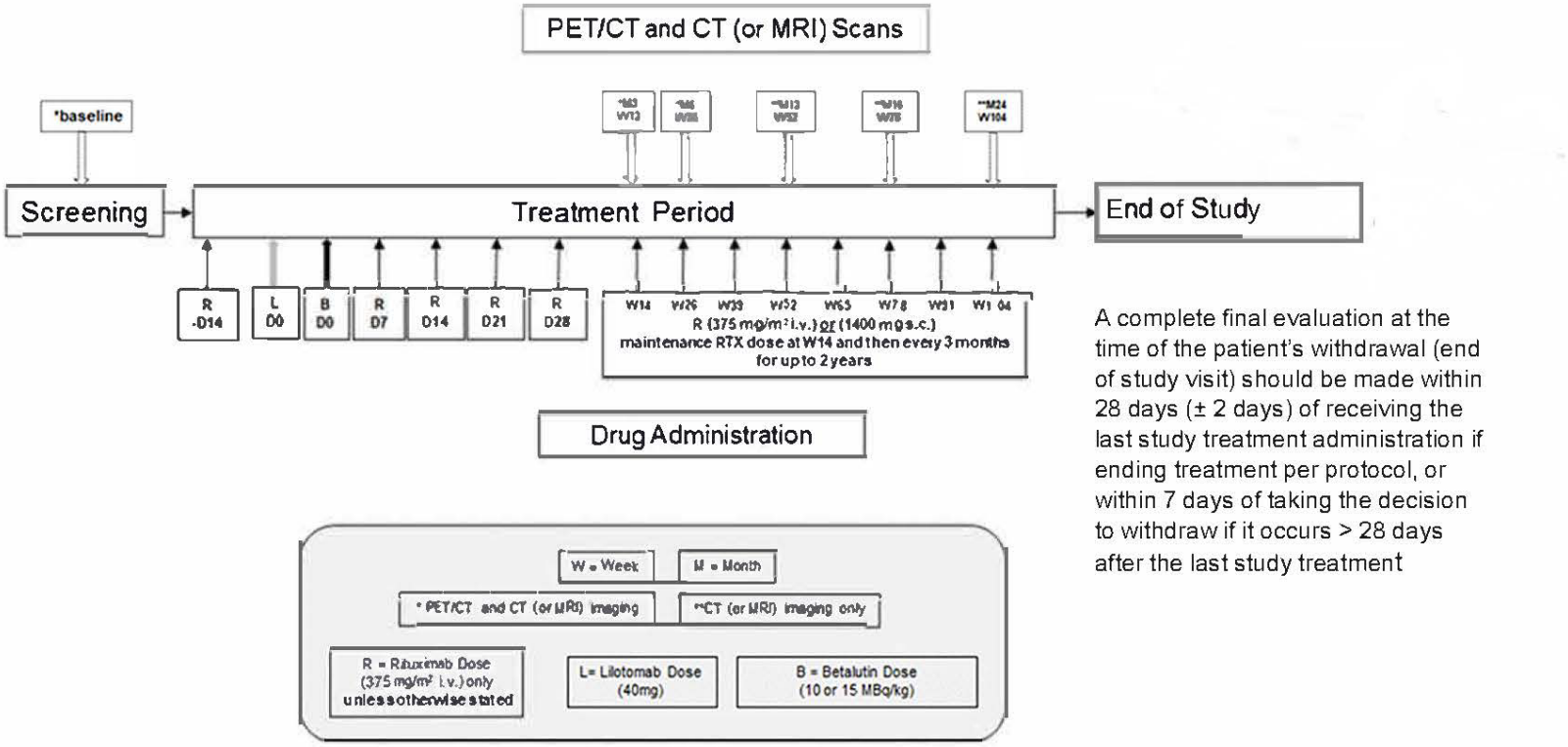
Tumour-tissue biopsies and blood samples will be collected to study the mechanisms of tumour response to therapy as described in the biomarkers section (Section 9.4). The collection of these samples is optional and, at Radium Hospital (Oslo, Norway) only.

PET/CT and CT imaging (or MRI) will be performed at baseline and then at 3 and 6 months. CT with contrast (or MRI) will be performed at 12, 18, 24 months or until disease progression or withdrawal from the study for any other reason (whichever comes first).

Patients who achieve SD, CR or PR on their Month 3 imaging scan will be administered maintenance RTX 375 mg/m^2 i.v. or 1400 mg s.c. every 3 months for up to 2 years (8 infusions in total), or until disease progression or withdrawal from the study for any other reason (whichever comes first).

The schedule plan for dosing and imaging is illustrated in Figure 4-1.

Figure 4-1 Study dosing and imaging plan



4.2. Rationale for Study Design

This phase 1b exploratory study will investigate the dosing of Betalutin in combination with RTX, whereby RTX is given 7 days following Betalutin to capitalise on potential enhanced CD20 expression following Betalutin administration. Repeat RTX doses (4-weekly, i.v.) have been safely administered to 55 treatment-naïve FL patients 1-2 weeks after 3 courses of CHOP-RTX followed by Zevalin once hematologic recovery was attained in a phase 2 study. [17]. All patients had full hematologic count recovery by 12 weeks post-RIT.

As summarised in Section 2.1, both Betalutin and RTX deplete B-lymphocytes and B-cell NHL cells. Grade 3 or higher myelosuppression (anaemia, neutropenia and thrombocytopenia) has been reported in ≤6% of NHL patients receiving RTX (MabThera prescribing information). Thus, it is anticipated that dosing RTX one week following Betalutin will not impact the development of myelosuppression acutely, although there is potential for prolonged B-lymphocyte depletion. Therefore, all patients will be closely followed clinically and with laboratory tests to monitor for infection. We hypothesise that combining Betalutin with RTX could enhance both the response rates and the durability of responses in patients with recurrent FL, providing an alternative to a chemotherapy-containing regimen for patients.

Patients with relapsed/refractory FL are reported to benefit from rituximab maintenance therapy, with improved overall survival [31]. Therefore, responding patients (i.e. those having a CR, PR or SD response following Betalutin and the 4-weekly doses of i.v. RTX) will receive maintenance RTX every 3 months for up to 2 years (a total of 8 doses), or until disease progression, commencing at Week 14. This may be administered by either i.v. (375 mg/m^2) or s.c. (fixed dose of 1400 mg) routes.

The safety of patients in this study will be monitored as described in Section 9.2 (Safety Assessments). Two cohorts of 3-6 patients will be initially evaluated for DLT before determining the subsequent Betalutin dose for the remainder of the study (see Section 6.1).

4.3. Rationale for Dose

This is the first study evaluating the combination of Betalutin and RTX. The starting dose of Betalutin (10 MBq/kg) following a lilotomab pre-dose of 40 mg is one dose level lower than the recommended phase 2 dose for expansion (15 MBq/kg) in the LYMRIT 37-01 study and has been safely administered to 3 NHL patients. This starting dose for Betalutin is chosen to reduce the risk for overlapping toxicities, and for subsequent patients, the Betalutin dosing regimen chosen (40 mg lilotomab pre-dose and 15 MBq/kg Betalutin) has been administered to 36 patients in the LYMRIT 37-01 study, and has been well-tolerated (see Section 2.2.2.1). As of the writing of this protocol, 11 patients (evaluable for safety) have received a lilotomab pre-dose of 100 mg/m^2 followed by 20 MBq/kg Betalutin, therefore the clinical profile of the former regimen is better characterised.

Regarding immunogenicity, the presence of anti-drug antibodies (ADA) was reported for 7 out of 62 patients enrolled. The observed ADA response was transitory, detected after 7 days (n=1) or 1 month (n=6). For one of the two patients with 12-months post-treatment results available, a new onset of ADA was observed. Two patients who were treated with a lilotomab pre-dose of 100 mg/m^2 developed ADAs at 1 month that disappeared by 3 months. None of the patients treated with 40 mg lilotomab and 15 MBq/kg Betalutin developed ADAs.

The dose regimen of RTX chosen is that which had been approved for use in relapsed/refractory FL patients. RTX has single agent activity in relapsed FL and has been safely combined using both single and multiple doses with a number of myelosuppressive chemotherapeutic agents and regimens including bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CVP (cyclophosphamide, vincristine, prednisone) as standard therapy for NHL patients. In contrast to standard chemotherapy, side effects of RTX are modest (mostly chills, fevers, headache and infusion reactions) and mainly confined to the first infusion of rituximab. In combination with CHOP and CVP, the incidence of grade 3 or 4 neutropenia is approximately 10% higher than with CVP or CHOP alone, without a difference in overall infection rate or sepsis [24, 33].

As discussed in the previous section, as patients with relapsed/refractory FL are reported to benefit from rituximab maintenance therapy [31], responding patients (i.e. those having a CR, PR or SD response following Betalutin and the 4-weekly doses of i.v. RTX) will receive maintenance RTX every 3 months for up to 2 years (a total of 8 doses), or until disease progression or withdrawal from the study for any other reason (whichever comes first), commencing at Week 14.

4.4. Patient and Study Completion

Approximately 10-15 patients will be screened to achieve 6-12 patients assigned to study treatment and evaluable.

4.5. End of Study Definition

The end of study for all patients will be the date of the last patient last visit upon completion of their end of study visit(25 months after receiving their Betalutin treatment if ending study treatment per protocol, or after disease progression or withdrawal from the study for any other reason, (whichever comes first) or if the study is terminated early.

5. Population

This study will be conducted in adult patients with relapsed FL or who are refractory (not anti-CD20 antibody refractory) and have received one or more prior therapies, including anti-CD20 therapy.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1) Patient must be ≥18 years at the time of signing the informed consent
2) A pre-study Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
3) Histologically confirmed diagnosis (by 2008 World Health Organization [WHO] classification) of indolent non-Hodgkin B-cell FL (grade 1, 2 or 3a)
4) At least one (but not more than 3) prior regimens with an anti-CD20 antibody (alone or in combination with chemotherapy), with documented relapsed, refractory disease (must not be anti-CD20 antibody-refractory) or PD
5) Presence of at least one bi-dimensionally measurable lesion by CT or MRI: longest diameter (LDi) >1.5 cm for a nodal lesion; LDi >1.0 cm for an extranodal lesion within 28 days prior to start of treatment
6) Normal organ and bone marrow function defined as:
    a. Absolute neutrophil count ≥1.5 x 10^9/L;
    b. Platelet count ≥150 x 10^9/L;
    c. Haemoglobin ≥9 g/dL;
    d. Total bilirubin ≤1.5 x upper limit of normal (ULN) (except patients with documented Gilbert's syndrome [<3.0 mg/dL]);
    e. Liver enzymes: Aspartate transaminase (AST); Alanine transaminase (ALT) or Alkaline phosphatase (ALP) ≤2.5 x ULN (or ≤5.0 x ULN if liver involvement by primary disease);
    f. Adequate renal function as demonstrated by a serum creatinine within the upper limit of normal range
7) Bone marrow involvement by lymphoma <25%
8) Life expectancy >3 months
9) Negative hepatitis B, hepatitis C and human immunodeficiency virus (HIV) screening tests
10) Undetectable human anti-murine antibody (HAMA) at screening
11) Women of childbearing potential (see Appendix 3) must:
    a. have a negative serum pregnancy test at screening
    b. understand that the study medication is expected to have teratogenic risk
    c. agree to use, and be able to comply with, highly effective method of birth control with a Pearl-Index ≤1%

    Contraception is required without interruption, from 4 weeks before starting study drug, throughout study drug therapy and for 12 months after end of study drug therapy, even if she has amenorrhea

12) Male patients must agree to use condoms (See Appendix 3) during intercourse throughout study drug therapy and for 12 months after end of study drug therapy
13) The patient is willing and able to comply with the protocol, and agrees to return to the hospital for follow-up visits and examination
14) Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1) Previous haematopoietic stem cell transplantation (autologous and allogenic)
2) Evidence of histological transformation from FL to DLBCL at time of screening.
3) Previous total body irradiation
4) Chemotherapy, immunotherapy or investigational therapy within 28 days before the start of study drug administration (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) or failure to recover from AEs associated with prior treatment
5) Previous treatment with radioimmunotherapy
6) Patients who are receiving any other investigational medicinal products
7) Known or suspected central nervous system (CNS) involvement of lymphoma
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 or localised prostate cancer undergoing surveillance or surgery
   d) localised breast cancer treated with surgery and radiotherapy but not including systemic chemotherapy
   e) other adequately treated Stage 1 or 2 cancer currently in CR
9) Pregnant or lactating women (See Appendix 3)
10) Exposure to another CD37 targeting drug
11) A known hypersensitivity to RTX, lilotomab, Betalutin or murine proteins or any excipient used in RTX, lilotomab or Betalutin
12) Receipt of 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, 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) in the past 24 weeks

6. Study Treatment

For this study, the term "study drug(s)" refer to RTX, lilotomab or Betalutin.

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

Detailed written instructions on labelling and preparation will be given to the study site prior to patient inclusion. See also Investigator's Brochure and RTX prescribing information.

6.1. Dosing regimen

Two cohorts of 3-6 patients will initially be evaluated. The first cohort of 3 patients will be treated with a single i.v. dose of RTX (375 mg/m^2) on Day -14, and then on Day 0, sequential i.v. administration of lilotomab (40 mg) followed by Betalutin (10 MBq/kg) within 4 hours on Day 0. The patients will then be administered RTX (375 mg/m^2) i.v. on Days 7, 14, 21 and 28.

Patients must have received all doses of study drug and have had an adequate period of follow-up (i.e. having achieved haematological recovery to ≤ grade 2) to be considered evaluable for a dose escalation decision or to determine the dose for further Phase 2 studies following enrolment of the second cohort of 3-6 patients. The dose for the next cohort of 3 patients will be determined by the Investigator(s) and Nordic Nanovector study personnel via teleconference. Decisions will be based on a review of all safety data (clinical and laboratory) and are outlined as follows:

1. If 0/3 patients experience a DLT (defined below), the next cohort of 3 patients will receive lilotomab 40 mg plus Betalutin 15 MBq/kg prior to RTX on Day 0.
2. If 1/3 patients experience a DLT, then 3 more patients will be enrolled in the current cohort at this dose level (Betalutin 10 MBq/kg).
3. If 2/3 patients experience a DLT, then subsequent Betalutin/lilotomab and/or RTX dosing will be determined by the Investigator(s) and Sponsor after a review of the safety data.
4. If 1/6 patients experience a DLT, the next cohort of 3 patients will be treated with Betalutin 15 MBq/kg.
5. If 0/3 patients receiving Betalutin 15 MBq/kg experience a DLT, the remainder of the patients in the study will continue to be treated with Betalutin 15 MBq/kg.
6. If 1/3 patients experience a DLT, then 3 more patients will be enrolled at this dose level (Betalutin 15 MBq/kg).
7. If 1/6 patients receiving Betalutin 15 MBq/kg experience a DLT, the dose for further Phase 2 studies will be Betalutin 15 MBq/kg.
8. If 2/6 patients experience a DLT, then 3 more patients will be treated at the lower Betalutin dose (10 MBq/kg).
9. The final recommendation for Betalutin/lilotomab dosing for further Phase 2 studies will be determined by the Investigator(s) and Sponsor after a review of the available safety data.

DLT is defined as:

Haematological: Anemia, neutropenia or thrombocytopenia CTCAE (v4.03) grade 4 lasting >7 days, or grade 3 thrombocytopenia with clinically significant bleeding, or febrile neutropenia (ANC <1000/mm^3 with a temperature >38.3˚C).

Non-haematological: An AE of CTCAE (v4.03) grade 3 or higher where the relationship to study treatment cannot be ruled out, and is not primarily related to disease, disease progression, intercurrent illness or concomitant medications that occurs within the first 12 weeks of treatment. Other clinically significant toxicities may also be considered to be DLTs by the Investigators and Sponsors, even if not CTCAE grade 3 or higher.

Responding patients (i.e. those having a CR, PR or SD response following Betalutin and the 4-weekly doses of i.v. RTX) will receive maintenance RTX every 3 months for up to 2 years (a total of 8 doses), or until disease progression, commencing at Week 14. This may be administered by either i.v. (375 mg/m^2) or s.c. (fixed dose of 1400 mg) routes.

6.2. Treatments Administered

Study Treatment Name:	Rituximab	Lilotomab	Betalutin
Dosage formulation:	As per approved product information	Single use vial containing 10 mL of lilotomab at a concentration of 5 mg/mL formulated in 40 mM phosphate buffer (35.5 mM disodium hydrogen phosphate dodecahydrate and 4.5 mM sodium dihydrogen phosphate dihydrate), pH 7.6, 8.7 mM NaCl, 5% sucrose and 0.02% polysorbate-20	Single use vial containing 8-10 mL of Lutetium (^{177}Lu) lilotomab satetraxetan at a concentration of 0.78 mg/mL formulated in: 6.2 mM (0.48 mg/mL) Ammonium acetate, 161.5 mM (32 mg/mL) of sodium ascorbate, 0.81 mM (0.32 mg/mL) of diethylenetriamine pentaacetic acid (DTPA), 19.3 mM (0.77 mg/mL) of NaOH, 64 mg/mL of recombinant Albumin, 25.4 mM (3.5 mg/mL) of Sodium dihydrogen phosphate monohydrate and 77 mM (4.5 mg/mL) of NaCl. HCl is added in trace amounts to reach a pH in the Betalutin drug product of 6.9 ±0.5. Recombinant albumin constitutes for about 60% of the dry weight of the Betalutin drug product. The total radioactivity in the vial is in the range from 3222-3938 MBq.
Unit dose strength(s)/Dosage level(s):	375 mg/m^2	40 mg	10 or 15 MBq/kg
Route of Administration	i.v. infusion through dedicated line or s.c. injection (as per site practice). s.c. injection (different dose) may only be used for the maintenance RTX dosing commencing at Week 14.	i.v. infusion through dedicated line	Slow bolus i.v. injection
Dosing instructions:	As per approved product information	Provided in drug specific Handling Plan	Provided in drug specific Handling Plan
Packaging and Labeling	As per approved product information	Treatment will be provided in a glass vial. Each vial will be labeled as required per country requirement.	Treatment will be provided in a glass vial. Each vial will be labeled as required per country requirement.

6.3. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
2. Only patients enrolled in the study may receive study drug and only authorised site staff may supply or administer study drug. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorised site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Detailed handling and preparation for the study drugs can be found in the appropriate Drug Handling Plans.
5. Further guidance and information for the final disposition of unused study drug are provided in in the appropriate Drug Handling Plans.

6.3.1. Preparation and administration of Betalutin

The total activity to be injected will be calculated volumetrically using the patient's body weight (kg) on the day of injection, 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 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). Patients will receive Betalutin under supervision of a nuclear medicine specialist and the total radioactivity injected, the activity dose and the volume injected will also be recorded as above. The measured dose of Betalutin must be within ±10% of the intended prescribed dose.

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

$$\textit{Volume (ml)} = \frac{\textit{dose 10 or 15 MBq/kg x body weight (up to a max of 130 kg)}}{\textit{Decay corr factor x radioactivity conc. (MBq/ml)}}$$

Filling of the syringe should take place at a dedicated area for working with radioactive solutions. Site staff 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 electronic case report form (eCRF) page.

The syringe should be shielded from 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 i.v. 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), as detailed in the Drug Handling Plan. The equipment used in connection with the preparation and administration of the study drug, are to be treated as radioactive waste and should be disposed in accordance with hospital procedure for handling of radioactive material.

6.3.2. 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, dependent on local regulations.

6.3.3. Administration of Rituximab

RTX will be ordered through the standard procedure at the study site. The study drug should be administered according to the approved product information (prescribing information) for RTX. **Pre-medication consisting of an antipyretic and an antihistamine, e.g. paracetamol and dexchlorpheniramine or cetirizine, should always be administered before each infusion of RTX. The types of pre-medication used prior to RTX infusion will follow each study site routine, including any use of corticosteroids.** The prepared RTX solution should be administered as an i.v. infusion through a dedicated line or s.c. injection (as per study site practice). Subcutaneous RTX may be used for the maintenance dosing only. RTX should not be administered as an i.v. push or bolus. The standard hospital procedure for infusion of RTX 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. Any AEs and information about pre-medication will be recorded in the eCRF. Other information such as drug accountability will be detailed in the RTX Drug Handling Plan.

6.3.4. Administration of Lilotomab

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.

The patient 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. If any AEs occur, such as a drop in blood pressure, chills, fever and/or dyspnea, the infusion should be stopped. When the symptoms disappear, the infusion should be started again at 50% reduced infusion rate. The infusion rate of lilotomab may be adjusted depending on how well lilotomab is tolerated. Medication and supportive care measures should always be available during an infusion and information about pre-medication be recorded in the eCRF.

6.3.5. Drug Accountability

The study drugs, i.e. RTX, Betalutin and lilotomab, should be kept in a secure place and must be administered only to patients in the study. For all three study drugs, an appointed individual is responsible for maintaining accurate records of the study drug. A list of study drug (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.

6.4. Treatment Compliance

Site staff will check the administration volume for all RTX, lilotomab and Betalutin doses and record these in the patient's source documents and eCRF. Patients will receive Betalutin under supervision of a nuclear medicine specialist and the total radioactivity injected, the activity dose and the volume injected will also be recorded as described in Section 6.3.

6.5. Supportive Care Guidelines

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

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

Neutropenia with fever (neutrophils/granulocytes <1 x 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 <20 x 10^9/L) or bleeding with platelets <50 x 10^9/L

Patients will be transfused with platelets to maintain a platelet count >20 x 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 blood cells to maintain haemoglobin level >8.0 g/dL.

Hypersensitivity

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 RTX, lilotomab or Betalutin.

Extravascular administration

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

6.6. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the patient is receiving at the time of enrolment or receives during the study until 4 weeks following final RTX administration must be recorded in the eCRF along with:

- Reason for use
- The generic or trade name
- Start and end dates of administration
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

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 $<50 \times 10^9$/L, and be temporarily stopped if platelets are $<25 \times 10^9$/L.

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

Use of live or attenuated vaccines is prohibited throughout the course of the study.

7. Discontinuation of Study Treatment and Patient Withdrawal / Discontinuation

7.1. Discontinuation of Study Treatment

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

- Occurrence of serious adverse reactions, including abnormalities in laboratory analysis and vital signs which by virtue of their nature, severity and duration are considered evidence that the safety of the study patients is no longer assured
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of drug development

7.2. Patient Withdrawal/Discontinuation from the Study

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.

Should a patient decide to withdraw after administration of the study drug(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 (end of study visit) should be made within 28 days (± 3 days) of receiving the last study treatment administration if ending treatment per protocol, or within 7 days of taking the decision to withdraw if it occurs > 28 days after the last study treatment administration 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. If the reason for withdrawal is due to disease progression, the study site should make all effort to continue with the safety monitoring.

Haematological toxicity was observed in the phase 1/2 LYMRIT-37-01 study, with nadir values 5 to 7 weeks after injection of Betalutin. It is advisable to monitor the haematology parameters of the withdrawn patients between 6 and 9 weeks after the last RTX administration or until recovery to CTCAE grade 1 or less.

Single patient study discontinuation is per definition, when the patient:

- has completed Month 24 administration of rituximab, per protocol or
- experiences one of the following situations before per protocol end of study:
  - withdraws consent to participate in the study
  - has died
  - is lost to follow up
  - has disease progression
  - starts further anticancer therapy or
- when the patient is withdrawn for a reason other than described above

If 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 eCRF.

Furthermore:

- Survival information, Adverse Drug Reaction (ADR) and Adverse Events of Special Interest (AESI) will continue to be collected for any single patient until end of study visit, consent withdrawal, lost to follow up or death
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent
- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study site records
- The Investigator and Sponsor may continue to use publicly available information to establish the survival status of patients who have withdrawn consent

See Schedule of activities (Section 1.2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Replacement policy

Patients will not be replaced in the study. However, if a patient is considered to be non-evaluable for dose evaluation, enrolment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients.

7.4. Lost to Follow-Up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

Discontinuation of specific sites or termination of the study as a whole is discussed in Study Governance Considerations (Appendix 2).

8. Study Procedures

Safety and efficacy measurements obtained during the course of the study are summarised in the Schedule of activities (Section 1.2) and Section 4.

As highlighted in Section 8.2.2, safety assessments are to be performed before lilotomab infusion during Visit 3. Betalutin to be administered within 4 hours of lilotomab infusion.

Unless specified, blood samples at each visit to be taken before study drug administration. The urine pregnancy test at day 0 to be taken and negative results confirmed before lilotomab or Betalutin adminisitered.

12-lead ECG to be performed during visits described below and also at any other stage during the study if clinically indicated.

8.1. Screening Period

During the initial screening visit at the study site, the Investigator must inform each prospective study patient of the nature of the study, explain the potential risks, and obtain written informed consent from the patient prior to performing any study-related screening procedures. Once the informed consent document has been signed, the patient may undergo the screening procedures.

Pre-treatment period is defined from start of screening to the administration of the first RTX dose.

The tests and assessments outlined in Table 8-1 will be performed within 4 weeks prior to RTX infusion (pre-treatment period).

Table 8-1 Procedure and assessments at Screening Visit (Visit 1)

Assessment or Procedure	Explanation
Obtain Informed Consent	The patient must be fully informed about the study and sign the Informed consent form (ICF). The ICF needs to be signed before any treatment or study-related procedures are initiated.
Demographics	Date of birth, sex, ethnic origin, race should be recorded
Inclusion/exclusion criteria	See Section 5
Medical History	Record details of all previous or concomitant conditions or surgical procedures
Urinalysis	To check for urinary infection
Concomitant medication/therapy	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
Physical examination	Check and describe any significant abnormal physical examinations findings (heart, lung, abdomen, general, skin, oral cavity, chest and lymph nodes). Any abnormalities will be recorded on Medical History record
Height and weight	Record height and weight details
Vital signs	Systolic/diastolic blood pressure, heart rate, and body temperature

12-lead ECG	A copy of the medically reviewed ECG page will be signed, dated and interpreted before storing in the patient file
ECOG	ECOG performance status for study inclusion
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, alkaline phosphatase (ALP), aspartate transaminase (ASAT), alanine transaminase (ALAT), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), glucose, total bilirubin and albumin
Immunophenotyping	Define absolute cell counts for circulating T-cells, CD4 T-cells, CD8 T-cells, B-cells and NK cells, respectively defined as CD3+, $CD3^+CD4^+$, $CD3^+CD8^+$, CD19+ and $CD3^-$ $CD16^+$ $CD56^+$ lymphocytes by flow cytometry
Coagulation	International normalised ratio (INR), partial thromboplastin time (PTT)
Serum virology	HIV test, Hepatitis B test (HBsAg and anti-HBc), Hepatitis C
Pregnancy test	For women of childbearing potential: serum beta human-chorionic gonadotropin (ß-HCG) pregnancy test
Immunoglobulin levels	Quantitative serum immunoglobulins (IgG, IgA and IgM)
HAMA screening	To screen for pre-existing human anti-mouse antibodies. A serum sample will be sent to a central laboratory (mandatory). Eligibility can be assessed using a local test such as the Milenia Quickline® HAMA test (optional)
Immunogenicity	Monitoring ADA response (RTX, lilotomab and Betalutin baseline)
Tumour tissue biopsy (if no available archived FFPE block, a new surgical tumour tissue biopsy will be performed)	Assessments to be performed: • **Mandatory**: CD20 and CD37 expression in tumour by immunohistochemistry • **Mandatory**: Calibration of the blood MRD test • **Optional**: Gene expression analysis in tumour (DNA, RNA, proteins) to evaluate the relationship between anti-tumour activity and NHL-related genes. *Note*: If FFPE block not biobanked at Covance Central Laboratories (CCLS), preparation of the 5µM FFPE slides for the respective analyses only after Sponsor request
Optional: HLA haplotyping – (saliva sample direct or mouth swab, only if not possible to collect blood sample)	Human Major Histocompatibility Complex (MHC) class I/II haplotyping
Minimal Residual Disease (biopsy[1] and peripheral blood sample)	MRD monitoring to assess early treatment response and detect relapse (baseline)
Bone marrow, biopsy	To verify <25% tumour cells in bone marrow, biopsy taken from a site not previously irradiated.
Radiology - FDG PET/CT	Using standard institutional guidelines. Patient needs to be fasting 6 hours prior to PET/CT examination. Information about FDG administration and standardised uptake value (SUV_{max}) will be recorded. The same camera should preferably be used throughout the study.

Radiology - CT scans with contrast or MRI	CT/MRI 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.
Optional, only at Radium Hospital, (Oslo, Norway): Exploration of the anti-tumour T cell responses	The following human biosamples will be collected: • New tumour tissue biopsy (surgical) • Additional peripheral blood samples
Adverse events	Any AEs occurring after informed consent has been signed should be recorded

[1]A sample of an archived tumour biopsy collected before treatment or a new tumour tissue biopsy collected at screening will be used to calibrate the blood MRD test (see tumour tissue biopsy).

8.2. Treatment Period

Patients will undergo the following visits during the treatment period.

8.2.1. Visit 2 (Day -14) – Hospital Visit

Procedures outlined in Table 8-2 will be performed at Visit 2 (Day -14). This will be 2 weeks before Betalutin administration.

Table 8-2 Procedures and assessments for rituximab administration at Visit 2 (Day -14) [±2 days]

Assessment or Procedure	Explanation
Concomitant medication/therapy	Recording of concomitant medication used since the screening visit
Physical examination	Any abnormal findings should be recorded in the AE record.
Weight	Record weight details
Vital signs	Systolic/diastolic blood pressure, heart rate, and body temperature
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Rituximab administration (375 mg/m^2) i.v.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded
Adverse events	Any AEs occurring after Visit 1 should be recorded

8.2.2. Visit 3 (Day 0) – Hospital Visit

The procedures outlined in this section are for procedures and assessments during Visit 3:

a) before lilotomab administration (Table 8-3)
b) lilotomab administration (Table 8-4)
c) Betalutin administration (Table 8-5)

The procedures outlined in Table 8-3 will be performed at Visit 3 before lilotomab administration. This can be one day before (Day-1) or on the same day (Day 0) as lilotomab administration.

Table 8-3 Procedures and assessments before lilotomab administration at Visit 3 (Day 0)

Assessment or Procedure	Explanation
Concomitant medication/therapy	Concomitant medication used since prior visit will be recorded
Weight	Record weight details
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
12-lead ECG	A copy of the medically reviewed ECG page will be signed, dated and interpreted before storing in the patient file
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Immunophenotyping	Define absolute cell counts for circulating T-cells, CD4 T-cells, CD8 T-cells, B-cells and NK cells, respectively defined as CD3+, $CD3^+CD4^+$, $CD3^+CD8^+$, CD19+ and $CD3^-$ $CD16^+$ $CD56^+$ lymphocytes by flow cytometry
Pregnancy test	For women of childbearing potential: urine pregnancy test. Result to be confirmed as negative prior to lilotomab administration.
Optional, only at Radium Hospital (Oslo, Norway): Exploration of the anti-tumour T cell responses	New tumour tissue biopsy (fine needle aspirate) will be collected. This sample may be collected on DAY-1 or DAY0 (before lilotomab dosing)
PK sampling (Radium Hospital, Oslo, Norway) only. otherwise optional	PK sample before lilotomab infusion will be taken for total radioactivity in blood assessment
Adverse events	Any AEs occurring since prior visit will be recorded

Following the above procedures, lilotomab will be administered as outlined in Table 8-4.

Table 8-4 Procedures and assessments for lilotomab administration at Visit 3 (Day 0)

Assessment or Procedure	Explanation
Lilotomab infusion (40 mg) 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 minutes, 30 minutes, 45 minutes, 1 hour after infusion start and 30 minutes and 1hour post-infusion
Adverse events	Any AEs occurring after lilotomab infusion will be recorded

Following the above procedures, Betalutin will be administered as outlined in Table 8-5.

Table 8-5 Procedures and assessments for Betalutin administration at Visit 3 (Day 0)

Assessment or Procedure	Explanation
Betalutin injection (10 or 15 MBq/kg) – see Section 6.1 Betalutin administered within 4 hours of lilotomab infusion	Patient weight, assigned dose level, volume injected, batch number, time of injection and radioactivity in syringe prior and after injection need to be recorded
PK sampling - Radium Hospital, (Oslo, Norway) only. otherwise optional	PK samples will be taken for total radioactivity in blood assessment. Approximate time points: 5 minutes, 60 minutes, 2 hours, 24 hours and Day 4 after Betalutin administration. The exact clock time that samples are taken need to be recorded in eCRF.
Physical examination	2 hours post-dose: Describe any significant findings
Vital signs	Will be taken 2-4 hours post-Betalutin dose: systolic/diastolic blood pressure, heart rate and body temperature
SPECT/CT - Radium Hospital, (Oslo, Norway) only. Otherwise optional	At 2 hours after dosing, at 24 hours and at Day 4 for biodistribution evaluation
Concomitant medication/therapy	Concomitant medication received since receiving lilotomab should be recorded
Adverse events	Any AEs occurring after Betalutin administration should be recorded

8.2.3. Visit 4 (Day 7) – Hospital Visit

Procedures outlined in Table 8-6 will be performed at Visit 4 (Day 7), when a further dose RTX will be administered. This will be 1 week after Betalutin administration.

Table 8-6 Procedures and assessments for rituximab administration at Visit 4 (Day 7 [±2 days])

Assessment or Procedure	Explanation
Concomitant medication/therapy	Concomitant medication used since prior visit will be recorded
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
12-lead ECG	A copy of the medically reviewed ECG page will be signed, dated and interpreted before storing in the patient file
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
SPECT/CT - Radium Hospital, (Oslo, Norway) only. Otherwise optional	For biodistribution evaluation
PK sampling - Radium Hospital (Oslo, Norway) only. otherwise optional [1]	PK sample will be taken for total radioactivity in blood assessment.
Rituximab administration (375 mg/m^2) i.v.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded
Adverse events	Any AEs occurring since prior visit will be recorded

[1]Before RTX dosing

8.2.4. Visit 5 (Day 14) – Hospital Visit

Procedures outlined in Table 8-7 will be performed at Visit 5 (Day 14), when a further dose of RTX will be administered. This will be 2 weeks after Betalutin administration.

Table 8-7 Procedures and assessments for rituximab administration at Visit 5 (Day 14 [±2 days])

Assessment or Procedure	Explanation
Concomitant medication/therapy	Concomitant medication used since prior visit will be recorded
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Rituximab administration (375 mg/m^2) i.v.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded
Adverse events	Any AEs occurring since prior visit will be recorded

8.2.5. Visit 6 (Day 21) – Hospital Visit

Procedures outlined in Table 8-8 will be performed at Visit 6 (Day 21), when a further dose RTX will be administered. This will be 3 weeks after Betalutin administration.

Table 8-8 Procedures and assessments for rituximab administration at Visit 6 (Day 21 [±2 days])

Assessment or Procedure	Explanation
Concomitant medication/therapy	Concomitant medication used since prior visit will be recorded
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Rituximab administration (375 mg/m^2) i.v.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded
Adverse events	Any AEs occurring since prior visit will be recorded

8.2.6. Visit 7 (Day 28) – Hospital Visit

Procedures outlined in Table 8-9 will be performed at Visit 7 (Day 28), when a further dose RTX will be administered. This will be 4 weeks after Betalutin administration.

Table 8-9 Procedures and assessments for rituximab administration at Visit 7 (Day 28 [±2 days])

Assessment or Procedure	Explanation
Concomitant medication/therapy	Concomitant medication used since prior visit will be recorded
Physical examination	Any abnormal findings should be recorded in the AE record.
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
12-lead ECG	A copy of the medically reviewed ECG page will be signed, dated and interpreted before storing in the patient file
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Immunophenotyping	Define absolute cell counts for circulating T-cells, CD4 T-cells, CD8 T-cells, B-cells and NK cells, respectively defined as CD3+, $CD3^+CD4^+$, $CD3^+CD8^+$, CD19+ and $CD3^-$ $CD16^+$ $CD56^+$ lymphocytes by flow cytometry
Pregnancy test	For women of childbearing potential: serum beta human-chorionic gonadotropin (ß-HCG) pregnancy test
Immunoglobulin levels	Quantitative serum immunoglobulins (IgG, IgA and IgM)
Immunogenicity	Monitoring ADA response (lilotomab, Betalutin, RTX)
PK sampling - Radium Hospital (Oslo, Norway) only. otherwise optional [1]	PK sample will be taken for total radioactivity in blood assessment
Rituximab administration (375 mg/m^2) i.v.	Weight, body surface area, dose administered, start and end time of infusion and pre-medication will be recorded
Adverse events	Any AEs occurring since prior visit will be recorded

[1]Before RTX dosing

8.2.7. Visit 8, 9 and 10 (Week 5, 6 and 7) – Lab Visit

Procedures outlined in Table 8-10 will be performed at Visits 8, 9 and 10 (Weeks 5, 6 and 7).

Table 8-10 Procedures and assessments at Visit 8, 9 and 10 (Week 5, 6 and 7 [±2 days])

Assessment or Procedure	Explanation
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin

8.2.8. Visit 11 (Month 2/Week 8) – Hospital Visit

Procedures outlined in Table 8-11 will be performed at Visit 11 (Week 8). This will be 4 weeks after the last RTX administration.

Table 8-11 Procedures and assessments at Visit 11 (Week 8 [±2 days])

Assessment or Procedure	Explanation
Concomitant medication/therapy	Concomitant medication used since prior visit will be recorded
Physical examination	Any abnormal findings will be recorded in the AE record
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Adverse events	Any AEs occurring since prior visit will be recorded

8.2.9. Visits 12, 13 and 14 (Weeks 9, 10 and 11) – Lab Visit

Procedures outlined in Table 8-12 will be performed at Visits 12, 13 and 14 (Weeks 9, 10 and 11).

Table 8-12 Procedures and assessments at Visits 12, 13 and 14 (Weeks 9, 10 and 11 [±2 days])

Assessment or Procedure	Explanation
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin

8.2.10. Visit 15 (Month 3/Week 12) – Hospital Visit

Safety follow-up and imaging procedures outlined in Table 8-13 will be performed at Visit 15 (Week 12).

Table 8-13 Procedures and assessments at Visit 15 (Week 12 [±7 days])

Assessment or Procedure	Explanation
Concomitant medication/therapy	Concomitant medication used since prior visit will be recorded
Weight	Record weight details
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
12-lead ECG	A copy of the medically reviewed ECG page will be signed, dated and interpreted before storing in the patient file
ECOG	ECOG performance status

Assessment or Procedure	Explanation
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Immunophenotyping	Define absolute cell counts for circulating T-cells, CD4 T-cells, CD8 T-cells, B-cells and NK cells, respectively defined as CD3+, $CD3^+CD4^+$, $CD3^+CD8^+$, CD19+ and $CD3^-$ $CD16^+$ $CD56^+$ lymphocytes by flow cytometry
Coagulation	INR, PTT
Immunoglobulin levels	Quantitative serum immunoglobulins (IgG, IgA and IgM)
Immunogenicity	Monitoring ADA response (lilotomab, Betalutin, RTX)
Minimal Residual Disease[1] (peripheral blood sample)	MRD monitoring to assess early treatment response and detect relapse
Bone marrow biopsy	BM biopsy required for initial confirmation of CR if patient had BM infiltration at baseline
Radiology - 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 (SUVmax) will be recorded. The same camera should preferably be used throughout the study
Radiology - CT scans with contrast or MRI	CT or MRI 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
Optional, only at Radium Hospital (Oslo, Norway): Exploration of the anti-tumour T cell responses	The following human biosamples will be collected: • New tumour tissue biopsy (fine needle aspiration) • Additional peripheral blood samples
Adverse events	Any AEs occurring since prior visit will be recorded

[1] Mandatory, unless relapse or disease progression has been clinically observed since the previous blood sampling

8.2.11. Visits 16 (Month 3/Week 14) – Hospital Visit

Providing patient is deemed not to have PD following the Week 12 imaging scan (above), Rituximab maintenance dosing will commence, as outlined in Table 8-14.

Table 8-14 Procedures and assessments at Visit 16 (Week 14 [±7 days])

Assessment or Procedure	Explanation
Concomitant medication/therapy	Concomitant medication used since prior visit will be recorded
Physical examination	Any abnormal findings will be recorded in the AE record
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
Rituximab administration 375 mg/m^2 iv or 1400 mg s.c.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded
Adverse events	Any AEs occurring since prior visit will be recorded

8.2.12. Visits 17 (Month 6/Week 26) – Hospital Visit

Rituximab maintenance dosing and imaging, as outlined in Table 8-15.

Table 8-15 Procedures and assessments at Visit 17 (Month 6/Week 26 [±7 days])

Assessment or Procedure	Explanation
Concomitant medication	Concomitant medication used since prior visit will be recorded
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Immunophenotyping	Define absolute cell counts for circulating T-cells, CD4 T-cells, CD8 T-cells, B-cells and NK cells, respectively defined as CD3+, $CD3^+CD4^+$, $CD3^+CD8^+$, CD19+ and $CD3^-$ $CD16^+$ $CD56^+$ lymphocytes by flow cytometry
Immunoglobulin levels	Quantitative serum immunoglobulins (IgG, IgA and IgM)
Immunogenicity	Monitoring ADA response (lilotomab, Betalutin, RTX)
Minimal Residual Disease[1] (peripheral blood sample)	MRD monitoring to assess early treatment response and detect relapse
Bone marrow biopsy	BM biopsy required for initial confirmation of CR if patient had BM infiltration at baseline
Radiology - 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 (SUVmax) will be recorded. The same camera should preferably be used throughout the study
Radiology - CT scans with contrast or MRI	CT or MRI 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
Optional, only at Radium Hospital: Exploration of the anti-tumour T cell responses	New tumour tissue biopsy (fine needle aspiration)[2]
Rituximab administration 375 mg/m^2 i.v. or 1400 mg s.c.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded
Adverse events	Any AEs occurring since prior visit will be recorded

[1] Mandatory, unless relapse or disease progression has been clinically observed since the previous blood sampling

[2] Optional biopsy, to be taken before RTX dosing and only if there is sufficient tumour remaining at this timepoint

8.2.13. Visits 18 (Month 9/Week 39) – Hospital Visit

Rituximab maintenance dosing, as outlined in Table 8-16.

Table 8-16 Procedures and assessments at Visit 18 (Month 9/Week 39 [±7 days])

Assessment or Procedure	Explanation
Concomitant medication/therapy	Recording of concomitant medication used since the previous visit
Physical examination	Any abnormal findings will be recorded in the AE record

Assessment or Procedure	Explanation
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Immunophenotyping	Define absolute cell counts for circulating T-cells, CD4 T-cells, CD8 T-cells, B-cells and NK cells, respectively defined as CD3+, $CD3^+CD4^+$, $CD3^+CD8^+$, CD19+ and $CD3^-$ $CD16^+$ $CD56^+$ lymphocytes by flow cytometry.
Optional, only at Radium Hospital: Exploration of the anti-tumour T cell responses	Additional peripheral blood samples[1]
Rituximab administration 375 mg/m^2 i.v. or 1400 mg s.c.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded
Adverse events	Any AEs occurring since prior visit will be recorded

[1] To be taken before RTX dosing

8.2.14. Visit 19 (Month 12/Week 52) – Hospital Visit

Rituximab maintenance dosing and imaging, as outlined in Table 8-17.

Table 8-17 Procedures and assessments at Visit 19 (Month 12/Week 52 [±7 days])

Assessment or Procedure	Explanation
Concomitant medication	Recording of concomitant medication used since the previous visit
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Immunophenotyping	Define absolute cell counts for circulating T-cells, CD4 T-cells, CD8 T-cells, B-cells and NK cells, respectively defined as CD3+, $CD3^+CD4^+$, $CD3^+CD8^+$, CD19+ and $CD3^-$ $CD16^+$ $CD56^+$ lymphocytes by flow cytometry
Immunoglobulin levels	Quantitative serum immunoglobulins (IgG, IgA and IgM)
Immunogenicity	Monitoring ADA response (lilotomab, Betalutin, RTX)
Minimal Residual Disease[1] (peripheral blood sample)	MRD monitoring to assess early treatment response and detect relapse
Bone marrow biopsy	BM biopsy required for initial confirmation of CR if patient had BM infiltration at baseline
Radiology - CT scans with contrast or MRI	CT or MRI 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

Assessment or Procedure	Explanation
Rituximab administration 375 mg/m^2 i.v. or 1400 mg s.c.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded
Adverse events	Any AEs occurring since prior visit will be recorded

[1] Mandatory, unless relapse or disease progression has been clinically observed

8.2.15. Visit 20 (Month 15/Week 65) – Hospital Visit

Rituximab maintenance dosing, as outlined in Table 8-18.

Table 8-18 Procedures and assessments at Visit 20 (Month 15/Week 65 [±7 days])

Assessment or Procedure	Explanation
Concomitant medication	Recording of concomitant medication used since the previous visit
Physical examination	Any abnormal findings will be recorded in the AE record
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Rituximab administration 375 mg/m^2 i.v. or 1400 mg s.c.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded
Adverse events	Any AEs occurring since prior visit will be recorded

8.2.16. Visit 21 (Month 18/Week 78) – Hospital Visit

Rituximab maintenance dosing and imaging, as outlined in Table 8-19.

Table 8-19 Procedures and assessments at Visit 21 (Month 18/Week 78 [±7 days])

Assessment or Procedure	Explanation
Concomitant medication	Recording of concomitant medication used since the previous visit
Physical examination	Any abnormal findings will be recorded in the AE record
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Immunogenicity	Monitoring ADA response (lilotomab, Betalutin, RTX)
Bone marrow biopsy	BM biopsy required for initial confirmation of CR if patient had BM infiltration at baseline
Radiology - CT scans with contrast or MRI	CT or MRI 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
Rituximab administration 375 mg/m^2 i.v. or 1400 mg s.c.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded

Assessment or Procedure	Explanation
Adverse events	Any AEs occurring since prior visit will be recorded

8.2.17. Visit 22 (Month 21/Week 91) – Hospital Visit

Rituximab maintenance dosing, as outlined in Table 8-20.

Table 8-20 Procedures and assessments at Visit 22 (Month 21/Week 91 [±7 days])

Assessment or Procedure	Explanation
Concomitant medication/therapy	Recording of concomitant medication used since the previous visit
Physical examination	Any abnormal findings will be recorded in the AE record
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Rituximab administration 375 mg/m^2 i.v. or 1400 mg s.c.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded
Adverse events	Any AEs occurring since prior visit will be recorded

8.2.18. Visit 23 (Month 24/Week 104) – Hospital Visit

Rituximab maintenance dosing and imaging, as outlined in Table 8-21.

Table 8-21 Procedures and assessments at Visit 23 (Month 24/Week 104 [±7 days])

Assessment or Procedure	Explanation
Concomitant medication	Recording of concomitant medication used since the previous visit
Physical examination	Any abnormal findings will be recorded in the AE record
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Immunogenicity	Monitoring ADA response (lilotomab, Betalutin, RTX)
Minimal Residual Disease[1] (peripheral blood sample)	MRD monitoring to assess early treatment response and detect relapse
Bone marrow biopsy	BM biopsy required for initial confirmation of CR if patient had BM infiltration at baseline
Radiology - CT scans with contrast or MRI	CT or MRI 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
Rituximab administration 375 mg/m^2 i.v. or 1400 mg s.c.	Weight, body surface area, dose administered, start and end time of administration and pre-medication will be recorded

Assessment or Procedure	Explanation
Adverse events	Any AEs occurring since prior visit will be recorded

1 Mandatory, unless relapse or disease progression has been clinically observed

8.2.19. End of study visit – Hospital Visit

The end of study visit should occur:

- 28 days (± 3 days) post last rituximab administration for patients, who complete the study per protocol (Month 25/Week 108)
- Within 7 days of decision of withdrawing from the study is made if the decision occurs > 28 days post last administration of study treatment for patients who discontinue from the study before Month 24 (e.g. disease progression, start of new anti-cancer therapy, other reason) An end of study visit is not expected for patients, who discontinue due to death, lost to follow up or withdrawal of consent.

Safety follow-up procedures 4 weeks after administration of the final RTX study dose are outlined in Table 8-22.

Patients in survival follow-up at the time of Protocol v4.0 approval can have the EOS visit at their next scheduled visit or an earlier convenient time point

Table 8-22 Procedures and assessments at end of study visit

Assessment or Procedure	Explanation
Concomitant medication	Recording of concomitant medication used since the previous visit
Physical examination	Any abnormal findings will be recorded in the AE record
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature
ECOG	ECOG performance status
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin
Adverse events	Any AEs / AESIs occurring since prior visit will be recorded

8.3. Additional Optional Procedures

During the treatment period optional procedures may be performed at visits following relapse or disease progression. Table 8-23 outlines these procedures.

Table 8-23 Optional Procedures and assessments following relapse or disease progression

Assessment or Procedure	Explanation
Tumour tissue biopsy (new tumour tissue biopsy will be performed surgically)	Assessments to be performed: • **Optional**: CD20 and CD37 expression in tumour by immunohistochemistry

Assessment or Procedure	Explanation
	• **Optional**: Gene expression analysis in tumour (DNA, RNA, proteins) to evaluate the relationship between anti-tumour activity and NHL-related genes. *Note*: If FFPE block not biobanked at CCLS, preparation of the 5µM FFPE slides for the respective analyses only after Sponsor request

9. Study Assessments

9.1. Efficacy Assessments

Tumour response will be determined locally according to Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and non-Hodgkin Lymphoma [36]. Investigator assessment will be applied as a measure for assessment of tumour response and as a basis for all protocol guidelines for management of the patient related to disease status. CT or MRI scans are the required methods for tumour assessments. The same method of assessment and the same technique should be used to characterize each lesion at baseline and during follow-up.

All scans and other data supporting efficacy measurements will be stored at the study site and available for subsequent collection, if necessary, for review by the Sponsor and/or independent external reviewer(s).

9.1.1. Contrast enhanced CT examination or MRI

A baseline contrast-enhanced CT scan or MRI must be performed within 4 weeks prior to the first RTX infusion. Table 1-1 and Table 1-2 show the frequency of subsequent contrast enhanced CT scans/MRI per patient for follow-up.

A CT volume scan re-constructed in 3 mm slides with use of i.v.-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.

9.1.2. PET/CT and CT/MRI examination

PET/CT and CT or MRI imaging will be done at baseline and then at 3 and 6 months. CT with contrast or MRI will be performed at 12, 18, 24 months or until disease progression or other withdrawal for any other reason (whichever comes first). Baseline imaging must be performed within 4 weeks prior to administration of the first RTX infusion.

Standard institutional guidelines will be followed. The patient needs to be fasting during 6 hours prior to PET/CT imaging, water is allowed. The blood glucose level must be <11 mmol/L before injection of ^{18}Fluor doxy glucose (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 i.v. 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 when both modalities are to be done on the same day.

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

Guidelines for baseline CT/MRI examination:

1) Target lesions on the CT/MRI scans do not need to match those evaluated on the PET scan.
2) Target nodes should be chosen according to Cheson criteria, version 2014 [35]
3) Up to 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 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/MRI 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

9.1.3. PET/CT score

PET is scored on a 5-point scale (5PS), 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.

5-point scale (5PS)

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.

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

9.1.4. Definitions of Tumour Response Criteria

Investigator assessment will be applied as a measure for assessment of tumour response and as a basis for all protocol guidelines for management of the patient related to disease status using Cheson criteria version 2014 [35] (see Table 9-1).

Table 9-1 Criteria for tumour response evaluation

Response and Site	PET/CT-Based Response	CT/MRI-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 (Sec 9.1.3). It is recognised that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g. with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. 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 on 5PS (Sec 9.1.3) 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 measurable nodes target and extranodal sites - When a lesion is too small to measure on CT, assign 5 x 5 mm as the default value - When no longer visible, 0 x 0 mm - For a node >5 x 5 mm, but smaller than normal, use actual measurement for calculation
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

Response and Site	PET/CT-Based Response	CT/MRI-Based Response
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 magnetic resonance imaging (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 on 5PS (Sec 9.1.3) 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 individual product of the perpendicular diameters (PPD) progression:
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 on 5PS (Sec 9.1.3) 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/MRI-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

9.2. Safety Assessments

Safety assessments will consist of monitoring and recording of AEs, including SAEs, the monitoring of haematology, blood chemistry, immunogenicity, vital signs, ECGs, physical condition and body weight as detailed in Section 1.2.

9.2.1. Definition

9.2.1.1. 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 signed ICF 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 a study drug, whether or not considered related to the study drug.

Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g. blood or platelet 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.

AEs that begin or worsen after informed consent should be recorded in the eCRF. Conditions that were already present at the time of informed consent should be recorded in the patient's Medical History CRF page. All AEs should be reported until 4 weeks following their last RTX maintenance dose or 12 weeks after Betalutin administration for patients who do not qualify for RTX maintenance therapy (see Section 4.1). Only ADR (see Section 9.2.1.2) and AESI (see Section 9.2.1.7) will be reported during follow-up.

Please see Section 9.2.4 for guidance on AE reporting.

9.2.1.2. Definition of adverse drug reaction

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

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

9.2.1.3. Definition of serious adverse event

An 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/probably related to the study drug should also be reported as serious.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing inpatient 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).

9.2.1.4. 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). When the outcome of the ADR is not consistent with the applicable product information this ADR should be considered as unexpected.

9.2.1.5. Suspected unexpected serious adverse reaction (SUSAR)

All suspected ADRs that are considered related to any of the study medication and are both unexpected and serious (SUSARs) are subject to expedited reporting. It is the Sponsor who reports the SUSARs, based on information from the Investigator, see Section 9.2.5.1.

9.2.1.6. Definition of treatment-emergent adverse event

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

9.2.1.7. Definition of adverse events of special interest (AESI)

AESIs 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 myelodysplastic syndrome (MDS), acute leukaemia and others. During the protocol-mandated follow-up visits, the Investigator will observe for indications of potential late-toxicity, such as the development of secondary malignancies, MDS, acute leukaemia or aplastic anaemia. These events will be recorded as SAEs. In addition, physical examination will be performed and blood samples for haematology and serum biochemistry taken.

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

9.2.2. Safety review

A safety monitoring board will not be used for this study. Instead, Nordic Nanovector will have frequent access to the safety and other clinical data and will host Investigator teleconferences on a regular basis during the study to review the ongoing safety of the patients.

After the first 3 patients are enrolled, and once haematological recovery has occurred, Nordic Nanovector will convene a teleconference with the Investigators to discuss and evaluate all of the safety data before dosing additional patients.

The following safety data will be collected and evaluated (see Section 9.2.6):

- AEs
- Laboratory variables: haematology, serum biochemistry and immunoglobulin levels data
- Immunogenicity
- Vital signs
- 12-lead ECGs
- Physical examination
- Long-term toxicity

The time points for all assessments are shown in the Schedule of activities (Section 1.2) AEs will be graded and recorded throughout the study according to NCI CTCAE version 4.03.

9.2.3. Assessments of adverse events; seriousness, causality, severity and expectedness

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

Seriousness will be determined according to the definition, see Section 9.2.1.3.

Causality will be determined based on the definition in Section 9.2.1.2. All AEs judged by the Investigator or the Sponsor as having a reasonable suspected causal relationship to a study drug qualify as ADRs. 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 of the Sponsor will be provided with the report.

All toxicities/AEs will be graded according to NCI CTCAE version 4.03. In the eCRF the Investigator's opinion of the relationship of the AEs to the study drug, 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 study drug administration cannot be ruled out.

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

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 NCI CTCAE version 4.03 by the Investigator. NCI CTCAE grade 5 (death) will not be used in this study; rather information about deaths will be collected through a death form. 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; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**

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

*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.

Expectedness Reports have to 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. The event is unexpected if it is not consistent with the applicable product information, i.e. the Investigator's Brochure for Betalutin and lilotomab or the approved product information (prescribing information) for RTX.

9.2.4. Reporting of adverse events

Any AEs that occur after a patient has signed the ICF and up to 12 weeks after their Betalutin or 4 weeks following their last maintenance RTX drug administration, must be reported, whether or not it is considered related to any of the study drugs. 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 their Betalutin administration or 4 weeks after their last maintenance RTX drug administration, that are judged to be related to any of the study drugs 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 2 years after Betalutin administration or relapse of disease, including information about treatment given to the patient due to NHL (See Section 9.2.1.7).

Death is not defined as an AE but as an outcome of an AE. It is important that the event leading to the death be reported. It will be reported as an AE up to 12 weeks after their last study drug administration. 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 study drug.

Progression of disease:

Disease progression is not reported as an AE if it is clearly consistent with the suspected progression as determined by the protocol. Hospitalization due solely to disease progression should NOT be reported as an SAE. Any associated symptoms may be reported as AEs 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 RTX injection: The expected AEs with RTX are described in the package insert for RTX. This should be taken into consideration when reporting an AE.

AEs may be reported spontaneously by the patient or elicited through open (non-leading) questioning during each visit to the study site and at the end of the AEs follow-up. As far as possible all AEs must be described by their duration (start and stop date), severity (graded according to NCI CTCAE version 4.03), relationship to treatment (unrelated, possible, probable), according to the need of other specific therapy and outcome.

The following information should be recorded in the AE eCRF page:

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

9.2.5. Reporting of serious adverse events

9.2.5.1. Investigator's Responsibilities

The Investigator shall report all SAEs, regardless of suspected causality, occurring after the patient has provided informed consent up to 12 weeks after their Betalutin or 4 weeks following their last maintenance RTX drug administration, immediately (within 24 hours of the Investigator becoming aware of the event) to the Sponsor's representative. 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 their Betalutin or 4 weeks following their last maintenance RTX drug administration, whether or not considered related to study drug
- At any time beyond 12 weeks after their Betalutin or 4 weeks following their last maintenance RTX drug administration, 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 study drug. If such event is observed post end of study visit, it should be notified to the Sponsor using the following email address: SAE@nordicnanovector.com

Any SAEs experienced beyond 12 weeks after their Betalutin or 4 weeks following their last maintenance RTX drug administration should only be reported to Nordic Nanovector if the Investigator suspects a causal relationship to the study treatment, or if it is an AESI. 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 as follows:

1. Immediately (within 24 hours of discovery of the event) report the event to representative preferably by using the SAE module within the eCRF or by email, telephone or fax.
2. Complete the SAE report form within the eCRF or by using the paper form (only if the eCRF is not available) 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. 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.

The Sponsor or assigned designee is responsible for reporting all the relevant safety information to the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) and Competent Authorities concerned. Where applicable as per local requirements, the Investigator will inform the EC/IRB and/or the Competent Authority of the SAE. For reporting death of a patient, the Investigator shall supply the Sponsor and the IEC/IRB with any additional information requested.

Sponsor will inform all Investigators concerned of relevant information about SUSARs.

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

9.2.5.2. Sponsor's Responsibilities

The Sponsor is responsible for the ongoing safety evaluation of the study drug.

The Sponsor is responsible for the prompt notification to all concerned Investigators, the IECs/IRBs and Competent Authorities where Betalutin studies are ongoing, of findings that affect the health of the patients, impact on the conduct of the study or alter the Competent Authority's authorization 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, with regard to its seriousness and causal relationship to the study drug and/or concomitant therapy. The Sponsor will assess whether or not the AE is unexpected.

9.2.6. Other Safety Parameters

9.2.6.1. Physical examination

A physical examination will be performed at each hospital visit by the 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.

The Investigator will also assess the ECOG performance status at time points given in Schedule of activities (Section 1.2).

Table 9-2 Definition of ECOG performance status

Grade	ECOG*
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 ECOG scale from the baseline value.

9.2.6.2. Vital signs

Vital signs (systolic/diastolic blood pressure, heart rate and body temperature) will be measured as described in the Schedule of activities (Section 1.2). Additional vital signs assessments will be done under the Investigator's judgment.

Blood pressure will be measured on the arm contralateral to the site of study drug 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.

9.2.6.3. 12-lead electrocardiogram

A standard 12-lead ECG will be performed as per the Schedule of activities (Section 1.2). 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.

9.2.6.4. Clinical laboratory parameters

Blood samples for the determination of haematology and serum biochemistry parameters will be drawn at pre-specified time points, as per the Schedule of activities (Section 1.2).

The following laboratory tests will be performed:

Table 9-3 Clinical laboratory parameters

Serum Biochemistry	Haematology	Urine
Sodium	Haemoglobin	Urine pregnancy test at day 0
Potassium	Platelets	
Calcium	White blood cell count	
Creatinine	Differential	
Uric acid	Neutrophils	
Alkaline Phosphatase (total ALP)	Lymphocytes	
Aspartate aminotransferase (ASAT)	Monocytes	
Alanine aminotransferase (ALAT)	Eosinophils	
Lactate Dehydrogenase (LDH)	Basophils	
Glucose	Immunophenotyping**	
Bilirubin, total	Coagulation: International normalised ratio (INR), prothrombin time (PTT)	
Gamma-glutamyl transferase (GGT)		
Magnesium		
Albumin		
HIV test*		
Hepatitis B test (HBsAg and anti-HBc)*		
Hepatitis C*		
b-hCG (pregnancy test)*		
Quantitative serum immunoglobulins (IgG, IgA and IgM)		
HAMA at screening*		

* A serum sample will be sent for HAMA screening to a central laboratory (mandatory). Eligibility can be assessed using a local test such as the Milenia Quickline® HAMA test (optional). If the Milenia Quickline® HAMA test is positive, eligibility can only be assessed using the results from the central laboratory.
**Absolute cell counts for circulating T-cells, CD4 T-cells, CD8 T-cells, B-cells and NK cells, respectively defined as CD3+, $CD3^+CD4^+$, $CD3^+CD8^+$, CD19+ and $CD3^-$ $CD16^+$ $CD56^+$ lymphocytes by flow cytometry. At certain time points specified in Schedule of activities (Section 1.2).

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, 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 NCI CTCAE version 4.03. The laboratory values might be an SAE if meeting any of the seriousness criteria defined in Section 9.2.1.3. During the follow-up period only changes in laboratory values judged to be related to study drug 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 site.

9.2.6.5. Immunogenicity assessment

9.2.6.5.1. Assessments

Immunogenicity i.e. development of ADAs is of concern as ADA can reduce the efficacy of the therapeutic protein but also, in some specific cases, impact on patient safety [36-38].

In this study, the immunogenicity risk for the patient is related to the immunogenicity potential of (1) lilotomab, (2) the chemical linker p-SCN-Bn-DOTA (satetraxetan), and (3) RTX. The immunogenicity potential of ARC using satetraxetan is suggested to be dependent of the carrier molecule rather than DOTA itself [39]. RTX immunogenicity has been reported but without a demonstrated clinical relevance [40-42]. Therefore, immunogenicity assessments for ADA monitoring will be focused on lilotomab and RTX as follow:

- Monitoring of the ADA response after injection of lilotomab/Betalutin according to a tiered approach (https://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf), using a bridging assay format
- Monitoring of the ADA response after RTX dosing, before – during – and after combination with Betalutin. A commercial kit will be used for this assessment.
- HLA class II haplotype of the patients [43] (see section 9.4).

9.2.6.5.2. Human biosamples collection schedule

Sampling of peripheral blood for ADA monitoring will be performed at the following approximate time points:

- Screening (Baseline for lilotomab, Betalutin and RTX ADA monitoring)
- After Betalutin administration, at Day 28 and 3, 6, 12, 18 and 24 months. It has to be noted that at Day 28, peripheral blood sampling should be done before RTX dosing.

The time points mentioned are approximate time points. The exact time point when the sample is taken needs to be recorded in the eCRF.

9.2.6.5.3. Human biosamples handling

A volume of approximately 6 mL of peripheral blood will be collected by venipuncture at each time point (see above and Section 1-2) to monitor the development of an ADA response post lilotomab/Betalutin treatment. Serum samples will be isolated, aliquoted and frozen on site at ≤ -20°C the day of collection. All the aliquots of serum will be shipped on dry ice to Covance Central Laboratories (Geneva, Switzerland), where they will be biobanked for future use.

An additional volume of approximately 4 mL of peripheral blood will be collected in a similar fashion at each time point (see above and Section 1-2) for RTX immunogenicity assessment and monitoring of RTX concentration in serum (see Section 9.3). Serum samples will be isolated, aliquoted and frozen on site at ≤-20°C the day of collection. All serum aliquots will be shipped on dry ice to Covance Central Laboratories (Geneva, Switzerland), 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 laboratory manual.

9.2.7. 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 remains on study. Table 9-4 indicates the range for patients during the treatment period (28 months).

Table 9-4 Volume of blood to be drawn from each patient during the screening and treatment period (Screening to End of study visit)

Assessment	Max volume (1 draw)	No. of samples (30 days)	Max volume (30 days)	No. of samples (Total)	Max volume (Total)
On site laboratory analyses					
• Biochemistry	4 mL	Max 7	28 ml	Max 23	92 mL
• Haematology	4 mL	Max 7	28 mL	Max 23	92 mL
• Serum virology & pregnancy test (screening)	4.5 mL	Max 1	4.5 mL	Max 1	4.5 mL
• Immunoglobulin levels	5 mL	Max 2	10 mL	Max 5	25 mL
• Coagulation	4 mL	Max 1	4 mL	Max 2	8 mL
HAMA at screening	4 mL	Max 1	4 mL	Max 1	4 mL
Immunogenicity assessment[1] (lilotomab, Betalutin ADA)	6 mL	Max 2	12 mL	Max 7	42 mL
RTX immunogenicity (ADA)/PK[2]	4 mL	Max 2	8 mL	Max 7	28 mL
Minimal Residual Disease	8 mL	Max 1	8 mL	Max 5	40 mL
Pharmacokinetic – Total radioactivity[3]	2 mL	Max 8	16 mL	Max 8	16 mL
HLA haplotyping (optional)	2 mL	Max 1	2 mL	Max 1	2 mL
In vitro T-cell responses[4] (optional)	100 mL	Max 1	100 mL	Max 3	300 mL
TOTAL - maximum volume to be drawn for patients not participating in the PK[3] and *in vitro* T-cell assessments	45.5 mL	-	108.5 mL	-	337.5 mL
TOTAL - maximum volume for a few patients (<10) participating in the PK[3] but not *in vitro* T-cell assessments	47.5 mL	-	124.5 mL	-	353.5 mL
TOTAL - maximum volume to be drawn for patients participating in the *in vitro* T-cell but not PK[3] assessments	145.5 mL	-	208.5 mL	-	637.5 mL
TOTAL - maximum volume to be drawn for patients participating in both the PK[3] and *in vitro* T-cell assessments	147.5 mL	-	224.5 mL	-	653.5 mL

Max = maximum number of samples to be taken from screening to End of Study

[2] Monitoring of rituximab concentration in serum and the ADA response towards rituximab.

[3] To be performed at Radium Hospital (Oslo, Norway) only; otherwise optional

[4]At Radium Hospital (Oslo, Norway) only. Optional, additional blood volumes collected to explore the anti-tumour T cell responses

9.2.8. Pregnancy

- Details of all pregnancies in female patients and female partners of male patients will be collected after the start of study treatment. The pregnant patient or the patient's partner should be followed-up during the entire course of the pregnancy up to 6-8 weeks beyond the estimated delivery date.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies or ectopic pregnancy) are considered SAEs.

9.3. Pharmacokinetics

9.3.1. Assessments

Betalutin PK samples will be collected from patients to evaluate whether the combination with RTX impact the total radioactivity in blood profile observed in the LYMRIT 37-01 study. *In vitro* measurements will be performed by measuring the total radioactivity (Betalutin, ^{177}Lu-satetraxetan chelate, ^{177}Lu-DTPA chelate, and ^{177}Lu) per mL of blood using a gamma counter. This assessment will be mandatory at Radium Hospital (Oslo, Norway), otherwise optional.

It has to be noted that it is not expected to detect ^{177}Lu in blood due to its high binding affinity to satetraxetan and DTPA. DTPA chelates the ^{177}Lu not radiolabelled to satetraxetan in Betalutin formulation, with ^{177}Lu-DTPA chelate expected to have a fast-renal clearance [44-46].

RTX is widely used in onco-haematology at a dose of 375 mg/m^2, as neither dose-response relationship nor DLT were identified. As PK studies have demonstrated large inter-individual variability of rituximab exposure [47, 48], monitoring of RTX serum concentration will be performed to support the assessment of any potential interference of RTX in immunogenicity assessments (see Section 9.2.6.5).

9.3.2. Human biosamples collection schedule

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

- Before lilotomab administration (baseline)
- After Betalutin administration:
- 5 (±2), and 60 (±10) minutes
- 2 hours (±15 minutes), 24 (±4) hours, and 96 (±24) hours
- 7 (±2) days and 28 (±2) days

It has to be noted that on Days 7 and 28, PK sampling should be done before RTX dosing. 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.

Sampling of peripheral blood for RTX concentration in serum will be performed at the time points agreed for the immunogenicity assessments (See Section 9.2.6.5.2.).

9.3.3. Human biosamples handling

9.3.3.1. Total radioactivity in blood

A volume of approximately 2 mL of peripheral blood will be collected on EDTA at each time point (see above and Section 1-2). An exact volume of 1 mL of peripheral blood will be transferred on-site into a 5 mL transfer tube. Radioactivity measurement will be performed on-site at Nordic Nanovector ASA (Oslo, Norway) or selected sites that are experienced and equipped to perform these assessments. The total radioactivity per mL of blood will be determined from each sample.

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

9.3.3.2. Monitoring of RTX concentration in serum

A volume of approximately 4 mL of peripheral blood will be collected and handled as described in Section 9.2.6.5. and Section 1-2.

Serum samples will be shipped to Covance Central Laboratories (Geneva, Switzerland), 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 laboratory manual for this study.

9.4. Biodistribution and dosimetry

The biodistribution and dosimetry study will provide estimates for the absorbed radiation dose to normal body structures as well as to tumours that can be identified in the images. The radioactivity in the actual organs will be measured in absolute terms, at different times after injection. The time series will allow to estimate the cumulative activity in each organ and by measurements/estimates of organ weight the absorbed dose.

Measurements will be performed as described in Appendix 5.

The measurements will be performed on a SPECT/CT scanner containing 2 gamma camera heads (Siemens SYMBIA –T16) equipped with medium energy collimators, which. will be used for CT, SPECT, and whole-body scanning. Quantification will be carried out by use of the software of the vendor and using computer programs (IDL, ITT visual solutions) Full details of the scans required for biodistribution and dosimetry and of acquisition specifications are provided in a dedicated dosimetry protocol.

The images obtained will enable the characterisation of the biodynamics and the calculation of the cumulative activity in each organ, with dose estimates obtained using the OLINDA program.

The conjugated whole-body studies and the quantification in regions drawn around each organ together with assay of activity in blood will allow for:

- Estimation of whole-body retention of radioactivity at set imaging times post-injection.
- Estimation of the individual organ uptake/retention of radioactivity at set points after injection.
- Estimate retention of administered radioactivity in blood.
- Calculation of estimated absorbed radiation dose to target organs and to tumours.

9.5. Biomarkers

Biomarker research is part of this study. Following informed consent from the patients, human biosamples, including but not exclusive to tumour tissue biopsy, needle aspirate and peripheral blood samples, will be collected to evaluate pharmacodynamics [49, 50] and gene expression changes related to disease treatment and/or relapse/disease progression in tumour [51-56]. HLA class I and II haplotype of the patients will be addressed using DNA extracted from either peripheral blood leucocytes or saliva [43, 57]. Anti-tumour T-cell responses will be measured by flow cytometry after co-culture of peripheral blood mononuclear cells and autologous lymphoma cells [58] and other relevant in vitro biomarker analyses.

Details regarding the assessments, technologies in scope and biobanking are reported in Table 9-5. Except for CD37/CD20 expression in tumour prior to treatment and monitoring of the MRD, these assessments are optional, and some will be performed at selected sites only (e.g. anti-tumour T-cell responses). The results of these analyses are not required for enrolment into the study and may not be reported to the clinical study database, nor 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. Analyses performed to explore the anti-tumour T-cell responses will be mainly performed at Radium Hospital (Oslo, Norway) but some analyses may require having an aliquot of this biological material (collected and biobanked at Radium Hospital (Oslo, Norway) to be sent to contract research organisations located outside of Norway.

9.6. Biobanking

The patient may be asked if he/she is willing to have part of the available tumour biopsy samples (archived or newly obtained at screening visit, disease progression and/or relapse) to be biobanked at Covance Central Laboratories (Geneva, Switzerland) for future analysis of the tumour tissue samples or its derivatives (DNA, RNA, proteins). If a tumour block is provided, it will be returned to the hospital upon request.

Additional biological material collected for research studies focusing the anti-tumour T-cell responses (e.g. tumour biopsy and peripheral blood samples and derivatives such as cells, plasma, DNA, RNA) collected at Radium Hospital (Oslo, Norway) only, will be processed and biobanked on-site for future use.

Table 9-5 Biomarker assessments

Assessment	Human biosamples collected	Human biosamples or derivatives used in assay	Method	Schedule of assessments	Biobanking	Purpose
CD37 & CD20 expression in tumour tissue	Tumour tissue biopsy (surgical)	FFPE 5 µM slides	Immunohistochemistry, whole slide digital image quantitative analysis	Mandatory prior to treatment (archived or newly collected at screening) Optional at relapse or disease progression (newly collected biopsy)	FFPE block on-site or CCLS 5µM FFE slides to be prepared only upon sponsor request to ensure integrity of the biomaterial and quality of the analysis	To characterize PD and identify potential predictors of efficacy
Gene expression profiling in tumour	Tumour tissue biopsy (surgical)[1]	FFPE 5 µM slides and derivatives such as DNA, RNA and proteins	Gene expression arrays (RNA) RNA sequencing (RNA) DNA sequencing(DNA) Other relevant methods	Optional Archived tumour tissue biopsies or newly collected at screening, relapse and/or disease progression	5µM FFE slides to be prepared only upon sponsor request to ensure integrity of the biomaterial and quality of the analysis	To identify prognostic and/or treatment-related predictive biomarkers
Minimal Residual Disease	Tumour tissue biopsy (surgical)[1] Peripheral blood	FFPE 5 µM slides Cell and cell-free (in plasma) tumour DNA	Next generation sequencing (DNA)	Biopsy: Mandatory, archived tumour tissue biopsy or newly collected at screening[1] Blood: Mandatory, at prior to treatment, Week 12, Week 26, Week 52 and at EOS , unless relapse or disease progression has been clinically observed since the previous blood sample	5µM FFE slides to be prepared only upon sponsor request to ensure integrity of the biomaterial and quality of the analysis 5µM FFE slides to be prepared only upon sponsor request to ensure integrity of the biomaterial and quality of the analysis Bulk material (whole blood without plasma) and plasma, at CCLS	To calibrate the blood MRD test To assess early treatment response and detect relapse

Assessment	Human biosamples collected	Human biosamples or derivatives used in assay	Method	Schedule of assessments	Biobanking	Purpose
In vitro anti-tumour T-cell response	Peripheral blood and tumour tissue biopsy (surgical or needle aspirate – See Tables 1-1 and 1-2)	Peripheral blood leucocytes, tumour cells, plasma, and derivatives such as DNA, RNA and proteins	*In vitro* cell based assay using flow cytometry as readout and other biomarker analyses (DNA, RNA, proteins)	Optional Peripheral blood: Prior to treatment, Week 12 and Week 39 Tumour biopsy: Prior to treatment, Day -1 or Day 0, Week 12 and Week 25	Peripheral blood leucocytes, tumour cells, plasma and derivatives such as DNA, RNA, proteins, at Radium Hospital (Oslo, Norway)	To explore further the anti-tumour T-cell responses driven by the combination of lilotomab, Betalutin and RTX
HLA class I II haplotype	Peripheral blood Saliva sample or mouth swab is acceptable if blood collection not possible	DNA	Gene array (DNA)	Optional Prior to treatment	Peripheral blood, saliva, mouth swab and at CCLS	To (i) investigate the mechanism underlying a potential ADA response and (ii) characterize the anti-tumour T-cell response

[1] **NOTE:** No additional tumour tissue biopsy will be collected (sample may be taken from an archived and/or newly collected biopsy at screening, relapse and/or disease progression for CD20 & CD37 expression in tumour)

10. Statistical Considerations

10.1. Statistical Analyses

The study is a single-arm, open-label study to further assess the risk/benefit of a pre-dose of lilotomab and Betalutin to enhance tumour response to RTX therapy. Six to 12 patients is a reasonable sample size to evaluate any potential safety/tolerability signals and for obtaining preliminary estimates of the response rates and variability of the response rates.

The primary endpoint is the frequency and type of AEs. Study data will be summarised with respect to demographic and baseline characteristics, safety observations and measurements, efficacy observations and measurements (response rates, duration of response, PFS, TTP, OS), and PK measurements. Categorical data will be presented in tables; descriptive statistics will be used to summarise response rates, etc. Patients who have withdrawn from the study, including those who have died, will be counted as having PD for all visits after the time of withdrawal.

The number and percentage of patients with each response, and overall (CR + PR) will be presented for each time point for the ITT population. All data obtained after treatment with lilotomab/Betalutin will be summarized by the dose of Betalutin received and overall doses.

10.1.1. Populations for analysis

Intent-to-treat (ITT) population: The ITT population will consist of all patients who were enrolled and treated with lilotomab/Betalutin, regardless if RTX therapy was initiated.

Safety Population: The safety analysis population will include all patients who received at least one dose of any study drug.

PK population: The PK population consists of all patients who have a PK assessment with a sufficient number of evaluable blood samples.

10.1.2. Other Analyses

PK, and biomarker exploratory analyses will be described in the statistical analysis plan (SAP), which will be finalised before database lock. Analyses will be presented separately from the main clinical study report (CSR).

11. References

1. Barrena S, Almeida J, Yunta M, et al. Aberrant expression of tetraspanin molecules in B-cell chronic lymphoproliferative disorders and its correlation with normal B-cell maturation. *Leukemia* 2005; **19**(8): 1376-83.

2. Wang W, Li Y, Gao L, et al. Significance of CD37 expression in malignant B cells. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 2014; **22**(3): 644-7.

3. Zhao X, Lapalombella R, Joshi T, et al. Targeting CD37-positive lymphoid malignancies with a novel engineered small modular immunopharmaceutical. *Blood* 2007; **110**(7): 2569-77.

4. Kolstad A, Madsbu U, Beasley M, et al. LYMRIT 37-01: Updated results of a phase I/II study of ^{177}lu-lilotomab satetraxetan, a novel CD37-targeted antibody- radionuclide-conjugate in relapsed NHL patients. *Hematological Oncology* 2017; **35**: 269-70.**[abstract]**

5. Czuczman MS, Olejniczak S, Gowda A, et al. Acquirement of rituximab resistance in lymphoma cell lines is associated with both global CD20 gene and protein down-regulation regulated at the pre-transcriptional and post-transcriptional levels. *Clin Cancer Res* 2008; **14**(5): 1561-70.

6. Tsai PC, Hernandez-Ilizaliturri FJ, Bangia N, et al. Regulation of CD20 in rituximab-resistant cell lines and B-cell non-Hodgkin lymphoma. *Clin Cancer Res* 2012; **18**(4): 1039-50.

7. van Meerten T, van Rijn RS, Hol S, et al. Complement-induced cell death by rituximab depends on CD20 expression level and acts complementary to antibody-dependent cellular cytotoxicity. *Clin Cancer Res* 2006; **12**(13): 4027-35.

8. Rezvani AR, Maloney DG. Rituximab resistance. *Best Pract Res Clin Haematol* 2011; **24**(2): 203-16.

9. Singh V, Gupta D, Arora R, et al. Surface levels of CD20 determine anti-CD20 antibodies mediated cell death in vitro. *PLoS One* 2014; **9**(11): e111113.

10. Johnson NA, Boyle M, Bashashati A, et al. Diffuse large B-cell lymphoma: reduced CD20 expression is associated with an inferior survival. *Blood* 2009; **113**(16): 3773-80.

11. Repetto-Llamazares AHV, Malenge MM, O'Shea A, et al. Combination of 177Lu-lilotomab with rituximab significantly improves the therapeutic outcome in preclinical models of non-Hodgkin's lymphoma. *Eur J Haematol*. 2018; **101**: 522–531.

12. Repetto-Llamazares AH, Larsen RH, Landsverk KS, et al. Treatment with ^{177}Lu-HH1 Increases CD20 Expression in Non-Hodgkin Lymphoma Cells in Vitro and In Vivo. *Blood* 2015; **126**(23).**[abstract]**

13. Weber T, Bötticher B, Mier W, et al. High treatment efficacy by dual targeting of Burkitt's lymphoma xenografted mice with a (177)Lu-based CD22-specific radioimmunoconjugate and rituximab. *Eur J Nucl Med Mol Imaging* 2016; **43**(3): 489-98.

14. Simpson TR, Li F, Montalvo-Ortiz W, et al. Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma. *J Exp Med* 2013; **210**(9): 1695-710.

15. Formenti SC, Demaria S. Systemic effects of local radiotherapy. *Lancet Oncol* 2009; **10**(7): 718-26.

16. Leonard JP, Jung SH, Johnson J, et al. Randomized Trial of Lenalidomide Alone Versus Lenalidomide Plus Rituximab in Patients With Recurrent Follicular Lymphoma: CALGB 50401 (Alliance). *J Clin Oncol* 2015; **33**(31): 3635-40.

17. Jacobs SA, Swerdlow SH, Kant J, et al. Phase II trial of short-course CHOP-R followed by 90Y-ibritumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. *Clin Cancer Res* 2008; **14**(21): 7088-94.

18. Rajguru S, Kristinsdottir T, Eickhoff J, et al. Yttrium 90-ibritumomab tiuxetan plus rituximab maintenance as initial therapy for patients with high-tumor-burden follicular lymphoma: a Wisconsin Oncology Network study. *Clin Adv Hematol Oncol* 2014; **12**(8): 509-15.**[abstract]**

19. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016; **127**(20): 2375-90.

20. Abdollahi S, Chong EA, Olin RL, et al. The Impact of Rituximab Resistance on Overall Survival Rate in Low-Grade Follicular Lymphoma. *Blood* 2008; **112**(11): 3783-.

21. Casulo C, Byrtek M, Dawson KL, et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. *J Clin Oncol* 2015; **33**(23): 2516-22.

22. Horwitz SM, Zelenetz AD, Gordon LI, et al. NCCN Guidelines Insights: Non-Hodgkin's Lymphomas, Version 3.2016. *J Natl Compr Canc Netw* 2016; **14**(9): 1067-79.

23. Kahl BS, Spurgeon SE, Furman RR, et al. A phase 1 study of the PI3Kδ inhibitor idelalisib in patients with relapsed/refractory mantle cell lymphoma (MCL). *Blood* 2014; **123**(22): 3398-405.

24. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2005; **106**(12): 3725-32.

25. Herold M, Dölken G, Fiedler F, et al. Randomized phase III study for the treatment of advanced indolent non-Hodgkin's lymphomas (NHL) and mantle cell lymphoma: chemotherapy versus chemotherapy plus rituximab. *Ann Hematol* 2003; **82**(2): 77-9.

26. Schaefer NG, Huang P, Buchanan JW, et al. Radioimmunotherapy in non-Hodgkin lymphoma: opinions of nuclear medicine physicians and radiation oncologists. *J Nucl Med* 2011; **52**(5): 830-8.

27. Dahle J, Repetto-Llamazares AH, Mollatt CS, et al. Evaluating antigen targeting and anti-tumor activity of a new anti-CD37 radioimmunoconjugate against non-Hodgkin's lymphoma. *Anticancer Res* 2013; **33**(1): 85-95.

28. Repetto-Llamazares AH, Larsen RH, Patzke S, et al. Targeted Cancer Therapy with a Novel Anti-CD37 Beta-Particle Emitting Radioimmunoconjugate for Treatment of Non-Hodgkin Lymphoma. *PLoS One* 2015; **10**(6): e0128816.

29. Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; **27**(suppl 5): v83-v90.

30. Maloney DG, Grillo-Lopez AJ, White CA, et al. IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood* 1997; **90**(6): 2188-95.

31. Feuring-Buske M, Kneba M, Unterhalt M, et al. IDEC-C2B8 (Rituximab) anti-CD20 antibody treatment in relapsed advanced-stage follicular lymphomas: results of a phase-II study of the German Low-Grade Lymphoma Study Group. *Ann Hematol* 2000; **79**(9): 493-500.

32. Vidal L, Gafter-Gvili A, Salles G, et al. Rituximab maintenance for the treatment of patients with follicular lymphoma: an updated systematic review and meta-analysis of randomized trials. *J Natl Cancer Inst* 2011; **103**(23): 1799-806.

32. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 2005; **105**(4): 1417-23.

34. Shankar G, Arkin S, Cocea L, et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. *AAPS J* 2014; **16**(4): 658-73.

35. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32**(27): 3059-68.

36. Rosenberg AS. Immunogenicity of biological therapeutics: a hierarchy of concerns. *Dev Biol (Basel)* 2003; **112**: 15-21.

37. Richter WS, Ivancevic V, Meller J, et al. 99mTc-besilesomab (Scintimun) in peripheral osteomyelitis: comparison with 99mTc-labelled white blood cells. *Eur J Nucl Med Mol Imaging* 2011; **38**(5): 899-910.

38. Steenholdt C, Palarasah Y, Bendtzen K, et al. Pre-existing IgG antibodies cross-reacting with the Fab region of infliximab predict efficacy and safety of infliximab therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **37**(12): 1172-83.

39. Perico ME, Chinol M, Nacca A, et al. The humoral immune response to macrocyclic chelating agent DOTA depends on the carrier molecule. *J Nucl Med* 2001; **42**(11): 1697-703.

40. Van Walle I, Gansemans Y, Parren PW, et al. Immunogenicity screening in protein drug development. *Expert Opin Biol Ther* 2007; **7**(3): 405-18.

41. Keating GM. Rituximab: a review of its use in chronic lymphocytic leukaemia, low-grade or follicular lymphoma and diffuse large B-cell lymphoma. *Drugs* 2010; **70**(11): 1445-76.

42. Dunn N, Juto A, Ryner M, et al. Rituximab in multiple sclerosis: Frequency and clinical relevance of anti-drug antibodies. *Mult Scler* 2018; **24**(9): 1224-33.

43. Barbosa MD, Vielmetter J, Chu S, et al. Clinical link between MHC class II haplotype and interferon-beta (IFN-beta) immunogenicity. *Clin Immunol* 2006; **118**(1): 42-50.

44. Li WP, Ma DS, Higginbotham C, et al. Development of an in vitro model for assessing the in vivo stability of lanthanide chelates. *Nucl Med Biol* 2001; **28**(2): 145-54.

45. Breeman WA, van der Wansem K, Bernard BF, et al. The addition of DTPA to [^{177}Lu-DOTA0,Tyr3]octreotate prior to administration reduces rat skeleton uptake of radioactivity. *Eur J Nucl Med Mol Imaging* 2003; **30**(2): 312-5.

46. Forrer F, Chen J, Fani M, et al. In vitro characterization of (177)Lu-radiolabelled chimeric anti-CD20 monoclonal antibody and a preliminary dosimetry study. *Eur J Nucl Med Mol Imaging* 2009; **36**(9): 1443-52.

47. Cartron G, Blasco H, Paintaud G, et al. Pharmacokinetics of rituximab and its clinical use: thought for the best use? *Crit Rev Oncol Hematol* 2007; **62**(1): 43-52.

48. Tout M, Casasnovas O, Meignan M, et al. Rituximab exposure is influenced by baseline metabolic tumor volume and predicts outcome of DLBCL patients: a Lymphoma Study Association report. *Blood* 2017; **129**(19): 2616-23.

49. Schaue D, Kachikwu EL, McBride WH. Cytokines in radiobiological responses: a review. *Radiat Res* 2012; **178**(6): 505-23.

50. Werner E, Wang H, Doetsch PW. Role of Pro-inflammatory Cytokines in Radiation-Induced Genomic Instability in Human Bronchial Epithelial Cells. *Radiat Res* 2015; **184**(6): 621-9.

51. Pastore A, Jurinovic V, Kridel R, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. *Lancet Oncol* 2015; **16**(9): 1111-22.

52. Roschewski M, Staudt LM, Wilson WH. Dynamic monitoring of circulating tumor DNA in non-Hodgkin lymphoma. *Blood* 2016; **127**(25): 3127-32.

53. He J, Abdel-Wahab O, Nahas MK, et al. Integrated genomic DNA/RNA profiling of hematologic malignancies in the clinical setting. *Blood* 2016; **127**(24): 3004-14.

54. Weigert O, Weinstock DM. The promises and challenges of using gene mutations for patient stratification in follicular lymphoma. *Blood* 2017; **130**(13): 1491-8.

55. Pott C, Belada D, Danesi N, et al. Analysis of Minimal Residual Disease in Follicular Lymphoma Patients in Gadolin, a Phase III Study of Obinutuzumab Plus Bendamustine Versus Bendamustine in Relapsed/Refractory Indolent Non-Hodgkin Lymphoma. *Blood* 2015; **126**(23): 3978-.

56. Herrera AF, Kim HT, Kong KA, et al. Next-generation sequencing-based detection of circulating tumour DNA After allogeneic stem cell transplantation for lymphoma. *Br J Haematol* 2016; **175**(5): 841-50.

57. Rosenberg AS, Sauna ZE. Immunogenicity assessment during the development of protein therapeutics. *J Pharm Pharmacol* 2018; **70**(5): 584-94.

58. Kolstad A, Kumari S, Walczak M, et al. Sequential intranodal immunotherapy induces antitumor immunity and correlated regression of disseminated follicular lymphoma. *Blood* 2015; **125**(1): 82-9.

12. Appendices

Appendix 1: Abbreviations

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
ALAT	Alanine transaminase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ARC	Antibody-radionuclide-conjugate
ASAT	Aspartate transaminase
AUC	Area under plasma drug concentration-time curve
β-HCG	beta human-chorionic gonadotropin
CCLS	Covance Central Laboratories
CHOP	Cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone
C_{max}	Maximum plasma drug concentration;
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, vincristine and prednisolone
DC	Decay correction factor
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose limiting toxicity
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
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
E_{max}	Maximum energy
FACT-Lym	Functional Assessment of Cancer Therapy–Lymphoma
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FDG	(^{18}F) Fluor deoxy glucose
FL	Follicular lymphoma
FSH	Follicle stimulating hormone
GCP	Good clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyl transferase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HAMA	Human anti-murine antibody

HBsAg	Hepatitis B surface antigen
HRT	Hormonal replacement therapy
Anti-HBc	Antibody to hepatitis B core antigen
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
I	Iodine
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
In	Indium
INR	International Normalized Ratio
iNHL	Indolent non-Hodgkin B-cell lymphoma
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
i.v.	Intravenous
LDi	Longest diameter
Lu	Lutetium
Max	Maximum
MBq	Mega becquerel
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MAB	Monoclonal antibody
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MS	Mass spectrometry
MTD	Maximum tolerated dose
MDS	Myelodysplastic syndrome
NCI	National Cancer Institute
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
PK	Pharmacokinetic
PPD	Individual product of the perpendicular diameters
PR	Partial response
PTT	Partial Thromboplastin Time
QoL	Quality of Life
RIT	Radioimmunotherapy
RTX	Rituximab
SAE	Serious adverse event
SAP	Statistical analysis plan
s.c.	Subcutaneous

SCID	Severe combined immune deficient
SD	Stable disease
SPD	Sum of products of the 2 target tumour diameters
SPECT	Single Photon Emission Computed Tomography
SUV	Standardized uptake value
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TMF	Trial Master File
ULN	Upper limit of normal
Y	Yttrium
WHO	World Health Organization
WHO PS	WHO Performance Status
WOCBP	Woman of Child Bearing Potential

Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines such as the Declaration of Helsinki.
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IEC/IRB by the Investigator and reviewed and approved by the IEC/IRB before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
- Providing written summaries of the status of the study to the IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB
- Notifying the IEC/IRB of SAEs or other significant safety findings as required by IEC/IRB procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 CFR, ICH guidelines, the IEC/IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IEC/IRB or study site.

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed ICF(s) must be provided to the patient or the patient's legally authorised representative.

Patients who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

Data Protection

- Patients will be assigned a unique number. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed and consent that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

Data Quality Assurance

- All patient data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the data entered in the CRF.
- The investigator must permit study-related monitoring, audits, IEC/IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site staff are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is

being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Source documents required will be defined in the monitoring plan.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. In addition, current medical records must be available.

Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study treatment development

Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Documentation can come from the site staff review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and those whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Contraception Guidance

Male patients

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following throughout study drug therapy and the following 12 months:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom when having penile-vaginal intercourse with a WOCBP who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration [during the protocol-defined time frame].

Refrain from donating sperm for the duration of the study and for 12 months after the last dose of study drug.

Female patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 12-1.

Table 12-1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
• Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
• **Vasectomised partner** *A vasectomised partner is a highly effective contraception method provided the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• **Sexual abstinence** *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilised during the treatment period and for at least 12 months after the last dose of study treatment

Pregnancy Testing

Additional pregnancy testing should be performed 28 days after Betalutin treatment. Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male patients with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive study treatment.
- 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 within 24 hours of learning of the partner's pregnancy. 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.

Female Patients who become pregnant

- Should be immediately withdrawn from study.
- The Investigator will collect pregnancy information on any female patient 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 patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6-8 weeks 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 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 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 as described in Section 9.2.5. While the Investigator is not obligated to actively seek this information in former study patients, he/she may learn of an SAE through spontaneous reporting.

Appendix 4: Genetics

Use/Analysis of DNA/RNA

- Gene expression variation may influence a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to the expression of genetic determinants at the DNA or RNA level that influence drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IEC/IRB allow, a blood, saliva and/or tissue biopsy sample will be collected for DNA analysis from consenting patients.
- DNA/RNA samples will be used for research related to study drug or indication and related diseases. They may also be used to develop tests/assays including diagnostic tests related to study drug and/or treatments of this drug class and indication. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA/RNA samples will be analysed for described planned analyses. Additional analyses may be conducted if it is hypothesised that this may help further understand the clinical data.
- DNA/RNA samples will be analysed (See Section 9.4 for details). Additional analyses may be conducted if it is hypothesised that this may help resolve issues with the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to study treatment or study treatments of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The Sponsor will store the DNA/RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study treatment or study treatments of this class or indication continues but no longer than 15 years or other period as per local requirements.

Appendix 5: Biodistribution and dosimetry assessments

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 wholebody 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 wholebody 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, wholebody 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 wholebody 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 wholebody 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.

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

Appendix 6: List of Changes since Version 3.0

Changes to each section are identified; deleted text present in Version 3.0 is shown in strikethrough and new text introduced into Version 4.0 in bold font.

Initial Wording	Modified or Additional Wording	Justification
Sponsor Signature Page **Authorised Representative on behalf of Nordic Nanovector ASA:** Lisa Rojkjaer MD Chief Medical Officer Nordic Nanovector ASA Kjelsåsveien 168B N-0884 Oslo, Norway Susan Spruill, MS, PStat® Biostatistician Applied Statistics and Consulting 1205 Chestnut Mountain Road Spruce Pine North Carolina 28777, United States	Sponsor Signature Page **Authorised Representative on behalf of Nordic Nanovector ASA:** ~~Lisa Rojkjaer~~ **Christine Wilkinson Blanc** MD Chief Medical Officer Nordic Nanovector ASA Kjelsåsveien 168B N-0884 Oslo, Norway ~~Susan Spruill, MS, PStat®~~ ~~Biostatistician~~ ~~Applied Statistics and Consulting~~ ~~1205 Chestnut Mountain Road~~ ~~Spruce Pine~~ ~~North Carolina 28777, United States~~ **Albert Chau** **Biostatistician** **Datacision Limited** **55 Station Road** **Beaconsfield, Buckinghamshire** **HP9 1QL, United Kingdom**	4
Coordinating Investigator Signature Page Printed name: ARNE KOLSTAD Email: ARNEK@ous-hf.no	Coordinating Investigator Signature Page Printed name: ~~ARNE KOLSTAD~~ **Alexander FOSSÅ** ~~Email: ARNEK@ous-hf.no~~	4
Synopsis, Objectives Secondary • To evaluate the preliminary anti-tumour activity of combination treatment based on Investigator assessment of tumour response rates • To evaluate the duration of tumour control in patients receiving Betalutin in combination with RTX	Synopsis, Objectives Secondary • **To establish a recommended dose of Betalutin in combination with RTX for phase 2 studies in NHL patients** • To evaluate the preliminary anti-tumour activity of combination treatment based on Investigator assessment of tumour response rates	3

Initial Wording	Modified or Additional Wording	Justification
• To investigate the immunogenicity of Betalutin in combination with RTX	• To evaluate the duration of tumour control in patients receiving Betalutin in combination with RTX • To investigate the immunogenicity of Betalutin in combination with RTX	
Synopsis, Study Design Two cohorts of 3-6 patients will be initially evaluated for dose limiting toxicity, in a 3+3 escalation pattern, before determining the subsequent Betalutin dose for the remainder of the study. Patients will undergo clinical and laboratory assessments during screening/baseline and periodically during treatment. PET/CT and CT (or MRI) imaging will be performed at baseline and then at 3 and 6 months. CT with contrast (or MRI) will be performed at 12, 18, 24 months and then yearly until disease progression or for a maximum of 5 years after Betalutin administration for all patients. Patients who achieve SD, CR or PR on their Month 3 imaging scan will be administered maintenance RTX 375 mg/m^2 i.v. or 1400 mg s.c. every 3 months for up to 2 years (8 infusions in total), or until disease progression.	Synopsis, Study Design Two cohorts of 3-6 patients will be ~~initially~~ evaluated for dose limiting toxicity, in a 3+3 escalation pattern, ~~before~~**to** ~~determining~~ **determine** the ~~subsequent~~ Betalutin dose for ~~the remainder of the study~~ **future phase 2 studies in NHL.** Patients will undergo clinical and laboratory assessments during screening/baseline and periodically during treatment. PET/CT and CT (or MRI) imaging will be performed at baseline and then at 3 and 6 months. CT with contrast (or MRI) will be performed at 12, 18, 24 months ~~and then yearly~~ **or** until disease progression **or withdrawal from the study for any other reason (whichever comes first)** ~~or for a maximum of 5 years after Betalutin administration for all patients~~. Patients who achieve SD, CR or PR on their Month 3 imaging scan will be administered maintenance RTX 375 mg/m^2 i.v. or 1400 mg s.c. every 3 months for up to 2 years (8 infusions in total), or until disease progression **or withdrawal from the study for any other reason (whichever comes first).**	1, 2
Synopsis, Sample Size 20 to 25 patients will be enrolled	Synopsis, Sample Size ~~20 to 25~~ **6 to 12** patients will be enrolled	1
Synopsis; Treatment groups, dose, route of administration, treatment regimen Rituximab **-** 375 mg/m^2 to be administered by i.v. infusion through dedicated line at Days -14, 7, 14, 21 and 28. Patients who achieve SD, CR or PR on their Month 3 imaging scan will be administered maintenance RTX 375 mg/m^2 i.v. or 1400 mg s.c. every 3 months for up to 2 years (8 infusions in total), or until disease progression	Synopsis; Treatment groups, dose, route of administration, treatment regimen Rituximab **-** 375 mg/m^2 to be administered by i.v. infusion through dedicated line at Days -14, 7, 14, 21 and 28. Patients who achieve SD, CR or PR on their Month 3 imaging scan will be administered maintenance RTX 375 mg/m^2 i.v. or 1400 mg s.c. every 3 months for up to 2 years (8 infusions in total), or until disease progression **or withdrawal from the study for any other reason (whichever comes first).**	2

Initial Wording	Modified or Additional Wording	Justification
Synopsis, Efficacy assessment(s) PET/CT and CT (or MRI) imaging will be performed at baseline and then at 3 and 6 months. CT with contrast (or MRI) will be performed at 12, 18, 24 months and then yearly until disease progression or for a maximum of 5 years after Betalutin administration for all patients.	Synopsis, Efficacy assessment(s) PET/CT and CT (or MRI) imaging will be performed at baseline and then at 3 and 6 months. CT with contrast (or MRI) will be performed at 12, 18, 24 months **or** until disease progression **or withdrawal from the study for any other reason (whichever comes first)** ~~after Betalutin administration for all patients.~~	2
Synopsis, Safety Assessments During the follow-up period, vital signs, ECG (final visit only), physical examination, haematology, serum biochemistry, Adverse Drug Reaction (ADR) and Adverse Events of Special Interest (AESI) will be collected every 6 months for 2 years after end of study treatment period.	Synopsis, Safety Assessments ~~During the follow-up period~~**After the last dose of rituximab**, vital signs, ECG (final visit only), physical examination, haematology, serum biochemistry, Adverse Drug Reaction (ADR) and Adverse Events of Special Interest (AESI) will be collected ~~every 6 months for 2 years after end of study treatment period~~ **at an end of study visit that will occur at least 28 days post last administration of study treatment. Patients in survival follow-up at time of Protocol v4.0 approval can have the EOS visit at their next scheduled visit or an earlier convenient time point.**	2
Synopsis, Biomarker Assessments Pharmacodynamics assessments including CD20 and CD37 expression in tumour tissue biopsy and immunophenotyping of circulating lymphocyte subsets (absolute cell counts), will be performed at various time points throughout the study	Synopsis, Biomarker Assessments ~~Pharmacodynamics~~ **Biomarkers** assessments including CD20 and CD37 expression in tumour tissue biopsy and immunophenotyping of circulating lymphocyte subsets (absolute cell counts), will be performed at various time points throughout the study	3
Synopsis, Statistical Methods and Data Analyses Pharmacokinetic, pharmacodynamic and biomarker exploratory analyses will be described in the statistical analysis plan finalised before database lock.	Synopsis, Statistical Methods and Data Analyses Pharmacokinetic, ~~pharmacodynamic~~ **biodistribution** and biomarker exploratory analyses will be described in the statistical analysis plan finalised before database lock.	3
Synopsis, Key Dates All patients will be followed up for up to 5 years after Betalutin administration.	Synopsis, Key Dates ~~All P~~patients will be followed up for up to ~~5~~ **25** ~~years~~ **months (End of study visit)** after Betalutin administration. **Patients in survival follow at time of Protocol version 4.0 approval can have the EOS visit at their next scheduled visit or an earlier convenient time point**	2

<table>
<tr><th>Initial Wording</th><th>Modified or Additional Wording</th><th>Justification</th></tr>
<tr><td>Section 1.2 Schedule of Activities
Table 1-2 Treatment, safety and efficacy (Month 3/Week 14 to Month 60/Week 260)
23) If the ADA test is found positive at Week 104, then a blood sample will be taken every year until the ADA test is found negative</td><td>Section 1.2 Schedule of Activities
Table 1-2 Treatment, safety and efficacy (Month 3/Week 14 to Month ~~60~~25/Week ~~260~~108 - EOS)
~~23) If the ADA test is found positive at Week 104, then a blood sample will be taken every year until the ADA test is found negative~~
25) Patients in survival follow-up at time of Protocol v4.0 approval can have the EOS visit at their next scheduled visit or an earlier convenient time point. Collection of concomitant medications is not mandated for these patients, but AESIs must be assessed
Table updated</td><td>2</td></tr>
<tr><td>Section 3 Objectives and Endpoints<table><tr><th>Objectives</th><th>Endpoints</th></tr><tr><td>Secondary</td><td></td></tr><tr><td></td><td></td></tr><tr><td>Exploratory</td><td></td></tr><tr><td>• To characterise the pharmacokinetics (PK) of Betalutin in combination with RTX</td><td>• PK parameters</td></tr><tr><td>• To assess the pharmacodynamic effect~~s~~ of Betalutin in combination with RTX</td><td>• Change from baseline in peripheral blood B-cell, T-cell and NK cell counts, tumour CD20 and CD37 expression</td></tr></table></td><td>Section 3 Objectives and Endpoints<table><tr><th>Objectives</th><th>Endpoints</th></tr><tr><td>Secondary</td><td></td></tr><tr><td>• To establish a recommended dose of Betalutin in combination with RTX for phase 2 studies in NHL patients</td><td>• Frequency and severity of AEs, SAEs and changes in laboratory values graded according to CTCAE version 4.03</td></tr><tr><td>Exploratory</td><td></td></tr><tr><td>• To characterise the pharmacokinetics (PK) of Betalutin in combination with RTX</td><td>• ~~PK parameters~~ Estimation of the levels of remnant administered radioactivity in blood over time (Betalutin PK)</td></tr><tr><td>• To assess the pharmacodynamic effect~~s~~ of Betalutin in combination with RTX</td><td>• Change from baseline in peripheral blood B-cell, T-cell and NK cell counts, tumour CD20 and CD37 expression
• Biomarker assessments</td></tr><tr><td>• To investigate the biodistribution of Betalutin in combination with RTX</td><td>• 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.</td></tr></table></td><td>3</td></tr>
</table>

Initial Wording	Modified or Additional Wording	Justification
	• **Calculation of estimated absorbed radiation dose to target organ.**	
Section 4.1 Overall Design It is planned that 20-25 patients will be enrolled in the study. PET/CT and CT imaging (or MRI) will be performed at baseline and then at 3 and 6 months. CT with contrast (or MRI) will be performed at 12, 18, 24 months and then yearly until disease progression or for a maximum of 5 years after Betalutin administration for all patients. Patients who achieve SD, CR or PR on their Month 3 imaging scan will be administered maintenance RTX 375 mg/m^2 i.v. or 1400 mg s.c. every 3 months for up to 2 years (8 infusions in total), or until disease progression.	Section 4.1 Overall Design It is planned that ~~20-25~~ **6-12 evaluable** patients will be enrolled in the study. PET/CT and CT imaging (or MRI) will be performed at baseline and then at 3 and 6 months. CT with contrast (or MRI) will be performed at 12, 18, 24 months ~~and then yearly~~ **or** until disease progression **or withdrawal from the study for any other reason** ~~for a maximum of 5 years after Betalutin administration for all patients~~ **(whichever comes first)**. Patients who achieve SD, CR or PR on their Month 3 imaging scan will be administered maintenance RTX 375 mg/m^2 i.v. or 1400 mg s.c. every 3 months for up to 2 years (8 infusions in total), or until disease progression **or withdrawal from the study for any other reason (whichever comes first).**	1, 2
Section 4.1 Overall Design Figure 4-1	Section 4.1 Overall Design Figure 4-1 *Updated to reflect removal of follow-up period*	2
Section 4.3 Rationale for Dose As discussed in the previous section, as patients with relapsed/refractory FL are reported to benefit from rituximab maintenance therapy [31], responding patients (i.e. those having a CR, PR or SD response following Betalutin and the 4-weekly doses of i.v. RTX) will receive maintenance RTX every 3 months for up to 2 years (a total of 8 doses), or until disease progression commencing at Week 14.	Section 4.3 Rationale for Dose As discussed in the previous section, as patients with relapsed/refractory FL are reported to benefit from rituximab maintenance therapy [31], responding patients (i.e. those having a CR, PR or SD response following Betalutin and the 4-weekly doses of i.v. RTX) will receive maintenance RTX every 3 months for up to 2 years (a total of 8 doses), or until disease progression **or withdrawal from the study for any other reason (whichever comes first),** commencing at Week 14.	2
Section 4.4 Patient and Study Completion Approximately 25 patients will be screened to achieve 20-25 patients assigned to study treatment and evaluable.	Section 4.4 Patient and Study Completion Approximately ~~25~~ **10-15** patients will be screened to achieve ~~20-25~~**6-12** patients assigned to study treatment and evaluable.	1
Section 4.5 End of Study Definition The end of study for all patients will be the date of the last visit upon completion of the follow-up period (5 years after receiving their Betalutin	Section 4.5 End of Study Definition The end of study for all patients will be the date of the **last patient** last visit upon completion of the**ir end of study visit** ~~follow-up period (5 years~~ **25 months** after receiving their Betalutin treatment **if ending study**	2

Initial Wording	Modified or Additional Wording	Justification
treatment), or until discontinuation from the study for any other reason, or if the study is terminated early.	**treatment per protocol, or after disease progression** or ~~until discontinuation~~ **withdrawal** from the study for any other reason, **(whichever comes first)** or if the study is terminated early.	
Section 6.1 Dosing Regimen Patients must have received all doses of study drug and have had an adequate period of follow-up (i.e. having achieved haematological recovery to ≤ grade 2) to be considered evaluable for a dose escalation decision or to continue to be treated with Betalutin 15 MBq/kg following enrolment of the second cohort of 3-6 patients.	Section 6.1 Dosing Regimen Patients must have received all doses of study drug and have had an adequate period of follow-up (i.e. having achieved haematological recovery to ≤ grade 2) to be considered evaluable for a dose escalation decision or to ~~continue to be treated with Betalutin 15 MBq/kg~~ **determine the dose for further Phase 2 studies** following enrolment of the second cohort of 3-6 patients.	1
Section 6.1 Dosing Regimen 7. If 1/6 patients receiving Betalutin 15 MBq/kg experience a DLT, the remainder of the patients in the study will continue to be treated with Betalutin 15 MBq/kg. 8. If 2/6 patients experience a DLT, then 3 more patients will be treated at the lower Betalutin dose (10 MBq/kg). 9. Subsequent Betalutin/lilotomab dosing will be determined by the Investigator(s) and Sponsor after a review of the available safety data.	Section 6.1 Dosing Regimen 7. If 1/6 patients receiving Betalutin 15 MBq/kg experience a DLT, the ~~remainder of the patients in the study will continue to be treated with~~ **dose for further Phase 2 studies will be** Betalutin 15 MBq/kg. 8. If 2/6 patients experience a DLT, then 3 more patients will be treated at the lower Betalutin dose (10 MBq/kg). 9. ~~Subsequent~~ **The final recommendation for** Betalutin/lilotomab dosing **for further Phase 2 studies** will be determined by the Investigator(s) and Sponsor after a review of the available safety data.	1
Section 7.2 Patient Withdrawal/Discontinuation from the Study Should a patient decide to withdraw after administration of the study drug(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. If the reason for withdrawal is due to disease progression, the study site should make all effort to continue with the safety monitoring.	Section 7.2 Patient Withdrawal/Discontinuation from the Study Should a patient decide to withdraw after administration of the study drug(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 **(end of study visit)** should be made **within 28 days (± 3 days) of receiving the last study treatment administration if ending treatment per protocol, or within 7 days of taking the decision to withdraw if it occurs > 28 days after the last study treatment administration** 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. If	2

Initial Wording	Modified or Additional Wording	Justification
Haematological toxicity was observed in the phase 1/2 LYMRIT-37-01 study, with nadir values 5 to 7 weeks after injection of Betalutin. It is advisable to monitor the haematology parameters of the withdrawn patients between 6 and 9 weeks after the last RTX administration or until recovery to CTCAE grade 1 or less. Single patient termination is per definition: • when the patient is withdrawn • when the patient has died • start of further anticancer therapy after Betalutin injection • completed the Year 5 follow-up visit If 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 eCRF. Furthermore: • Survival information, Adverse Drug Reaction (ADR) and Adverse Events of Special Interest (AESI) will continue to be collected for any single patient terminations throughout the study, unless the patient specifically withdraws their consent for this to take place	the reason for withdrawal is due to disease progression, the study site should make all effort to continue with the safety monitoring. Haematological toxicity was observed in the phase 1/2 LYMRIT-37-01 study, with nadir values 5 to 7 weeks after injection of Betalutin. It is advisable to monitor the haematology parameters of the withdrawn patients between 6 and 9 weeks after the last RTX administration or until recovery to CTCAE grade 1 or less. Single patient ~~termination~~ **study discontinuation** is per definition, **when the patient**: • **has completed Month 24 administration of rituximab, per protocol or** • **experiences one of the following situations before per protocol end of study:** – ~~when the patient is withdrawn~~ **withdraws consent to participate in the study** – ~~when the patient~~ **has died** – **is lost to follow up** – **has disease progression** – start**s** ~~of~~ further anticancer therapy **or** ~~after Betalutin injection completed the Year 5 follow-up visit~~ • **when the patient is withdrawn for a reason other than described above** If 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 eCRF. Furthermore: • Survival information, Adverse Drug Reaction (ADR) and Adverse Events of Special Interest (AESI) will continue to be collected for any single patient ~~terminations~~ **until end of study visit, consent withdrawal, lost to follow up or death** ~~throughout the study, unless the patient specifically withdraws their consent for this to take place~~	

<table>
<tr><th>Initial Wording</th><th>Modified or Additional Wording</th><th>Justification</th></tr>
<tr><td>Section 8.2.12 Visit 17 (Month 6/Week 26) – Hospital Visit
Concomitant medication: Recording of concomitant medication used since the screening visit</td><td>Section 8.2.12 Visit 17 (Month 6/Week 26) – Hospital Visit
Concomitant medication: ~~Recording of c~~Concomitant medication used since prior visit will be recorded ~~the screening visit~~</td><td>5</td></tr>
<tr><td>Section 8.2.14 Visit 19 (Month 12/Week 52) – Hospital Visit
Concomitant medication: Recording of concomitant medication used since the screening visit</td><td>Section 8.2.14 Visit 19 (Month 12/Week 52) – Hospital Visit
Concomitant medication: Recording of concomitant medication used since the ~~screening~~ previous visit</td><td>5</td></tr>
<tr><td>Section 8.2.14 Visit 21 (Month 18/Week 78) – Hospital Visit
Concomitant medication: Recording of concomitant medication used since the screening visit</td><td>Section 8.2.14 Visit 21 (Month 18/Week 78) – Hospital Visit
Concomitant medication: Recording of concomitant medication used since the ~~screening~~ previous visit</td><td>5</td></tr>
<tr><td>Section 8.2.14 Visit 23 (Month 24/Week 104) – Hospital Visit
Concomitant medication: Recording of concomitant medication used since the screening visit</td><td>Section 8.2.14 Visit 23 (Month 24/Week 104) – Hospital Visit
Concomitant medication: Recording of concomitant medication used since the ~~screening~~ previous visit</td><td>5</td></tr>
<tr><td>Section 8.2.19 Visit 24 (Month 25/Week 108) – Hospital Visit
Safety follow-up procedures 4 weeks after administration of the final RTX study dose are outlined in Table 8-22.
Table 8-22 Procedures and assessments at Visit 24 (Month 25/Week 108 [±7 days])
<table>
<tr><th>Assessment or Procedure</th><th>Explanation</th></tr>
<tr><td>Concomitant medication/therapy</td><td>Recording of concomitant medication used since the previous visit</td></tr>
<tr><td>Physical examination</td><td>Any abnormal findings will be recorded in the AE record</td></tr>
<tr><td>Vital signs</td><td>Systolic/diastolic blood pressure, heart rate and body temperature</td></tr>
<tr><td>ECOG</td><td>ECOG performance status</td></tr>
<tr><td>Haematology</td><td>Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)</td></tr>
</table></td><td>Section 8.2.19 ~~Visit 24 (Month 25/Week 108)~~ End of Study Visit – Hospital Visit
The end of study visit should occur:
• 28 days (± 3 days) post last rituximab administration for patients, who complete the study per protocol (Month 25/Week 108)
• Within 7 days of decision of withdrawing from the study is made if the decision occurs > 28 days post last administration of study treatment for patients who discontinue from the study before Month 24 (e.g. disease progression, start of new anti-cancer therapy, other reason) An end of study visit is not expected for patients, who discontinue due to death, lost to follow up or withdrawal of consent.
Safety follow-up procedures 4 weeks after administration of the final RTX study dose are outlined in Table 8-22.
Patients in survival follow-up at the time of Protocol v4.0 approval can have the EOS visit at their next scheduled visit or an earlier convenient time point</td><td>2, 5</td></tr>
</table>

<table>
<tr><th>Initial Wording</th><th>Modified or Additional Wording</th><th>Justification</th></tr>
<tr>
<td>
<table>
<tr><td>Serum biochemistry</td><td>Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin</td></tr>
<tr><td>Adverse events</td><td>Any AEs occurring since prior visit will be recorded</td></tr>
</table>
</td>
<td>
Table 8-22 Procedures and assessments at end of study visit ~~Visit 24 (Month 25/Week 108 [±7 days])~~
<table>
<tr><th>Assessment or Procedure</th><th>Explanation</th></tr>
<tr><td>Concomitant medication/~~therapy~~</td><td>Recording of concomitant medication used since the previous visit</td></tr>
<tr><td>Physical examination</td><td>Any abnormal findings will be recorded in the AE record</td></tr>
<tr><td>Vital signs</td><td>Systolic/diastolic blood pressure, heart rate and body temperature</td></tr>
<tr><td>ECOG</td><td>ECOG performance status</td></tr>
<tr><td>Haematology</td><td>Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)</td></tr>
<tr><td>Serum biochemistry</td><td>Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin</td></tr>
<tr><td>Adverse events</td><td>Any AEs / AESIs occurring since prior visit will be recorded</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>
Section 8.3 Follow-up Period
The follow-up period starts from Week 109 or until relapse of disease, whichever occurs first, for a period of up to 5 years (Week 260) from Day 0. The patient will have a hospital visit at Months 36 (Week 156), 48 (Week 208) and 60 (Week 260). Table 8-23 outlines the procedures and assessments during these visits.
Table 8-23 Procedures and assessments at Visits 25, 26 and 27 (at Months 36 (Week 156), 48 (Week 208) and 60 (Week 260) [±7 days each])
<table>
<tr><th>Assessment or Procedure</th><th>Explanation</th></tr>
<tr><td>Prior antineoplastic therapy</td><td>Record if the patient has received any antineoplastic treatment since their previous visit</td></tr>
<tr><td>Physical examination</td><td>Any abnormal findings will be recorded in the AE record</td></tr>
</table>
</td>
<td>
~~Section 8.3 Follow-up Period~~
~~The follow-up period starts from Week 109 or until relapse of disease, whichever occurs first, for a period of up to 5 years (Week 260) from Day 0. The patient will have a hospital visit at Months 36 (Week 156), 48 (Week 208) and 60 (Week 260). Table 8-23 outlines the procedures and assessments during these visits.~~
~~Table 8-23 Procedures and assessments at Visits 25, 26 and 27 (at Months 36 (Week 156), 48 (Week 208) and 60 (Week 260) [±7 days each])~~
<table>
<tr><th>~~Assessment or Procedure~~</th><th>~~Explanation~~</th></tr>
<tr><td>~~Prior antineoplastic therapy~~</td><td>~~Record if the patient has received any antineoplastic treatment since their previous visit~~</td></tr>
<tr><td>~~Physical examination~~</td><td>~~Any abnormal findings will be recorded in the AE record~~</td></tr>
</table>
</td>
<td>2</td>
</tr>
</table>

Initial Wording		Modified or Additional Wording		Justification
Weight	Record weight details	~~Weight~~	~~Record weight details~~	
Vital signs	Systolic/diastolic blood pressure, heart rate and body temperature	~~Vital signs~~	~~Systolic/diastolic blood pressure, heart rate and body temperature~~	
ECOG	ECOG performance status	~~ECOG~~	~~ECOG performance status~~	
Haematology	Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)	~~Haematology~~	~~Including haemoglobin, platelet count, white blood cell count and differential (absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils)~~	
Serum biochemistry	Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin	~~Serum biochemistry~~	~~Including sodium, potassium, calcium, magnesium, creatinine, urea, uric acid, ALP, ASAT, ALAT, LDH, GGT, glucose, total bilirubin and albumin~~	
Immunogenicity[1]	Monitoring ADA response (lilotomab, Betalutin, rituximab)	~~Immunogenicity[1]~~	~~Monitoring ADA response (lilotomab, Betalutin, rituximab)~~	
Minimal Residual Disease[2] (peripheral blood sample)	MRD monitoring to assess early treatment response and detect relapse	~~Minimal Residual Disease[2] (peripheral blood sample)~~	~~MRD monitoring to assess early treatment response and detect relapse~~	
Bone marrow biopsy	BM biopsy required for confirmation of initial CR if patient had BM infiltration at baseline	~~Bone marrow biopsy~~	~~BM biopsy required for confirmation of initial CR if patient had BM infiltration at baseline~~	
Radiology - CT scans with contrast or MRI	CT or MRI 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.	~~Radiology – CT scans with contrast or MRI~~	~~CT or MRI 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.~~	
ADR & AESI monitoring	Since previous visit	~~ADR & AESI monitoring~~	~~Since previous visit~~	
Survival status[3]	Patient status (survival), cause of death and date of death	~~Survival status[3]~~	~~Patient status (survival), cause of death and date of death~~	
[1] If the ADA test is found positive at Week 104, then a blood sample will be taken once a year until the ADA test is found negative [34]		~~[1] If the ADA test is found positive at Week 104, then a blood sample will be taken once a year until the ADA test is found negative [34]~~		
[2] Mandatory, unless relapse or disease progression has been clinically observed		~~[2] Mandatory, unless relapse or disease progression has been clinically observed~~		
[3] To be followed up every 6 months during scheduled visit or by telephone		~~[3] To be followed up every 6 months during scheduled visit or by telephone~~		

Initial Wording	Modified or Additional Wording	Justification
Section 8.4 Additional Operational Procedures During the treatment and follow up periods optional procedures may be performed at visits following relapse or disease progression. Table 8-23 outlines these procedures.	Section 8.4**3** Additional Operational Procedures During the treatment ~~and follow up~~ period~~s~~ optional procedures may be performed at visits following relapse or disease progression. Table 8-23 outlines these procedures.	2
Section 9.1 Efficacy Assessments Tumour response will be determined locally according to Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and non-Hodgkin Lymphoma [36]. Investigator assessment will be applied as a measure for assessment of tumour response and as a basis for all protocol guidelines for management of the patient related to disease status. CT or MRI scans are the required methods for tumour assessments. The same method of assessment and the same technique should be used to characterize each lesion at baseline and during follow-up.	Section 9.1 Efficacy Assessments Tumour response will be determined locally according to Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and non-Hodgkin Lymphoma [36]. Investigator assessment will be applied as a measure for assessment of tumour response and as a basis for all protocol guidelines for management of the patient related to disease status. CT or MRI scans are the required methods for tumour assessments. The same method of assessment and the same technique should be used to characterize each lesion at baseline and during follow-up. **All scans and other data supporting efficacy measurements will be stored at the study site and available for subsequent collection, if necessary, for review by the Sponsor and/or independent external reviewer(s).**	6
Section 9.1.2 PET/CT and CT/MRI examination PET/CT and CT or MRI imaging will be done at baseline and then at 3 and 6 months. CT with contrast or MRI will be performed at 12, 18, 24 months and then yearly until disease progression or for a maximum of 5 years after Betalutin administration for all patients. Baseline imaging must be performed within 4 weeks prior to administration of the first RTX infusion.	Section 9.1.2 PET/CT and CT/MRI examination PET/CT and CT or MRI imaging will be done at baseline and then at 3 and 6 months. CT with contrast or MRI will be performed at 12, 18, 24 months ~~and~~ **or until disease progression or other withdrawal for any other reason** ~~then yearly until disease progression or for a maximum of 5 years after Betalutin administration for all patients~~**(whichever comes first).** Baseline imaging must be performed within 4 weeks prior to administration of the first RTX infusion.	2
Section 9.2.4 Reporting of adverse events Specific information about secondary malignancies such as leukaemia, MDS and aplastic anaemia or any other malignancy, will be collected up to 5 years after Betalutin administration or relapse of disease, including information about treatment given to the patient due to NHL (See Section 9.2.1.7).	Section 9.2.4 Reporting of adverse events Specific information about secondary malignancies such as leukaemia, MDS and aplastic anaemia or any other malignancy, will be collected up to **2**~~5~~ years after Betalutin administration or relapse of disease, including information about treatment given to the patient due to NHL (See Section 9.2.1.7).	2

Initial Wording	Modified or Additional Wording	Justification
Section 9.2.5.1 Investigator's Responsibilities 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 their Betalutin or 4 weeks following their last maintenance RTX drug administration, whether or not considered related to study drug • At any time beyond 12 weeks after their Betalutin or 4 weeks following their last maintenance RTX drug administration, 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 study drug	Section 9.2.5.1 Investigator's Responsibilities 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 their Betalutin or 4 weeks following their last maintenance RTX drug administration, whether or not considered related to study drug • At any time beyond 12 weeks after their Betalutin or 4 weeks following their last maintenance RTX drug administration, 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 study drug. **If such event is observed post end of study vist, it should be notified to the Sponsor using the following email address: SAE@nordicnanovector.com**	4
Section 9.2.5.1 Investigator's Responsibilities **Contact address for reporting SAEs:** PharmaLex Norway AS Karoline Kristiansens vei 1, 0661 Oslo, Norway Principal contact: Ingvild Juul-Hansen Phone: +47 22 23 88 80 Fax: +47 21 01 80 19 Email: PV-nordic@pharmalex.com	Section 9.2.5.1 Investigator's Responsibilities **Contact address for reporting SAEs:** PharmaLex Norway AS Karoline Kristiansens vei 1, 0661 Oslo, Norway ~~Principal contact:~~ ~~Ingvild Juul-Hansen~~ Phone: +47 22 23 88 80 Fax: +47 21 01 80 19 Email: PV-nordic@pharmalex.com	4
Section 9.2.6.5.2 Human biosamples collection schedule Sampling of peripheral blood for ADA monitoring will be performed at the following approximate time points: • Screening (Baseline for lilotomab, Betalutin and RTX ADA monitoring) • After Betalutin administration, at Day 28 and 3, 6, 12, 18 and 24 months. It has to be noted that at Day 28, peripheral blood sampling should be done before RTX dosing.	Section 9.2.6.5.2 Human biosamples collection schedule Sampling of peripheral blood for ADA monitoring will be performed at the following approximate time points: • Screening (Baseline for lilotomab, Betalutin and RTX ADA monitoring) • After Betalutin administration, at Day 28 and 3, 6, 12, 18 and 24 months. It has to be noted that at Day 28, peripheral blood sampling should be done before RTX dosing.	2

Initial Wording	Modified or Additional Wording	Justification
• Additional sampling may become necessary if a test is found to be ADA-positive at 24 months. Persistence of the ADA response will then be assessed annually, until the ADA test is negative [34].	• ~~Additional sampling may become necessary if a test is found to be ADA-positive at 24 months. Persistence of the ADA response will then be assessed annually, until the ADA test is negative [34].~~	
Section 9.2.7 Volume of blood to be drawn from each patient Table 9-4 Volume of blood to be drawn from each patient during the screening and treatment period (Screening to Month 25) Max = maximum number of samples to be taken from screening to Month 25 [1] Additional sampling could be performed if ADA test positive at Week 104 [2] Monitoring of rituximab concentration in serum and the ADA response towards rituximab. Additional sampling could be performed if (a) the RTX ADA test is found positive at Week 104 and/or RTX concentration in serum is detectable at week 104, and (b) a blood sample is taken to screen for ADA against lilotomab/Betalutin	Section 9.2.7 Volume of blood to be drawn from each patient Table 9-4 Volume of blood to be drawn from each patient during the screening and treatment period (Screening to ~~Month 25~~ **End of study visit**) Max = maximum number of samples to be taken from screening to **End of Study** ~~Month 25~~ ~~[1] Additional sampling could be performed if ADA test positive at Week 104~~ [2] Monitoring of rituximab concentration in serum ~~and the ADA response towards rituximab. Additional sampling could be performed if (a) the RTX ADA test is found positive at Week 104 and/or RTX concentration in serum is detectable at week 104, and (b) a blood sample is taken to screen for ADA against lilotomab/Betalutin~~	2
Section 9.2.8 Pregnancy If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.	Section 9.2.8 Pregnancy If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix ~~5~~**3**.	5
Section 9.4 Biodistribution and dosimetry *Not applicable – new section in Version 4.0*	**Section 9.4 Biodistribution and dosimetry** **The biodistribution and dosimetry study will provide estimates for the absorbed radiation dose to normal body structures as well as to tumours that can be identified in the images. The radioactivity in the actual organs will be measured in absolute terms, at different times after injection. The time series will allow to estimate the cumulative activity in each organ and by measurements/estimates of organ weight the absorbed dose.** **Measurements will be performed as described in Appendix 5.** **The measurements will be performed on a SPECT/CT scanner containing 2 gamma camera heads (Siemens SYMBIA –T16) equipped with medium energy collimators, which. will be used for CT, SPECT, and whole-body scanning. Quantification will be carried out by use of the software of the vendor and using computer programs (IDL, ITT**	3

Initial Wording	Modified or Additional Wording	Justification
	visual solutions) Full details of the scans required for biodistribution and dosimetry and of acquisition specifications are provided in a dedicated dosimetry protocol. **The images obtained will enable the characterisation of the biodynamics and the calculation of the cumulative activity in each organ, with dose estimates obtained using the OLINDA program.** **The conjugated whole-body studies and the quantification in regions drawn around each organ together with assay of activity in blood will allow for:** • **Estimation of whole-body retention of radioactivity at set imaging times post-injection.** • **Estimation of the individual organ uptake/retention of radioactivity at set points after injection.** • **Estimate retention of administered radioactivity in blood.** • **Calculation of estimated absorbed radiation dose to target organs and to tumours.**	
Section 9.4 Biomarkers	Section 9.4**5** Biomarkers *Heading numbering updated due to addition of new Section 9.4*	3
Section 9.5 Biobanking	Section 9.~~5~~**6** Biobanking *Heading numbering updated due to addition of new Section 9.4* *Table 9-5 updated to change peripheral blood sampling for minimal residual disease from "and annually thereafter "Week 52 to "at EOS"*	3
Section 10.1 Statistical Analysis The study is a single-arm, open-label study to further assess the risk/benefit of a pre-dose of lilotomab and Betalutin to enhance tumour response to RTX therapy. Twenty to 25 patients is a reasonable sample size to evaluate any potential safety/tolerability signals and for obtaining preliminary estimates of the response rates and variability of the response rates.	Section 10.1 Statistical Analysis The study is a single-arm, open-label study to further assess the risk/benefit of a pre-dose of lilotomab and Betalutin to enhance tumour response to RTX therapy. ~~Twenty to 25 patients~~ **Six to 12 patients** is a reasonable sample size to evaluate any potential safety/tolerability signals and for obtaining preliminary estimates of the response rates and variability of the response rates.	1

Initial Wording	Modified or Additional Wording	Justification
Section 10.1.2 Other Analyses PK, pharmacodynamic and biomarker exploratory analyses will be described in the statistical analysis plan (SAP), which will be finalised before database lock. The PK population analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).	Section 10.1.2 Other Analyses PK, ~~pharmacodynamic~~ and biomarker exploratory analyses will be described in the statistical analysis plan (SAP), which will be finalised before database lock. ~~The PK population analysis and the pharmacodynamic a~~**A**nalyses will be presented separately from the main clinical study report (CSR).	3
Appendix 5: Biodistribution and dosimetry assessments *Not applicable – new section in Version 4.0*	**Appendix 5: Biodistribution and dosimetry assessments** **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 wholebody 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 wholebody 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, wholebody 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 wholebody scans: scanning with a ^{99m}Tc line source before administration of activity to the patient or by calculating the necessary attenuation from CT**	3

Initial Wording	Modified or Additional Wording	Justification
	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 wholebody 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.** **Full details of the scans required are provided in the dosimetry protocol.**	

DocuSign

Certificate Of Completion

Envelope Id: 23D4F8E5BF7D4AB69360B2547ABDC8D6
Status: Completed
Subject: LYMRIT-37-07_Protocol_Version_4 Final_20211004
Source Envelope:
Document Pages: 119
Signatures: 3
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London

Envelope Originator:
Tereze Rozenberga
Kjelsåsveien 168 B Oslo
Oslo, Oslo N-0884
trozenberga@nordicnanovector.com
IP Address: 188.95.247.247

Record Tracking

Status: Original
04-Oct-2021 | 09:46
Holder: Tereze Rozenberga
trozenberga@nordicnanovector.com
Location: DocuSign

Signer Events	Signature	Timestamp
Albert Chau albert@datacision.co.uk Director Datacision Limited Security Level: Email, Account Authentication (Required)	 Signature Adoption: Drawn on Device Signature ID: 9E0EEC5D-CDE9-44CC-ADBF-63BA0CE6CA8E Using IP Address: 82.41.112.233 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 04-Oct-2021 | 09:49 Viewed: 04-Oct-2021 | 13:22 Signed: 04-Oct-2021 | 13:23
Electronic Record and Signature Disclosure: Accepted: 16-Sep-2020 | 17:07 ID: 95423460-22a7-4a5c-a4ea-5c7dd396cbf3		
Christine Wilkinson Blanc cwilkinsonblanc@nordicnanovector.com Nordic Nanovector Security Level: Email, Account Authentication (Required), Login with SSO	 Signature Adoption: Pre-selected Style Signature ID: E5307C8A-CD72-4634-8A78-5BEC9F78CF9D Using IP Address: 82.132.232.19 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 04-Oct-2021 | 09:49 Viewed: 04-Oct-2021 | 13:40 Signed: 04-Oct-2021 | 13:51
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
Alexander Fossa AFF@ous-hf.no Security Level: Email, Account Authentication (Required)	DocuSigned by: Alexander Fossa Signer Name: Alexander Fossa Signing Reason: I have reviewed this document Signing Time: 04-Oct-2021 | 2:27:49 PM BST D136ADCF32E54DEA8406F281F25B3D06 Signature Adoption: Pre-selected Style Signature ID: D136ADCF-32E5-4DEA-8406-F281F25B3D06 Using IP Address: 91.186.70.21 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 04-Oct-2021 | 13:51 Viewed: 04-Oct-2021 | 14:26 Signed: 04-Oct-2021 | 14:28
Electronic Record and Signature Disclosure: Accepted: 04-Oct-2021 | 14:26 ID: 5597855e-dfa7-40c3-b29b-230657cfd735		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Kaye Connor kconnor_external@nordicnanovector.com Nordic Nanovector Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	COPIED	Sent: 04-Oct-2021 | 14:29 Viewed: 05-Oct-2021 | 10:43
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	04-Oct-2021 | 09:49
Certified Delivered	Security Checked	04-Oct-2021 | 14:26
Signing Complete	Security Checked	04-Oct-2021 | 14:28
Completed	Security Checked	04-Oct-2021 | 14:29
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Nordic Nanovector. (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Nordic Nanovector.:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: rcorrigan@nordicnanovector.com

To advise Nordic Nanovector. of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at rcorrigan@nordicnanovector.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Nordic Nanovector.

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to rcorrigan@nordicnanovector.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Nordic Nanovector.

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to rcorrigan@nordicnanovector.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Nordic Nanovector. as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Nordic Nanovector. during the course of your relationship with Nordic Nanovector..