LYMRIT-37-05

EudraCT number: 2015-001933-26

CLINICAL STUDY PROTOCOL

A Phase 1 Dose finding study of lutetium (^{177}Lu)-lilotomab satetraxetan (Betalutin®) in patients with relapsed/refractory, diffuse large B-cell lymphoma, not eligible for autologous stem cell transplant

Protocol: 26th April 2019

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Statement about Proper Study Conduct

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

Confidentiality Statement

The information in this document is provided to you as an investigator, potential investigator, consultant, or contractor, for review by you, your staff, and the appropriate Institutional Review Board or Ethics Committee. By accepting this document, you agree that the information contained herein will not be disclosed to others without written authorization from the lead site/sponsor, except to the extent necessary to initiate the study or conduct study-related activities.

LIST OF CHANGES IN THIS AMENDMENT

Section number	Section title	Description of change(s)
	List of Abbreviations	Updated
1	Protocol Synopsis	Relevant sections updated to reflect changes made in this amendment (below)
2.3	Rituximab	MabThera and Rituxan removed to allow for the use of biosimilars
2.5.4; 2.5.5; 2.6.1; 2.6.2.1; 2.6.3; 2.6.4	Potential Benefits and Risks; Rationale and Dose Selection	Inclusion of more recent data; aligned with IB vsn 11; removal of superseded data
3.1, 3.2 and 3.3	Study objectives	Minor administrative changes and inclusion of additional safety endpoint for monitoring of ADA response; clarification of the PK endpoints; separated out exploratory endpoints
4.1	Overview of study design	Expansion of MTD dose in 20 patients (10 relapsed, non-refractory and 10 refractory) to allow for further evaluation of safety, PK and preliminary efficacy.
4.5	Pharmacokinetics, biodistribution and dosimetry	Removal of superseded calculation method
Table 4	Schedule of Study Assessments	Updated HAMA to immunogenicity
Table 5	Schedule of study assessments for the pharmacokinetics, biodistribution and dosimetry sub-study	Removal of footnote
4.7	Study procedures by visit	Updated section numbering; changed references from HAMA to immunogenicity; a number of minor clarifications

5.1	Inclusion criteria	Minor administrative changes; clarification of refractory; updated criteria for high dose chemotherapy and autologous stem cell transplantation; updated murine to mouse in the HAMA description; changed bilirubin limits to align with other liver function criteria; updated contraception from acceptable to effective to align with IB vsn 11
5.2	Exclusion criteria	Removed corticosteroid restrictions as per SRC recommendation
6.1.1.3	Preparation and administration	Inclusion of limits for the intended prescribed dose
6.2	Treatment Allocation	Clarification of patient inclusion process
6.5; 7.1	Supportive Care Guidelines; Adverse Events	Updated section numbering to allow for easier navigation of the document
7.1.1.6	Definition of Adverse Events of Special Interest (AESI)	Inclusion of new section describing AESI
7.8	Immunogenicity Assessments	Updated HAMA references to immunogenicity (and throughout protocol); inclusion of additional information regarding the use of the immunogenicity biobanked samples; inclusion of HAMA results for patients treated in the study in cohorts 1-3
8.1.3	Overall Tumour Response Evaluation	Corrections made to align with Cheson 2014
9.1	Pharmacokinetics	Clarification of the pharmacokinetic tests that will be performed
11.1	Sample Size	Updated to include patients in the expansion phase
11.2	Analysis population	Clarification of planned populations analyses

11.5	Statistical Considerations	Minor administrative changes and clarifications; clarification of the parameters which will be analysed; inclusion of how the relapsed and refractory patient's data will be analysed
12.1	Patient Data Handling	Inclusion of GDPR text
16	References	Inclusion of a recent ASH 2018 reference

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Study Number: LYMRIT-37-05

Study Title: A phase 1 dose finding study of lutetium (^{177}Lu)-lilotomab satetraxetan (Betalutin®) in patients with relapsed/refractory, diffuse large B-cell lymphoma, not eligible for autologous stem cell transplant

Study Centre: University of Manchester, The Christie NHS Foundation Trust

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 trial protocol amendments, informed consent, EC procedures, the Declaration of Helsinki, ICH Good Clinical Practice guidelines and the local regulations governing the conduct of clinical studies

Signature: ..... Date: 26th April 2019

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LIST OF ABBREVIATIONS

^{177}Lu	β-particle–emitting radionuclide lutetium-177
ADA	Anti-drug antibody
ADL	Activity of Daily Living
AR	Adverse reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT or ALAT	Alanine transaminase
AML	Acute myeloid leukemia
APTT	Activated partial thromboplastin time
ARC	Antibody-radionuclide-conjugate
ASAT	Aspartate transaminase
AST	Aspartate transaminase
Betalutin	^{177}Lu-lilotomab satetraxetan
BUN	Blood urea nitrogen
b.w.	Body weight
CA	Competent authority
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CLL	Chronic lymphocytic leukaemia
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	Decay correction factor
DLBCL	Diffuse large b-cell lymphoma
DLBCL-NOS	Diffuse large b-cell lymphoma, not otherwise specified
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
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]
EC	Ethic Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
E_{max}	Maximal effect at high drug concentration
EU	European Union

eV	Electronvolt
FACT-Lym	Functional Assessment of Cancer Therapy–Lymphoma
FDA	Food and Drug Administration
FDG	^{18}Fluorodeoxy glucose
5PS	5-point scale
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
HAMA	Human anti-mouse antibody
HD-ASCT	High-dose chemotherapy with autologous stem cell transplantation
HH1	Lilotomab
HIV	Human immunodeficiency virus
HRU	Healthcare Resource Utilisation
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LDi	Longest transverse diameter of a lesion
Lu	Lutetium
MBq	Mega Becquerel
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
meV	Megaelectronvolt
MRI	Magnetic resonance imaging;
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic
PD	Progressive disease
PET	Positron-emission tomography
PFS	Progression free survival
PK	Pharmacokinetic

PPD	Cross product of the LDi and perpendicular diameter
PR	Partial response
QoL	Quality of life
R-CHOP	Rituximab and the chemotherapy combination of cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone
RBC	Red blood cell
RIT	Radioimmunotherapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCID	Severe combined immune deficient
SD	Stable disease
SDi	Shortest axis perpendicular to the LDi
SPD	Sum of the product of the perpendicular diameters for multiple lesions
SPECT	Single-photon emission computerized tomography
SUV	Standardized uptake value
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial Master File
T½	Half-life
ULN	Upper limit of normal
US	United States
WB	Whole body
WHO	World Health Organization

1 PROTOCOL SYNOPSIS

Protocol No: LYMRIT-37-05
Study Title: A Phase 1 dose finding study of lutetium (^{177}Lu)-lilotomab satetraxetan (Betalutin®) in patients with relapsed/refractory, diffuse large B-cell lymphoma, not eligible for autologous stem cell transplant
Name of Sponsor/Company: Nordic Nanovector ASA, Oslo, Norway
Name of Investigational Medicinal Product: Betalutin® **Name of Investigational Medicinal Product used for pre-dosing:** Lilotomab **Name of Investigational Medicinal Product used for pre-treatment:** Rituximab
Name of Investigational Substance: Lutetium (^{177}Lu)-lilotomab satetraxetan **Name of Investigational Substance used for pre-dosing:** Lilotomab **Name of Investigational Substance used for pre-treatment:** Rituximab
Phase of Development: Phase 1
Study Sites: Patients will be recruited at approximately 11 sites in this study. Additional sites may be added as required to facilitate timely enrolment.
Study Population: The study population are patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who have received at least one prior line of therapy including immune-chemotherapy and who are not eligible for, unwilling or declined autologous stem cell transplantation.
Number of Patients Planned: The number of patients enrolled will depend on the dose levels tested and the toxicity observed but will be up to approximately 24 patients. Once the MTD is identified, the MTD dose level will be further expanded by approximately 10 additional patients who relapsed ≥6 months after last therapy after having achieved a CR/PR, and approximately 10 patients who were refractory to their last line of therapy (PD, SD or CR/PR lasting <6 months) to further assess safety, anti-tumour activity and PK. Additional patients may be enrolled to allow for non-evaluable patients to be replaced (e.g. patients who are enrolled but are withdrawn prior to study drug or Betalutin administration).
Study Objectives: ***Primary objectives:*** 1. To define maximum tolerated dose of Betalutin for DLBCL patients ***Secondary objectives:*** 1. To establish a recommended dose of Betalutin for phase 2 for DLBCL patients 2. To investigate safety and toxicity of Betalutin. 3. To investigate biodistribution and pharmacokinetics (PK) of Betalutin. **4.** To explore the efficacy of Betalutin.
Safety Endpoints: • Incidence and severity of adverse events and serious adverse events graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE version 4). • Changes from baseline in laboratory variables • Incidence of potential late toxicity, such as new primary cancers and bone marrow changes (acute myelogenous leukaemia, myelodysplastic syndrome, and aplastic anaemia). • Monitoring of the anti-drug antibody (ADA) response towards lilotomab and Betalutin
Biodistribution and blood pharmacokinetics endpoints: Evaluation of biodistribution includes whole body activity assessment, the counts in region-of-interest (ROIs) from anterior and posterior whole-body images, total radioactivity in

blood measurements (Betalutin PK) and quantitative determination of total antibodies in serum (Total lilotomab antibodies PK). This will enable the following:

- Estimation of whole-body retention of radioactivity at each imaging time post-injection.
- Estimation of the individual organ uptake/retention of radioactivity at each imaging time-point after injection.
- Estimate the levels of remnant administered radioactivity in blood over time (Betalutin PK).
- Estimate the concentration of total lilotomab antibodies in serum over time (Total lilotomab antibodies PK)
- Calculation of estimated absorbed radiation dose to target organs

Efficacy Endpoints: Overall response rate (CR + PR). Tumour response duration. Progression-free survival and Overall survival

Exploratory Endpoint:

Quality of life (QoL) assessed using Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) questionnaire

Investigational Products:

Betalutin® is an antibody-radionuclide-conjugate (ARC) comprising the radioisotope lutetium-177, the linker satetraxetan and the murine anti-CD37 Immunoglobulin G1 (IgG1) antibody, lilotomab. The active moiety is the beta particle emitting nuclide lutetium-177. Lutetium-177 has a physical half-life of 6.7 days. The antibody lilotomab recognises epitopes on the CD37 antigen, which is abundant on the cell surface of tumours of B-cell origin, including non-Hodgkin lymphoma (NHL). Betalutin is provided as a solution for intravenous administration. The lilotomab satetraxetan concentration in the Betalutin formulation is 1 mg/mL, and between 8 and 10 mg lilotomab satetraxetan is injected per Betalutin administration. The dose is capped for patients who weigh more than 130 kg (patients heavier than 130 kg will receive the dose for a 130 kg patient). Betalutin will be supplied in vials containing a ready to use solution. The radiolabeled investigational product is referred to as Betalutin or lutetium (^{177}Lu)-lilotomab satetraxetan in the protocol.

Rituximab will be used as pre-treatment. Rituximab, a chimeric anti-CD20 antibody, will be used to clear the circulating normal peripheral B-lymphocytes in the blood and in the spleen before administrating Betalutin, which targets CD37. This rituximab pre-treatment may in addition ensure better access for Betalutin to less accessible compartments such as lymph nodes and larger tumour masses. Rituximab targets only CD20 and will not block the binding sites of Betalutin (to CD37) on the B-lymphocytes or tumour cells.

All patients will receive an intravenous infusion of 375 mg/m^2 rituximab at Day – 14 (+/- 2 days) prior to administration of Betalutin. Pre-medication consisting of an antipyretic and antihistamine medication should be administered as per local guideline before infusion of rituximab, according to the institutional guideline. For detailed guidance on use of rituximab and possible side effects see the summary of product characteristics or prescribing information.

Lilotomab (murine anti-CD37 antibody) is used as "cold antibody" pre-dosing. Lilotomab, the same antibody as contained in Betalutin, will be used as pre-dosing to block the binding of Betalutin to the remaining CD37 positive cells in the bone marrow, spleen, liver and peripheral blood. One intravenous infusion of 60 mg/m^2 lilotomab will be administered in cohort 1 before dose escalation to 100 mg/m^2 lilotomab in cohort 2. The dose of lilotomab to be used in subsequent cohorts will be determined following a review of the reported DLTs by the safety review committee. Administration of lilotomab in all cohorts will be performed within 4 hours before administration of Betalutin on Day 0 (up to a maximum dose of 2.7m^2). Pre-medication consisting of an antipyretic and antihistamine medication should be administered before infusion of lilotomab.

Study Design:

This is a Phase 1, single-arm, multi-centre, dose escalation study to determine the maximum tolerated dose of Belalutin in patients with relapsed/refractory DLBCL who are not eligible for, unwilling or declined autologous stem cell transplantation.

Patients enrolled into the study will be administered:

- pre-treatment with rituximab 375 mg/m^2 14 days (+/- 2) days before Betalutin injection
- pre-dosing with lilotomab (60 mg/m^2 in Cohort 1 and 100 mg/m^2 in cohort 2) within 4 hours prior to Betalutin injection on Day 0.

- Betalutin injection on Day 0

A 3+3 dose level design is used in this study to determine the MTD of Betalutin and two doses of lilotomab. The starting dose of Betalutin will be 10 MBq/kg body weight (b.w.) given as a single injection, within 4 hours of receiving 60 mg/m^2 of lilotomab. If dose escalation criteria are met, the dose of lilotomab will then be escalated to 100 mg/m^2 with 10MBq/kg of Betalutin. Dose escalation of Betalutin will then be tested in cohorts receiving 15 MBq/kg and if 15 MBq/kg is tolerated with bone marrow recovery, 20 MBq/kg will then be tested. With each dose escalation of Betalutin patients will receive the maximum dose of lilotomab considered to be safe (either 60 mg/m^2 or 100 mg/m^2) following a review of the safety data from cohorts 1 and 2. The possible treatment regimens to be assessed (depending on the DLTs observed) are:

- Cohort 1: 60 mg/m^2 lilotomab + 10 MBq/kg Betalutin
- Cohort 2: 100 mg/m^2 lilotomab + 10MBq/kg Betalutin
- Cohort 3: 100 mg/m^2 (or 60 mg/m^2 if 100 mg/m^2 is unsafe) + 15MBq/kg Betalutin
- Cohort 4: 100 mg/m^2 (or 60 mg/m^2 if 100 mg/m^2 is unsafe) + 20MBq/kg Betalutin

Dose escalation (either lilotomab or radioactive Lu-177 dose level escalation), will be stopped until at least three patients at each dose level, have been followed until peripheral blood count recovery, defined as neutrophils $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L or, alternatively until after the third patient completes 8 weeks of follow-up after Day 0 treatment (the follow-up may get extended up to 12 weeks if a patient's platelets or neutrophils do not recover to grade 1 by 8 weeks). If no DLT occurs, the next group of three patients will be treated at the next dose level. If one of the three initial patients at a given dose level experiences a DLT, the cohort of patients will be expanded to six patients. If less than two out of the six patients experience a DLT, then the next higher dose group will be initiated. If two or more (of a cohort of up to six) patients experience a DLT, no higher dose levels will be tested and the MTD will be deemed to have been exceeded. If additional radiation doses need to be explored later, the Safety Review Committee will advise which dose step to use based on thorough evaluation of the available safety data.

The MTD is defined as the highest dose studied for which the incidence of DLTs is less than two out of the six patients.

The Betalutin starting dose has been selected based on safety and tolerability data from a Phase 1, dose escalation study of Betalutin in patients with NHL, which has predominantly enrolled patients with follicular indolent lymphoma (Protocol LYMRIT-37-01).

The patients will attend study centre visits during the screening, treatment and follow-up period. The treatment period is defined from start of rituximab infusion (Day -14, +/- 2 days) to administration of Betalutin dosage on Day 0. The 12-week short term follow-up period is defined from completion of Betalutin injection (Day 0) to 12 weeks after Betalutin dosing. Patients will be followed in a subsequent long term follow-up period for resolution of any ongoing study drug toxicity for up to 2 years after administration of Betalutin or until disease progression with initiation of subsequent anticancer therapy, whichever occurs first.

Dose limiting toxicity for any given patient is defined as any of the following:

a. Hematologic toxicity
   i. Grade 4 neutropenia observed for greater than 7 days duration
   ii. Grade 4 thrombocytopenia observed for greater than 7 days duration
   iii. Grade 3-4 neutropenia associated with fever ($\geq$ 38.5 °C) of any duration
   iv. Grade 3-4 thrombocytopenia with bleeding
   v. Thrombocytopenia with any requirement for more than one platelet transfusion before recovering to grade 1 of less
   vi. Grade 4 anemia, unexplained by underlying disease

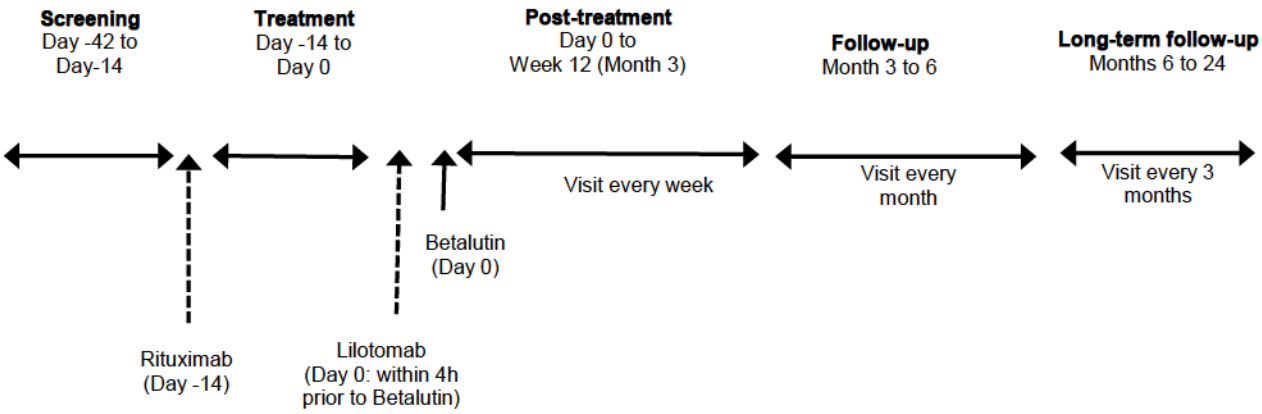
b. Non-Hematologic toxicity
   i. Grade 3 nausea/vomiting/diarrhea lasting longer than 72 hours despite maximal care or grade 4
   ii. Any other grade 3 or 4 non-hematologic toxicities
   iii. Any grade 3 or 4 electrolyte abnormalities that do not resolve to grade 1 or baseline within 24 hours

The Safety Review Committee will make the recommendation whether or not to move to next dose level after thorough review of the safety experience at prior dose levels.

Once the MTD is identified, the MTD dose level will be further expanded by approximately 10 additional patients who relapsed ≥6 months after last therapy after having achieved a CR/PR, and approximately 10 patients who were refractory to their last line of therapy (PD, SD or CR/PR lasting <6 months) to further assess safety, anti-tumour activity and PK. Additional patients may be enrolled to allow for non-evaluable patients to be replaced (e.g. patients who are enrolled but are withdrawn prior to study drug or Betalutin administration).

Treatment Schedule and Study Assessments:

Individual time schedule for all patients



Note that patients included in the pharmacokinetics, biodistribution and dosimetry sub-study will have additional visits during the first 3 weeks after Betalutin administration.
A visit window of ±2 days is permitted for Day 0 and Day -14. The dose of radioactivity will be based on the patient weight on the actual administration date.

Patients considered suitable to be screened for the study will undergo a screening assessment. Patients will attend the clinic on day -14, Day 0 (the dosing day) and every week up to 12 weeks after Betalutin injection. The patients will then be evaluated in the clinic monthly until Month 6 (i.e. 6 months from Day 0 [day of Betalutin injection]). On completion of the 6 month follow-up visit, patients will be followed with clinic visits every 3 months up to 24 months post-treatment, to assess disease progression and survival. The patient will be withdrawn from follow-up if further anticancer therapy is started.

Safety:

In the treatment period (from the time of the first rituximab infusion through Day 0 Betalutin administration) and the short term follow-up period (up to 12 weeks after Betalutin administration) vital signs, physical examination, haematology and serum biochemistry, all AEs and concomitant medications will be collected at specified time points or more frequently per discretion of the treating physician. During the long term follow-up period (from 12 weeks until 2 years), SAEs and AEs related to study drug, haematology, serum biochemistry, as well as any late toxicity such as second primary malignancies will be recorded every month during the first 6 months following study treatment and every 3 months thereafter, until the patient has been through his/her 2-year visit or until initiation of other cancer related treatment, whichever occurs first.

Pharmacokinetics, biodistribution and dosimetry:

Patients who participate in a biodistribution sub-study will have blood samples collected for radioactivity and antibody measurements at the following time points with reference to the lilotomab administration on Day 0: 0 (pre-dose), 5, 30, 60 and 120 minutes, and then at these time points following Betalutin administration: 0 (pre-dose), 15 minutes, 1, 2, 4 and 24 hours post-dose, plus Days 2, 3, 4, 7 (±1), 14 (±2) and 21 (±2)..

The dosimetry and biodistribution sub-study will also include whole body gamma scans and single-photon emission computerized tomography (SPECT)/computed tomography (CT) scans at 2-4 and 24 hours, Day 4 and 7 after Betalutin

treatment. Note that samples times may vary based on on-going analysis but will not exceed this maximum number of assessments. A Day 4 SPECT/CT scan is optional for patients not participating in the biodistribution sub-study. A window of ±1 day is permitted for the Day 4 SPECT/CT scan.

Efficacy:

Positron-emission tomography (PET)/CT and contrast enhanced CT images will be performed at baseline, and at 3 and 6 months after Betalutin administration. Thereafter, contrast enhanced CT scan will be done every 6 months up to Month 24. Survival data will be recorded for all patients until the last patient has been through the 2-year follow-up period.

Patient Selection:

Inclusion Criteria

Eligible patients must meet the following criteria at the time of enrolment:

1. Male or female aged ≥18 years.
2. Histologically confirmed DLBCL (WHO classification).
3. Received at least one prior line of therapy including immuno-chemotherapy.
4. In first or subsequent relapse, or refractory to the last treatment (defined as less than a complete metabolic response to the last treatment, or disease progression within 6 months from the last treatment)
5. Not suitable for or declined/unwilling to undergo intensive therapy, including high dose chemotherapy and autologous stem cell transplantation (ASCT). The decision of whether a patient is unsuitable or not for ASCT should be made by the investigator following a thorough review of the patient. For guidance possible reasons patients may be unsuitable for ASCT may include but are not limited to; excessively elderly or frail patients, those with an increased bilirubin or creatinine level (to be eligible for this study patients must still meet inclusion criteria 11), low cardiac ejection fraction, forced expiratory volume in 1 second and/or lower than predicted carbon monoxide diffusion test.
6. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (at least one objectively bi-dimensionally measurable (nodal) lesion (>1.5 cm in its largest dimension by CT scan).
7. Negative human anti-mouse antibody (HAMA) test.
8. Life expectancy of at least 3 months.
9. Bone marrow tumour infiltration <25% tumour cells (in biopsy taken from a site not previously irradiated).
10. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
11. Normal organ and bone marrow (normocellular) 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 ≤2.5 x upper limit of normal (ULN) (except patients with documented Gilbert's syndrome);
    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 ≤1.5 mg/dL or a creatinine clearance >60 mL/min;
    g. Normal coagulation parameters (elevated international normalized ratio (INR), prothrombin time or activated partial thromboplastin time (APTT) ≤1.3 ULN range acceptable).
12. Women of childbearing potential, defined as neither post-menopausal nor permanently sterile must agree to the contraceptive requirements below. Permanent sterilisation methods may include hysterectomy, bilateral salpingectomy and bilateral oophorectomy and postmenopausal is defined as no menses for 12 months without an alternative medical cause.

    Women of childbearing potential must

a. understand that the study medication may have teratogenic risk
b. have a negative serum pregnancy test at screening and before Betalutin injection
c. commit to continued abstinence from heterosexual intercourse (excluding periodic abstinence or the withdrawal method) or begin two effective methods of birth control with a Pearl-Index ≤ 1%. 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 amenorrhoea. Apart from abstinence, effective methods of birth control are:
    - Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
        - oral
        - intravaginal
        - transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation
        - oral
        - injectable
        - implantable
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomised partner

13. Male patients must agree to use condoms during intercourse throughout study drug therapy and the following 12 months.
14. Ability to give written, informed consent prior to any study-specific screening procedures, with the understanding that the consent may be withdrawn by the patient at any time without prejudice.
15. Capable of understanding the protocol requirements, is willing and able to comply with the study protocol procedures and has signed the informed consent document.
16. A negative Hepatitis B test (HBsAg and anti-HBc) and negative HIV test during screening

Exclusion Criteria

Eligible patients must not meet/have the following criteria:

1. Prior hematopoietic allogenic stem cell transplantation.
2. Prior autologous stem cell transplantation.
3. Previous total body irradiation.
4. Prior anti-lymphoma therapy (chemotherapy, immunotherapy or other investigational agent), excluding corticosteroids, within 4 weeks prior to start of study treatment (i.e. rituximab) (G-CSF or GM-CSF are permitted up to 2 weeks prior to start of study treatment.).
5. Patients who are receiving any other investigational agents.
6. Patients with known or suspected central nervous system involvement of lymphoma.
7. 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. localized 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 complete remission;
8. Pregnant or breastfeeding women.
9. Exposure to another CD37 targeting drug.

10. Allergy to X ray contrast agents.
11. A known hypersensitivity to rituximab, lilotomab, Betalutin or murine proteins or any excipient used in rituximab, lilotomab or Betalutin.
12. Has received a live attenuated vaccine within 30 days prior to enrolling in the study.
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.

Concomitant Medication:

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

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

Safety Review Committee:

The recommendation of whether to enrol patients in the next cohort with an increased dose, and the decision on the MTD for the expansion phase will be made by the Safety Review Committee based on the safety data in the database at the time the last patient in the current cohort has peripheral blood count recovery or until 8 weeks after the Betalutin dose (the follow-up may get extended up to 12 weeks if a patient's platelets or neutrophils do not recover to grade 1 by 8 weeks). The Safety Review Committee consists of at least three experts including the co-ordinating and principal investigators from ongoing Betalutin studies.

Statistical Methods and Sample Size:

The total number of patients enrolled into the study will depend on the number of dose levels explored and the toxicity observed. Up to approximately 24 patients may be enrolled into the dose escalation portion of the study and approximately an additional 20 patients for expansion of the MTD. The results from this study will be presented using descriptive statistical methods.

2 INTRODUCTION

2.1 Background

Non-Hodgkin lymphomas (NHL) as a group is the most common malignant haematological disease. NHLs are a diverse group of blood cancers that include any kind of lymphoma except Hodgkin lymphoma. NHLs vary in their clinical behaviour, morphologic appearance, immunologic and molecular phenotype (2). The various types represent neoplastic lymphoid cells arrested at different stages of differentiation. Based on their natural history, NHLs can be clinically classified as indolent, aggressive, and highly aggressive. Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma are the most common subtypes.

NHL (all subtypes combined) is the tenth most common cancer worldwide, with nearly 386,000 new cases diagnosed in 2012 (3% of the total). NHL incidence rates are highest in Northern America and lowest in South Central Asia, but this partly reflects varying data quality worldwide (3). In the USA, NHL is the fifth most common cause of cancer, with an estimated 71,850 new cases expected in 2015 (4). In developed countries, NHL registrations have increased approximately three-fold since the mid-1970s, with much of the rise occurring before the mid-1990s (5-8). The disease is uniformly fatal without treatment, but the majority of patients are effectively treated with current chemo-immunotherapy strategies. Patients with diffuse large B-cell lymphoma (DLBCL) tend to be older than those with other types of NHL; the peak incidence for DLBCL occurs in the seventh decade of life. [Savage KJ, Gregory SA. Lymphomas. In: Gregory SA, McCrae KR, eds. ash®-sap. ASH Self-Assessment Program. 4th ed. 2010:511–554.]

The initial management of DLBCL is centred around chemotherapy regimens, with various permutations of the anti-CD20 antibody rituximab and the chemotherapy combination of cyclophosphamide, hydroxydaunorubicin, vincristine (“Oncovin”) and prednisone (CHOP). Using CHOP with rituximab (R-CHOP), approximately 70% of patients with DLBCL will be disease-free at five years (9,10). Conversely, the remaining one-third of patients will have relapsed or have refractory disease. This represents a group with poor prognosis and an untreated overall survival of only about six months. They are, therefore, a patient population significantly devoid of effective therapeutic options (11). The most meaningful treatment approach for patients with relapsed or refractory disease is high-dose chemotherapy combined with autologous stem cell transplantation (HD-ASCT) (12). However, approximately half of patients with relapsed/refractory disease are ineligible for HD-ASCT, due to co-morbidities or a failure to demonstrate chemo-responsiveness to salvage therapy given prior to transplant (13). Of the remaining patients who can undergo HD-ASCT, only about 20% achieve a lasting response (13).

In recent years a novel way of treating NHL with radiation has emerged; radioimmunotherapy (RIT), which refers to using a radiolabelled monoclonal antibody to specifically target an

antigen expressed on tumour cells or within tumour tissue. Thus, the toxicity to normal cells without the antigen will be limited. Several studies have shown that beta-emitting radioimmunoconjugates possess high levels of antitumour activity in patients with relapsed or refractory B-cell lymphomas (14-17), including those refractory to rituximab (18,19) and chemotherapy (20). However, so far, no RIT has been approved for the treatment of DLBCL, as all the approved products are approved for follicular lymphoma, mantle cell lymphoma and chronic lymphocytic leukaemia.

Clinical data have indicated that RIT may be more cost effective and more efficacious than nonradioactive immunotherapy (21,22). More recently, single-arm studies with upfront RIT administered either alone or with chemotherapy to previously untreated indolent NHL patients have reported overall response rates of 90-100 %, complete response rates of 60-95 % and durable remissions (23-26).

A phase 3 study of RIT as part of frontline therapy for indolent NHL reported that consolidation therapy with ^{90}Y-ibritumomab tiuxetan (Zevalin®) after induction chemotherapy markedly prolonged progression free survival in patients with previously untreated stage II or IV follicular lymphoma (27). In another study, patients with indolent and aggressive NHLs received four cycles of chemotherapy followed by high myeloablative dose of ^{90}Y-ibritumomab tiuxetan followed by autologous stem cell support (28). After a follow-up time of 30 months the overall survival rate was 87% and the event free survival was 69%. Although myeloablative doses of ^{90}Y-ibritumomab tiuxetan were given, the RIT was well tolerated. The low dose-rate permits RIT to be effective for hematologic malignancies while causing minimal non-haematological toxicity.

When anti-CD20 RIT is given to patients, the RIT is administered with large quantities of unlabelled cold anti-CD20 antibody immediately before radiolabelled anti-CD20 antibodies. Such a priming dose is necessary to optimize radiolabelled antibody concentrations in tumour (16,29), presumably by partially saturating easily accessible B-cells in the blood and the spleen and permitting sufficient radiolabelled antibody to bypass these sites and penetrate less accessible compartments, such as lymph nodes and large tumour masses. However, too much cold anti-CD20 antibody over a long time can result in blocking of the CD20 antigen on tumour cells and thus reduce the effect of anti-CD20 RIT. Both clinical and non-clinical studies have shown that in some circumstances quite low rituximab concentrations in the blood can reduce tumour cell targeting and thus impair the clinical efficacy of CD20-directed RIT (30). A solution to this problem might be to omit cold rituximab from the last cycles of therapy before RIT. Alternatively, one could choose to target another B-cell surface antigen such as CD37.

The chloramine T method of ^{131}I-labeling was used in the early studies of CD37 RIT (31). ^{131}I labelled to antibodies with the iodogen or the chloramine T method are not retained in the cells if the antigen-antibody complex is internalized (32,33). Inside the cells the nuclide is removed from the antibody by intracellular enzymes and diffuses out and away from the tumour cells

(34). The same so-called dehalogenation has been shown with CD22 antibodies, which are also internalized (35). Metallic radionuclides labelled to antibodies with so-called chelators are, however, more stable and remain contained inside the tumour cells to a much higher degree (36). Use of metallic radionuclides facilitates therapeutic applications targeting internalizing antigens, and tumour uptake may also be higher than for non-internalizing antibodies.

2.2 Lutetium (^{177}Lu)-lilotomab satetraxetan (Betalutin®)

Betalutin (lilotomab labelled with lutetium-177 via the chelator p-SCN-benzyl-DOTA) has been developed by Nordic Nanovector in collaboration with the Norwegian Radium Hospital (Oslo, Norway) for the treatment of relapsed NHL patients.

Betalutin (lutetium (^{177}Lu)-lilotomab satetraxetan) targets the CD37 antigen, which is abundant on the cell surface of tumours of B-cell origin, including NHL and chronic lymphocytic leukaemia (CLL) (37-39). CD37 antigen is a promising target, which at present is not addressed by any approved treatment.

The most common radiopharmaceuticals used in therapy today utilize substances that disintegrate resulting in the emission of a beta particle. Beta particles are electrons emitted from the nucleus of an atom. Beta emitters currently approved for therapy include iodine-131 (half-life [T½] = 8 days), yttrium-90 ($T^{½}$ = 2.7 days) and lutetium-177 ($T^{½}$ = 6.7 days). Lutetium-177 has been selected for use in Betalutin since it has proven to be suitable for labelling of the lilotomab anti-CD37 antibody and has an energy of the emitted β-particle that is suitable for treatment of lymphoma (E^{max} = 0.497 MeV, $T_{½}$= 6.7 days). Furthermore, it has a low abundance of photons with almost ideal energy for imaging (E = 113 keV, abundance = 6.5%; E = 208 keV, abundance = 11%).

Therapy with an antibody-radionuclide-conjugate (ARC) such as Betalutin, which incorporates the beta-emitter lutetium-177, permits delivery of a therapeutic (lethal) dose of radiation directly to the DNA of tumour cells. The radiation emitted from the radiolabelled antibody affects not only the antibody-binding cell but also neighbouring cells up to an average of 0.23 mm from the radionuclide, via the “cross-fire” effect.

Betalutin has been tested for targeting, therapeutic and toxic effects in cells, in mice, and in humans. The murine monoclonal antibody against CD37, lilotomab, has similar or better binding properties to CD37 than rituximab has to CD20. Therapy against single cells showed a significantly better effect of Betalutin than of ^{177}Lu-rituximab. The maximum tolerated dose (MTD) of Betalutin in severe combined immune deficient (SCID) mice with tumour cells in the bone marrow was between 50 and 100 MBq/kg (150-300 MBq/m^2). Extrapolation to human dose by allometric equivalence based on body surface area, however, shows that 550 MBq/kg in mice (20 g body weight and surface area of 0.0066 m^2) is equivalent to 43 MBq/kg in humans (70 kg, 1,8 m^2 body surface area). The MTD in mice can be increased by giving it as multiple

injections. Biodistribution studies with Betalutin have shown high uptake in tumour and uptake in normal organs similar to the uptake of ^{177}Lu-rituximab. The preclinical data to date indicates that Betalutin has a suitable biodistribution profile with high uptake in tumour cells, and that the efficacy results in the mouse models show promise of potentially interesting clinical results.

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

Betalutin is prepared as a solution for intravenous administration. 1 mg/mL lilotomab antibody will be used, between 8 to 10 mg lilotomab antibody per patient. The amount of lutetium (^{177}Lu)-lilotomab satetraxetan injected per patient will depend on the dose level and the patient's weight.

The first clinical trial of Betalutin in patients with recurrent indolent NHL was initiated in December 2012. See Section **Error! Reference source not found.** for a summary of clinical data.

Please see the IB for further information about Betalutin.

2.3 Rituximab

In this study, rituximab, a chimeric anti-CD20 antibody will be used as pre-treatment to clear the circulating normal peripheral B-lymphocytes in the blood and in the spleen before administration of Betalutin. This pre-treatment is commonly used in RIT regimens in lymphoma and should ensure greater penetration of Betalutin to less accessible compartments such as lymph nodes and larger tumour masses. Rituximab targets CD20 and will not block the binding sites of Betalutin CD37 on the B-lymphocytes or tumour cells.

One intravenous infusion of 375 mg/m^2 rituximab as pre-treatment will be given to all patients on Day -14 (+/- 2 days) prior to administration of Betalutin. Pre-medication consisting of an antipyretic and antihistamine medication should be administered before each infusion of rituximab, according to the institutional guideline. For detailed guidance on use of rituximab and possible side effects see the summary of product characteristics.

Rituximab is used as a standard treatment for patients with B-cell NHL either as monotherapy or in combination with chemotherapy. The description of rituximab in this section is taken from its prescribing information and package insert.

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

CD20 is found on both normal and malignant B-cells, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fc• receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

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

For a description of the scientific rationale for the use of rituximab see section 2.6.2.

2.4 Lilotomab antibody

At the Norwegian Radium Hospital, the antibody lilotomab was developed against CD37 in the 1980s (Smeland 1985).

The CD37 antigen belongs to the tetraspanin transmembrane protein family. It is extensively glycosylated with a molecular weight of 40- to 52-kDa. CD37 internalizes but has modest shedding in transformed B-cells expressing the antigen. During B-cell development, CD37 is not expressed on progenitor B stem cells. CD37 is expressed in cells progressing from pre-B to peripheral mature B-cell stages and is absent on terminal differentiation to plasma cells (CD37 is B-cell selective and an attractive target for antibody-mediated immunotherapy and RIT).

Pre-dosing with 60mg/m^2 or 100 mg/m^2 of lilotomab “cold antibody” on Day 0 will be given to all patients enrolled into this study. Lilotomab will be infused within 4 hours before Betalutin administration on Day 0.

Rituximab has been shown in several studies to rapidly and specifically deplete normal circulating B-cells. The concentration of normal B-cells is higher in the spleen than in the blood, and the depletion of B-cells in the spleen may take a longer time following pre-treatment than in the peripheral blood (see section 2.6.2).

The CD37 antigen positive cells in the spleen, bone marrow and liver that are left after the rituximab pre-treatment can be blocked by pre-dosing with lilotomab before Betalutin. It is assumed that lilotomab will bind to the most easily accessible CD37 positive cells in the lymphoid organs and therefore prevent binding of Betalutin to the spleen and bone marrow, increasing its circulating half-life and therefore increasing the exposure to the tumour.

RIT with CD37 as target has been explored previously using a ^{131}I-labeled murine monoclonal antibody (MB-1) against CD37 both in a mouse model and in the clinic.

Clinical data from the Norwegian Radium Hospital has shown that 99.5% (216 of 217) of human lymphoma biopsies express CD37, confirming CD37 as a suitable target for lymphoma RIT (45).

Please see the IB for further information about lilotomab.

For a description of the scientific rationale for the use of lilotomab see section 2.6.3.

2.5 Potential Benefits and Risks

Intravenous administration of Betalutin is an experimental treatment for patients with relapsed/refractory DLBCL. No clinical studies have yet been completed. Limited clinical data are available. The following benefit–risk discussion is based on anticipated effects.

2.5.1 Disease and Patient Population and Alternative Treatments to Betalutin

The outcome of patients with relapsed/refractory DLBCL not eligible for autologous stem cell transplantation is very poor, with essentially no chance at prolonged control of disease (40). Attempts at conventional salvage regimens in this population of generally older patients do not result in disease control and have substantial morbidity. Therefore, goals of therapy in this setting are purely palliative, and toxicities of treatment need to be considered given their limited benefit. For this reason, in this population of patients, single-agent therapies, often in combination with rituximab, are recommended. Given these limited options, this group of patients should be referred for clinical trials. The only way to definitively improve outcome and change the natural history for this large majority of patients with relapsed/refractory DLBCL is with the incorporation of novel agents and approaches. This patient population is in need of new treatment options.

Patients to be included in this study are adults, presenting with relapsed/refractory DLBCL who have received at least 1 prior line of therapy and who are not eligible for, unwilling or declined autologous stem cell transplantation.

2.5.2 Non-clinical Risk Assessment of Betalutin

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

Betalutin is a beta-emitting ARC designed specifically for the treatment of NHL (including DLBCL). The radionuclide lutetium-177 was chosen since it allows effective irradiation of single cells as well as micro-metastases and larger tumours. The murine antibody lilotomab was chosen for its excellent properties in binding to the CD37 antigen. The radionuclide, antibody and chelator used for radiolabelling are prepared in compliance with Good Manufacturing Practice (GMP) regulations.

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

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

Even though there is a lack of pharmacologically relevant animal models for the evaluation of Betalutin mechanism of action or safety studies, there is a considerable clinical experience with anti-CD37 targeted antibodies, lutetium-177 radiolabelled agents and the DOTA chelator. Human experience is considered more relevant to the development of Betalutin and can provide significant insight into the anticipated clinical response. Lutetium-177-labelled rituximab, prepared using the same DOTA chelator as for Betalutin, has recently been administered clinically (41,42). The maximum tolerated dose was 50 mCi/m^2 (approximately 48 MBq/kg b.w.) and efficacy results in NHL patients were promising. This report confirms that the

radiolabelling procedure for Betalutin is compatible with human administration and provides supportive evidence of the safety of both DOTA and lutetium-177.

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

2.5.3 Risk with Rituximab Pre-treatment

The treatment regimen in this study begins on Day -14 (+/- 2 days) with the intravenous administration of the antibody rituximab.

It is likely that the majority of patients enrolled in the study will have received rituximab treatment before enrolment. Frequently experienced AEs associated with rituximab administration include fever, chills, nausea, abdominal pain, dyspnoea, dizziness, erythema and rash. Infusion related symptoms are often reported in association with the initial administration of the treatment, but the incidence decreases substantially with subsequent infusions. Additional information regarding reported AEs associated with rituximab administration is provided in the prescribing information for this drug. All patients enrolled in the study will receive pre-treatment with antihistaminic agents and anti-pyretics per standard of care for antibody infusions at the study centres.

2.5.4 Risk with Lilotomab Pre-dosing

All patients will be administered a single infusion of 60 mg/m^2 of lilotomab in cohort 1 and 100 mg/m^2 in cohort 2 on Day 0, within 4 hours before administration of Betalutin. The dose of lilotomab used in subsequent cohorts will be determined following a review of the reported DLTs in cohort 1 and 2 and will be 100 mg/m^2 unless this dose is considered by the safety review committee to be unsafe. The administration of lilotomab is designed to improve the biodistribution of Betalutin.

The same procedure used for the rituximab infusion will be used for lilotomab. If the patient experiences AEs including drop in blood pressure, chills, fever or dyspnoea the infusion will be stopped. When the symptoms disappear, the infusion will start again with 50% reduced infusion rate.

Since lilotomab is a fully murine antibody, a risk of developing an immune response is anticipated. Therefore, all patients will be screened for anti-mouse antibodies (HAMA), and monitored for the development of an immune response after injection of lilotomab and Betalutin.

The pre-treatment with "cold" lilotomab antibody should improve the biodistribution of Betalutin to the desired tumour sites, since CD37 binding sites in the spleen and bone marrow will be occupied by lilotomab. This could lead to improved circulation half-life of Betalutin, which could facilitate better tumour uptake of the radioimmunoconjugate, as suggested from development studies with CD37 targeting with ^{131}I-MB-1 (21).

2.5.5 Potential Risk Factors and Proposed Risk Minimization Activities

Haematological toxicity has been observed in the phase 1/2 LYMRIT-37-01 study, with nadir values 5 to 7 weeks after injection of Betalutin. It is also advisable to monitor haematology parameters for withdrawn patients at least through 6 and 9 weeks after Betalutin administration.

Potential risk factors of Betalutin treatment regimen and proposed risk minimization activities are presented in Table 1.

The efficacy and safety of Betalutin for patients with DLBCL has not been clinically tested. In the LYMRIT-37-01 study patients with relapsed indolent NHL, the majority with follicular lymphoma, have been exposed to doses up to 20 MBq/kg. For a summary of the safety profile reported during the LYMRIT-37-01 study please refer to the IB.

As seen in the LYMRIT-37-01 study, the ionizing radiation from Betalutin is expected to have a selective effect on the tumour cells.

Table 1 Potential risk factors of Betalutin treatment and proposed risk minimization activities

Anticipated Risk Factors	Proposed risk minimization treatment activities	Pharmacovigilance
Myelosuppression, transient reduction of haematological parameters	• A pre-defined minimum value for platelet counts and neutrophils are set prior to inclusion. • Only patients with <25% tumour cells in bone marrow biopsy (biopsy taken from a site not previously irradiated) will be included. • Patients with previous total body irradiation will be excluded. • Patients with previous hematopoietic allogenic stem cell transplantation will be excluded, and patient with prior autologous stem cell transplantation ≤2 years ago. • Blood counts will be closely followed and supportive measures such as transfusions administered as needed	• The inclusion and exclusion criteria in this clinical study protocol must be followed. • Haematological parameters will be closely followed as a safety measure. Supportive Care Guidelines are given in this protocol. • Dose escalation will be on hold until at least 3 patients at each dose level have been followed until peripheral blood count recovery, defined as neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L or, alternatively until after the third patient completes 8 weeks of follow-up after treatment, whichever occurs first. The follow-up may get extended up to 12 weeks if a patient's platelets or neutrophils do not recover to grade 1 by 8 weeks.
Carcinogenicity: Betalutin is a radioactive drug and in the longer term, may induce secondary malignancies, including myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) and other primary cancers	• The life expectancy of relapsed/refractory DLBCL patients is relatively short and therefore exposure to a single dose of RIT is unlikely to significantly alter the risk profile for patients. • Patients under the age of 18 are excluded to reduce the life time risk	• The inclusion and exclusion criteria in this clinical study protocol must be followed • Any secondary malignancies will be recorded as part of the long term follow-up.
Treatment with Betalutin also leads to temporary depletion of normal CD37-positive B-cells		• White blood cell counts will be monitored closely.
Pre-treatment with rituximab	• The study personnel should be familiar with rituximab administration, and the prescribing information of rituximab.	• AEs will be collected after administration of Rituximab

Anticipated Risk Factors	Proposed risk minimization treatment activities	Pharmacovigilance
Betalutin administration includes pre-treatment with lilotomab.	• The study personnel should be familiar with rituximab administration, as the same procedure applies for lilotomab administration.	• AEs will be collected after administration of lilotomab
The effect of Betalutin when given to pregnant or lactating women is not known.	• Pregnant or breastfeeding women are excluded from the study. • Patients will be informed of the potential risk to a foetus and must consent to the use of highly effective contraception for 12 months from the administration of Betalutin.	• The exclusion criterion should be followed. • Pregnancy in a patient or their partner should be reported and followed up during the entire course of the pregnancy and postpartum.
The adverse event profile is not established for Betalutin	• Emergency treatments and specialist medical staff will be available during and after injection. The patient will stay at least 2 hours after injection of Betalutin (unless local regulations require a longer surveillance period).	• The patient will be closely followed by the study personnel. All reported events will be recorded up to 12 weeks after injection; thereafter all treatment related adverse reactions will be reported, including potential late toxicity. • A Safety Review Committee will regularly review patient data, looking for any potential safety signals • No more than 1 patient will be dosed at the same time
Lilotomab is a murine antibody.	• The patients are screened for anti-human mouse antibodies (HAMA)before inclusion in the study and then monitored for immune response	• If another injection of murine antibody is to be performed in the future, the patient needs to be tested for pre-existing ADA towards lilotomab and Betalutin prior to injection of murine antibodies.

Anticipated Risk Factors	Proposed risk minimization treatment activities	Pharmacovigilance
Radiopharmaceutical agent	• Written instructions concerning safety precautions will be given to the patients before administration and to the hospital staff before handling. • The risk of exposure to the patient's carer/partner is minimised by educating the patient and carer, and reducing exposure through a number of methods including barrier contraception	

2.6 Rationale and Dose Selection

2.6.1 Selection of Dose of Betalutin

This is a Phase 1, single-arm, multi-centre, dose-escalation study to determine the maximum tolerated dose of Betalutin. Patients enrolled into the study will have relapsed/refractory DLBCL and received at least one prior line of therapy including immuno-chemotherapy and are not eligible for, unwilling or declined to undergo autologous stem cell transplantation.

The starting dose of Betalutin for this study was 10 MBq kg body weight (b.w, given as a single injection). The dose was selected based on preliminary safety and tolerability data from a Phase 1/2, dose escalation study of Betalutin in patients with relapsed indolent NHL, which has predominantly enrolled patients with follicular lymphoma (Protocol LYMRIT-37-01).

2.6.1.1 Justification of immunoconjugate dose

The amount of immunoconjugate (lilotomab satetraxetan) that will be administered (per patient) is expected to vary over a range 8-10 mg lilotomab satetraxetan (single vial of Betalutin), as the injected volume of Betalutin will differ as a result of inherent time differences between actual injection and planned injection time points and/or duration(s).

Preclinical data supportive of the proposed dosing levels were generated with product containing specific activity levels between 100 and 400 MBq/mg Betalutin.

Pre-clinical findings indicate that the relevant antibody dose range is 0.01 to 1 mg/kg.

As administered levels of antibody are directly relevant to potential clinical therapeutic benefit, it is worth noting that CD37 antigen expression is of a similar pattern to that of the CD20 antigen. It is therefore appropriate to compare the antibody dose identified for Betalutin

(8-10 mg/patient) with the antibody dose levels used for both Zevalin (3.2 mg/patient) and Bexxar (35 mg/patient) treatment.

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

2.6.2.1 Pre-treatment

The intention of the pre-treatment with rituximab is to clear circulating normal peripheral B lymphocytes in the blood and spleen in order to optimize the biodistribution of Betalutin. It is envisaged that, as a consequence of peripheral B lymphocyte clearance, increased levels of radiolabelled antibodies will be available and thereby penetrate less accessible yet therapeutically relevant compartments, such as lymph nodes and larger tumour masses, while potentially sparing bone marrow. Importantly, as rituximab targets CD20, this treatment is not considered likely to block the binding of Betalutin CD37 to either B lymphocytes or tumour cells.

The dose to be used is the same as for rituximab monotherapy, 375 mg/m^2. All patients will receive one infusion of rituximab at Day -14 (+/- 2 days) prior to administration of Betalutin. The administration of rituximab has been shown to rapidly and specifically deplete B-cells from the peripheral blood of lymphoma patients within 24 to 72 hours and this reduction continues for at least 2 to 3 months following administration (46). Therefore, a single administration of rituximab should be sufficient to reduce the circulating lymphocytes of patients without delaying the start of their treatment. A single dose of pre-treatment with rituximab is also similar to the pre-treatment schedule used for the treatment of lymphoma with ibritumomab.

Rituximab is used as a standard treatment for patients with B-cell NHL either as monotherapy or in combination with chemotherapy. The description of rituximab is to be found in the prescribing information and package insert for the product. However, due to the fact that these patients will already have relapsed/refractory disease after at least one treatment and that therapeutic treatment regimens with rituximab contain multiple administrations (4-8) no therapeutic effect can be expected from this pre-treatment with one infusion of rituximab.

2.6.3 Justification of Pre-dosing with lilotomab and Selection of Dose

A pre-dose of 60 mg/m^2 of lilotomab (up to a maximum of 2.7m^2) prior to Betalutin was selected for Cohorts 1 and 2 as an intermediate between the 40 mg pre-dose used in the LYMRIT-37-01 study and 100 mg/m^2, since preliminary data from the LYMRIT-37-01 study showed a reduction in the incidence of grade 4 cytopenias with lilotomab pre-dosing compared to no pre-dosing. It was also considered that increasing the dose of lilotomab above 40 mg may further improve the AE profile of Betalutin allowing for a higher MTD and improved efficacy.

Following a safety review by the SRC, a pre-dose of 100 mg/m^2 of lilotomab was administered in Cohort 3 and is also planned for Cohort 4. Pre-dosing with lilotomab reduces the non-tumour

specific binding of Betalutin by blocking CD37-positive B cells which are predominantly located in the spleen, bone marrow and liver, thereby reducing the severity of myelosuppression.

Based on the available pre-clinical and *in vitro* data of lilotomab, it was not previously considered that a higher dose of lilotomab would pose a risk to patient safety. This has now been confirmed in the LYMRIT-37-01 study. No relevant animal species have been identified that share a cross-reactive target antigen for lilotomab in immunohistology studies of lymphoma tissues and blood cells from different animals (mouse, rat, guinea pig, rabbit, minipig, dog, cynomolgus monkey, rhesus monkey and marmoset). Lilotomab does not elicit a response by human immune effectors in vitro. No significant antibody-dependent effect of lilotomab was observed by complement activation or immune cell cytotoxicity. The human tissue cross-reactivity studies showed that the morphology and distribution of cells stained with lilotomab were consistent with that of B-cells.

Lilotomab pre-doses of 40 mg, 60 mg/m^2 and 100 mg/m^2 have now been administered to 42, 3 and 22 patients respectively in the LYMRIT-37-01 study. A summary of the preliminary results from the first part of the study, including the DLTs observed is described in Section 2.6.4.

Using the same radioisotope as Betalutin, Forrer et al 2010 conducted a phase 1/2 dose escalation trial of 177-Lutetium labelled rituximab in follicular and mantle cell lymphoma patients (40). Using a Day 0 pre-dosing of unlabeled rituximab of 250 mg/m^2 (~475 mg total dose) patients were able to receive up to 1850 MBq/m^2 of radioactive isotope equivalent to approximately 45 MBq/kg.

Given the same isotope and patient populations are used in the two studies, the dose of 15 MBq/kg of Betalutin (with 40 mg lilotomab) selected for the phase 2 stage of the LYMRIT-37-01 study may be compared to the MTD of 45 MBq/kg with a pre-dose of ~475 mg rituximab. A linear extrapolation in a plot of MTD versus the size of the pre-dose in milligrams using both ^{177}Lu-rituximab and Betalutin indicates that increasing the dose of unlabeled antibody to 100 mg/m^2 may allow an MTD of approximately 25 MBq/kg of Betalutin. This extrapolation is complicated by the different antibodies and different targets used in the two studies. However, CD20 and CD37 are expressed on the same cell types in both the tumour tissue and normal tissue and the apparent expression level of the two targets appears to be similar. In addition, the toxicity defining the MTD for both ^{177}Lu-rituximab and ^{177}Lu-lilotomab is likely to be defined by the radioisotope (which is the same in both studies). With a minimal contribution to the toxicity profile defining the MTD in either study originating from the activity of the monoclonal antibody used (compared to the isotope). This extrapolation was considered to be a reasonable assumption in the absence of further clinical data at the time.

Two radio-labelled antibodies approved for the treatment of recurrent NHL (ibritumomab and tositumomab) used pre-dosing with unlabeled antibody on the day of administration to improve

the biodistribution. The dose of 100 mg/m^2 of unlabeled antibody is significantly below that used by either ibritumomab (250mg/m^2) or tositumomab (450mg).

Recently published dosimetry data for some of the phase 1 LYMRIT-37-01 patients from each arm of the study demonstrate that bone marrow absorption of Betalutin was highest in Arm 2, where no lilotomab pre-dose was given compared to Arms 1 and 4 (40 mg and 100 mg/m^2 lilotomab pre-dose respectively) (Stokke C et al, 2018). In addition, the tumour absorption of Betalutin appeared to be highest in Arm 4. Radiation dosimetry thus confirms the hypothesis that pre-dosing with lilotomab protects the bone marrow without decreasing the effect on the tumour cells. 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).

In summary, there is an improved side-effect profile of Betalutin with pre-dosing with 40 mg lilotomab, an altered PK characteristics and dosimetry that suggests that it is beneficial with predosing. Therefore, an increase in lilotomab dose is justified to examine whether this would further improve the side effect profile and tumour response. The dose of 100 mg/m^2 has been chosen after careful consideration of the antibody concentration used with similar products and the clinical, PK and dosimetric data from Betalutin.

2.6.4 Clinical experience with Betalutin

2.6.4.1 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. 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/recommended dose for phase 2 expansion (RDE) of Betalutin, and to collect additional PK data with a lilotomab pre-dose of 60 mg/m^2 (n=3; Arm 5). The Phase 1 part of the study utilised a 3+3 dose-escalation study design with the primary objective of defining the MTD of Betalutin. Secondary objectives were to identify a recommended dose of Betalutin for the Phase II part of the study (RDE), and investigate the safety, biodistribution, PK and efficacy of Betalutin.

A total of 74 patients were enrolled in the first part of the study (46). NHL subtypes were FL (n=57), mantle cell lymphoma (MCL) (n=7), marginal zone lymphoma (MZL) (n=9) and small lymphocytic lymphoma (n=1). The median age of the patients was 69; the median number of prior therapies was 3 (range 1-8); 48 patients (65%) received ≥2 prior therapies.

Three patients were enrolled in Arm 2 (no lilotomab pre-dosing); 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 100 mg/m^2 of lilotomab.

The ORR for all patients enrolled was 61% (CR 28%), and 65% (CR 28%) for the FL subset. The overall incidence of grade 3/4 neutropenia and thrombocytopenia was 54% and 45% respectively (grade 4 neutropenia and thrombocytopenia were reported in 14 patients (19%) and 15 patients (20%) respectively). Of these, there were 5 patients with grade 4 neutropenia lasting >7 days (1 from the Arm 1 RDE cohort, see below), and 4 with grade 4 thrombocytopenia >7 days, none at either RDE.

For Arm 1 (lilotomab pre-dose of 40 mg), the RDE of Betalutin was 15 MBq/kg. One patient developed grade 4 neutropenia and thrombocytopenia for 9 and 12 days respectively. Thirty additional patients were enrolled in a phase 2 expansion cohort (total: 36 patients at RDE). The ORR for 25 FL patients at the RDE was 64% (CR 32%).

For Arm 4 (lilotomab pre-dose of 100 mg/m^2), the RDE of Betalutin was 20 MBq/kg. One patient had a DLT of haematuria associated with a platelet count of 40 x 10^9/L and received a platelet transfusion. Twelve additional patients were enrolled in a phase 2 expansion cohort (total: 19 patients at RDE). The ORR for 16 FL patients at the RDE was 69% (CR 25%).

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; 7% were grade 3/4. The dosing regimen was generally well tolerated, with 2 infusion reactions reported that were both 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 2 RDE's from Arms 1 and 4 (lilotomab 40 mg + Betalutin 15 MBq/kg; lilotomab 100 mg/m^2 + Betalutin 20 MBq/kg) are now being compared in a randomized phase 2b arm of LYMRIT-37-01 in a population of relapsed, anti-CD20 refractory FL patients who have received ≥2 prior therapies.

In the phase I part of Study LYMRIT 37-01, the development of an immune response after treatment was monitored using either a commercial HAMA test or an immune-fluorometric bridging assay detecting the full spectrum of the potential ADA response towards lilotomab and Betalutin. The presence of ADA was reported for 5 out 62 patients enrolled. The observed ADA response was transitory, with an onset detected 1 month after treatment. Available data show that the ADA response onset was resolve at the 3 months (n=3) or 6 months (n=1) visit, with anew ADA onset observed for one patient. There were no reports of development of a HAMA response in Phase 1. Onset of HAMA was reported at the 12 months follow up visit for 2 patients enrolled in the Phase 2a of the study.

The preliminary 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 (Cmax) 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.

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

3 STUDY OBJECTIVES

3.1 Primary objectives:

- To define maximum tolerated dose of Betalutin for patients with relapsed/refractory DLBCL.
-

3.2 Secondary objectives:

- To establish a recommended dose of Betalutin for phase 2 for DLBCL patients.
- To investigate safety and toxicity of Betalutin.
- To investigate biodistribution and pharmacokinetics of Betalutin.
- To explore the efficacy of Betalutin.

3.3 Study endpoints

3.3.1 Safety Endpoints:

- Incidence and severity of adverse events and serious adverse events graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE version 4).
- Changes from baseline in laboratory variables
- Incidence of potential late toxicity, such as new primary cancers and bone marrow changes (acute myelogenous leukaemia, myelodysplastic syndrome, and aplastic anaemia).
- Monitoring of the ADA response towards lilotomab and Betalutin.

3.3.2 Biodistribution, and Pharmacokinetics endpoints:

Evaluation of biodistribution includes whole body activity assessment, the counts in region-of-interest (ROIs) from anterior and posterior whole-body images, total radioactivity in blood measurements (Betalutin PK) and quantitative determination of total antibodies in serum (Total lilotomab antibodies PK). This will enable the following:

- Estimation of whole-body retention of radioactivity at each imaging time post-injection.
- Estimation of the individual organ uptake/retention of radioactivity at each imaging time-point after injection.
- Estimate the levels of remnant administrated radioactivity in blood over time (Betalutin PK).
- Estimate the concentration of total lilotomab antibodies in serum over time (Total lilotomab antibodies PK).
- Calculation of estimated absorbed radiation dose to target organs.

3.3.3 Efficacy endpoints

Overall response rate (CR + PR), Tumour response duration. Progression-free survival and Overall survival

3.3.4 Exploratory endpoint:

Quality of life (QoL) assessed using Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) questionnaire.

4 STUDY DESIGN

4.1 Overview of Study Design

This is a Phase 1, single arm, multi-centre, dose escalation, study to determine the maximum tolerated dose of Betalutin in patients with relapsed/refractory DLBCL who have received at least one prior line of therapy including immune-chemotherapy and who are not eligible for, unwilling or declined autologous stem cell transplantation.

All patients will receive pre-treatment with rituximab 375 mg/m^2 14 days (+/- 2 days) before Betalutin injection. Patients in cohort 1 will receive 60 mg/m^2 of lilotomab within 4 hours of Betalutin, patients in cohort 2 will receive 100 mg/m^2 of lilotomab within 4 hours of Betalutin. A dose of 100 mg/m^2 will be used in subsequent cohorts with escalating doses of Betalutin unless following a review of the reported DLTs in cohorts 1 and 2 the dose of 100 mg/m^2 is considered unsafe by the safety review committee.

All patients will receive a single dose of Betalutin. The planned Betalutin starting dose and planned dose escalation are shown in Table 2.

Table 2 Betalutin Dose Escalation Schedule

Cohort	Treatment Rituximab Day -14 (+/- 2 days) Lilotomab Day 0 Betalutin Day 0	Number of patients
Cohort 1	10 MBq/kg Betalutin + 60 mg/m^2 lilotomab	3 patients with no DLT or expand to 6 patients if 1 DLT reported.
Cohort 2	10 MBq/kg + 100 mg/m^2 lilotomab	3 patients with no DLT or expand to 6 patients if 1 DLT reported.
Cohort 3	15 MBq/kg + 100 or 60 mg/m^2 lilotomab	3 patients with no DLT or expand to 6 patients if 1 DLT reported.
Cohort 4	20 MBq/kg + 100 or 60 mg/m^2 lilotomab	3 patients with no DLT or expand to 6 patients if 1 DLT reported.

The starting dose has been selected based on safety and tolerability data from a Phase 1, dose escalation study of Betalutin in patients with NHL, which has predominantly enrolled patients with follicular indolent lymphoma (Protocol LYMRIT-37-01).

Patients will be treated sequentially and no more than 1 patient will be dosed at the same time. The patients will attend study centre visits during the screening, treatment and follow-up period. The treatment period is defined from start of rituximab infusion on Day -14 (+/- 2 days) through administration of Betalutin dosage on Day 0. The 12-week short term follow-up period is defined from completion of Betalutin injection on Day 0 to 12 weeks after Betalutin dosing. Patients will be followed in a subsequent long term follow-up period for resolution of any ongoing study drug toxicity for up to 2 years after administration of Betalutin, or until disease progression with institution of subsequent anticancer therapy, whichever occurs first.

Once the MTD is identified, the MTD dose level will be further expanded by approximately 10 additional patients who relapsed ≥6 months after last therapy after having achieved a CR/PR, and approximately 10 patients who were refractory to their last line of therapy (PD, SD or CR/PR lasting <6 months) to further assess safety, anti-tumour activity and PK. Additional patients may be enrolled to allow for non-evaluable patients to be replaced (e.g. patients who are enrolled but are withdrawn prior to study drug or Betalutin administration).

4.2 Dose Limiting Toxicity Definition and Dose Escalation

4.2.1 Dose Limiting Toxicity

DLT is defined as:

a. Hematologic toxicity
- i. Grade 4 neutropenia observed for greater than 7 days duration
- ii. Grade 4 thrombocytopenia observed for greater than 7 days duration
- iii. Grade 3-4 neutropenia associated with fever (≥ 38.5 °C) of any duration
- iv. Grade 3-4 thrombocytopenia with bleeding
- v. Thrombocytopenia with any requirement for more than one platelet transfusion before recovering to grade 1 of less
- vi. Grade 4 anemia, unexplained by underlying disease

b. Non-Hematologic toxicity
- i. Grade 3 nausea/vomiting/diarrhea lasting longer than 72 hours despite maximal care or grade 4
- ii. Any other grade 3 or 4 non-hematologic toxicities
- iii. Any grade 3 or 4 electrolyte abnormalities that do not resolve to grade 1 or baseline within 24 hours

4.2.2 Dose-escalation:

The dose escalation rules are shown in Table 3.

Table 3 Dose Escalation Rules

Dose level	Betalutin and Lilotomab Dose (administered activity)	Pre-set dose escalation rules
1	10 MBq/kg + 60 mg/m^2 of lilotomab	Escalate dose when the third subject (or sixth subject in the case of 1 DLT) completes 8 weeks of follow-up after treatment, or when blood counts have recovered with ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L and no DLT occurred. The follow-up may get extended up to 12 weeks if a patient's platelets or neutrophils do not recover to grade 1 by 8 weeks.
2	10 MBq/kg + 100 mg/m^2 of lilotomab	Escalate dose when the third subject (or sixth subject in the case of 1 DLT) completes 8 weeks of follow-up after treatment, or when blood counts have recovered with ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L and no DLT occurred. The follow-up may get extended up to 12 weeks if a patient's platelets or neutrophils do not recover to grade 1 by 8 weeks. If more than 2 DLTs occur a dose reduction to 7.5MBq/kg will be considered only if the risk-benefit profile is considered likely to be favourable to the patients and if the safety review committee agree.
3	15 MBq/kg + 100 or 60 mg/m^2 of lilotomab	Escalate dose when the third subject (or sixth subject in the case of 1 DLT) completes 8 weeks of follow-up after treatment, or when blood counts have recovered with ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L and no DLT occurred. The follow-up may get extended up to 12 weeks if a patient's platelets or neutrophils do not recover to grade 1 by 8 weeks.
4	20 MBq/kg + 100 or 60 mg/m^2 of lilotomab	Maximum pre-determined dose to be tested.

An assessment of all available safety data at the time will be done prior to allowing the study to proceed to the next dose level. A report including an overall recommendation on the next step will be prepared. The final recommendation to move to the next dose level, as well as identification of the MTD for expansion will be done by the Safety Review Committee in the study.

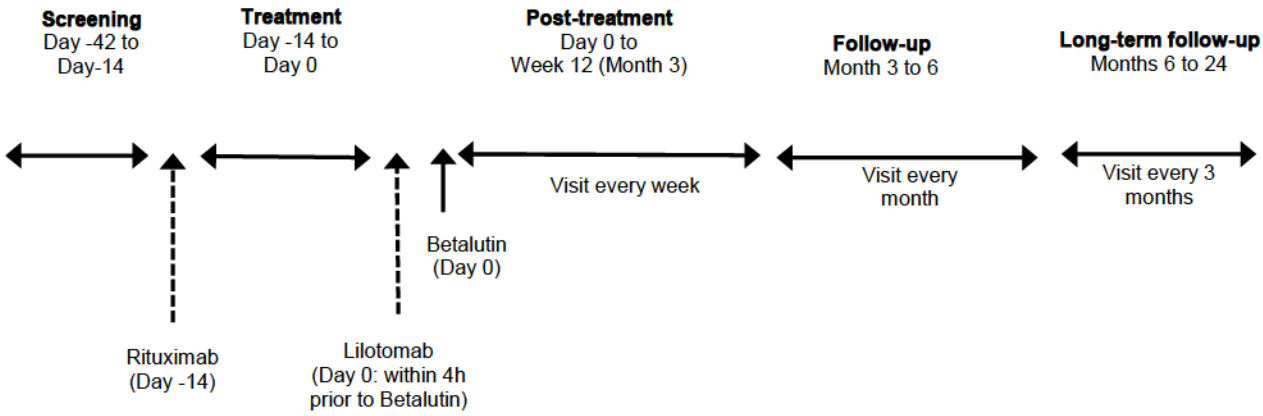
If additional radiation doses need to be explored, the Safety Review Committee will advise on the requirement for de-escalation or escalation of dose in smaller steps based on thorough evaluation of the available safety data.

The Safety Review Committee consists of at least three experts including the co-ordinating and principal investigators from ongoing Betalutin studies.

4.3 Schedule of Assessments

The study flow chart is shown in Figure 1 and the schedule of study assessments are shown in Table 4 and Table 5.

Figure 1 Study flow chart



Note that patients included in the pharmacokinetics, biodistribution and dosimetry sub-study will have additional visits during the first 3 weeks after Betalutin administration.
A visit window of ±2 days is permitted for Day 0 and Day -14. The bone marrow biopsy may have been taken up to 8 weeks prior to rituximab administration. The dose of radioactivity will be based on the actual administration date.

Patients considered suitable to be screened for the study will undergo screening assessments. Patients will attend the clinic on the dosing day and every week up to 12 weeks after Betalutin injection, however patients participating in the biodistribution and dosimetry sub study will be required to visit the hospital on days 1 to 4 as well. The patients will be followed up monthly until month 6 i.e. 6 months from Day 0 (day of Betalutin injection). On completion of the 6

months follow-up visit, patients will be followed up every 3 months to assess disease progression, survival, details of next treatment for DLBCL (where applicable), up to 24 months from Day 0. The patient will be withdrawn if further anticancer therapy is started.

4.4 Safety

In the treatment period (from the time of the first rituximab infusion up to Betalutin administration) and (the short term follow-up period up to 12 weeks after Betalutin administration) vital signs, physical examination, haematology and serum biochemistry, all AEs and concomitant medications will be collected at specified time points. During the long term follow-up period (from 12 weeks until 2 years), SAEs and AEs related to study drug, haematology, serum biochemistry, as well as any late toxicity such as second primary malignancies will be recorded every month during the first 6 months following study treatment and every 3 months thereafter, until the patient has been through his/her 2-year visit or until initiation of other cancer related treatment whichever occurs first.

4.5 Pharmacokinetics, biodistribution and dosimetry

Patients who participate in the PK, biodistribution and dosimetry sub study will have blood samples collected for radioactivity and antibody measurements at the following time points with reference to the lilotomab administration on Day 0: 0 (pre-dose), 5, 30, 60 and 120 minutes, and then at these time points following Betalutin administration: 0 (pre-dose), 15 minutes, 1, 2, 4 and 24 hours post-dose, plus Days 2, 3, 4, 7 (±1), 14 (±2) and 21 (±2).

These PK assessments are optional and performed at selected sites only.

The dosimetry and biodistribution sub-study will also include whole body gamma scans and single-photon emission computerized tomography (SPECT)/computed tomography (CT) scans at 2-4 and 24 hours, Day 4 and 7 after Betalutin treatment. Note that samples times may vary based on on-going analysis but will not exceed this maximum number of assessments. A Day 4 SPECT/CT scan is optional for patients not participating in the biodistribution sub-study. A window of ±1 day is permitted for the Day 4 SPECT/CT scan.

4.6 Efficacy

Positron-emission tomography (PET)/CT and contrast enhanced CT images will be performed at baseline, and at 3 and 6 months after Betalutin administration. Thereafter, contrast enhanced CT scan will be done every 6 months up to Month 24. Survival data will be recorded for all patients until the last patient has been through the 2-year follow-up period.

Table 4 Schedule of Study Assessments – see Section 4.7– Study Procedures by Visit

	Screening	Treatment Period			Short term follow-up										Long-term follow-up		Relapse	With-drawal
Day (D), Week (W) or Month (M)	D-42 to D-14	D-14	Baseline D-1 or D0[11]	Dosing day D0[11]	D4	D7 (W1)	D14 (W2)	D21 (W3)	D28 (W4)	W5,6,7	W8	W9, 10,11	W12 (M3)	M4,5,6	M9,12	M15, 18,21,24	Tests in addition to standard tests performed at visit when the relapse or withdrawal occurs	
Visit window		±2 d	Pre-Betalutin dose	Post-Betalutin dose	±1 d	±1 d	±2 d	±3 d	±3 d	±3 d	±3 d	±3 d	±2 w	±2 w	±2 w	±3 w		
Hospital visit	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Rituximab administration		X																
Lilotomab administration			X[1]															
Betalutin administration				X														
Informed consent	X																	
Demographics	X																	
Weight	X		X															
Disease staging, prior NHL treatments & medical history	X																	
Concomitant medication/ procedures	X	X	X	X		X	X	X	X	X	X	X	X	X[9]	X[9]	X[9]		
Physical examination	X		X			X	X	X	X	X	X	X	X	X	X	X		X
Lymph node examination	X		X						X		X		X	X	X			
Vital signs including temperature	X		X	X		X	X	X	X	X	X	X	X	X	X	X		X
12-lead ECG	X		X						X				X					
ECOG Performance Status	X		X						X		X		X	X	X	X		X
Haematology[2]	X		X			X	X	X	X	X	X	X	X	X	X	X		X
Serum biochemistry[2]	X		X			X	X	X	X	X	X	X	X	X	X	X		X
Urinalysis	X		X			X	X	X	X	X	X	X	X	X	X			
Serum pregnancy test	X		X															
HIV test	X																	
Hepatitis B test	X																	
Lymphocyte subset	X												X	X	X			
Immunoglobulin levels	X												X	X	X			
Immunogenicity	X[3]																	
CD37 expression	X																X[13]	
Bone marrow biopsy[12]	X																	
CT scan with contrast	X												X[5]	X[5]	X[5]	X[5]	X	
FDG/PET CT images	X												X	X[7]				
SPECT/CT scan[10]					X													
AEs (from start of first rituximab infusion)		X	X	X	X	X	X	X	X	X	X	X	X					
Adverse reaction only														X	X	X		
SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X					

	Screening	Treatment Period			Short term follow-up									Long-term follow-up		Relapse	Withdrawal
Day (D), Week (W) or Month (M)	D-42 to D-14	D-14	Baseline D-1 or D0[11]	Dosing day D0[11]	D4	D7 (W1)	D14 (W2)	D21 (W3)	D28 (W4)	W5,6,7	W8	W9, 10,11	W12 (M3)	M4,5,6	M9,12	M15, 18,21,24	Tests in addition to standard tests performed at visit when the relapse or withdrawal occurs	
Visit window		±2 d	Pre-Betalutin dose	Post-Betalutin dose	±1 d	±1 d	±2 d	±3 d	±3 d	±3 d	±3 d	±3 d	±2 w	±2 w	±2 w	±3 w		
FACT-LYM, QoL assessment	X												X		X[8]			
Survival status/disease progression/cancer-related medication and procedures														X	X	X		
Long-term toxicity														X	X	X		

(1) On Day 0, lilotomab is to be administered within 4 hours prior to Betalutin administration.
(2) At unscheduled visits, laboratory test results will be recorded in the eCRF.
(3) HAMA tested locally during screening where possible. Blood samples shipped to central laboratory for immunogenicity testing and biobanking. Performed at Month 3, 6 and 12
(4) Tumour tissue sample shipped to central laboratory, the test result is not required prior to enrolment.
(5) One CT scan at 3, 6, 12, 18 and 24 months.
(6) Month 12 only or if the patient withdraws prior to Month 12.
(7) FDG/PET month 6.
(8) Month 12 only.
(9) To be collected if Adverse reaction reported.
(10) Optional for those sites participating in the qualitative assessments.
(11) A visit window of ±2 days is permitted for Day 0 visit. The dose of radioactivity will be based on the actual administration date.
(12) A bone marrow biopsy taken up to 8 weeks prior to the administration of rituximab is permitted.
(13) Optional

Table 5 Schedule of study assessments for the pharmacokinetic, biodistribution and dosimetry sub-study

Day	Day -14	Day 0[4] (relative to lilotomab dosing)					Day 0[4] (relative to Betalutin dosing)					Day 1	Day 2	Day 3	Day 4	Day 7	Day 14	Day 21
	2 weeks prior to dosing	0 min (pre-dose)	5 min	30 min	1 hour	2 hours	0 min (pre-dose)	15 min	1 hour	2 hours	2-4 hours	24 hours	48 hours	72 hours	96 hours	168 hours	Week 2	Week 3
Visit window	±2 d															±1 d	±2 d	±2 d
Lilotomab PK analysis in blood[6]		X	X	X	X	X	X[1]	X	X	X	X[3]	X	X	X	X	X	X	X
Total Radioactivity in blood [6]							X[1]	X	X	X	X[3]	X	X		X	X	X	X
Urine collection[2]		From 0 to 2-4 hrs WB scan; from 2-4 hrs WB scan to 24 hours WB scan. First void collected separately.																
Serial whole body (WB) and SPECT/CT scan											X	X			X[5]	X		

In general, urine, blood samples and imaging for pharmacokinetic and biodistribution will be done until counts are no longer significant from background counts, and as long as the images are meaningful. The time points may be adjusted after experience from the first patients.

(1) One baseline blood sample before Betalutin injection.

(2) Urine collection when feasible

(3) Sample to be taken at 4 hours after Betalutin dosing.

(4) A visit window of ±2 days is permitted for Day 0. The dose of radioactivity will be based on the actual administration date.

(5) A window of ±1 day is permitted for the Day 4 whole body (WB) and SPECT/CT scan.

(6) lilotomab PK samples should be taken according to table above up to the time of Betalutin administration, at which point the sampling can be performed concurrently for both lilotomab PK and radioactivity in blood).

4.7 Study Procedures by Visit

Study assessments by visit are described below. Please also refer to the Schedule of Study Assessments in Table 4. The pharmacokinetics sub-study is described in Section 9.1 and the biodistribution sub-study is described in Section 9.2.

4.7.1 Pre-screening/screening (–42 to -14 days)

Informed consent including optional consent for fresh biopsy samples for biomarker and pharmacodynamic (PD) assessments.

Screening evaluations will be performed according to the eligibility criteria. Information will be collected regarding the number of patients who entered the screening phase but did not fulfil the inclusion and exclusion criteria together with the reasons for non-fulfilment.

The screening period is up to 28 days, defined from the start of screening to administration of rituximab. If screening assessments have been completed in less than 28 days treatment with rituximab can begin without delay.

If all screening procedures are not conducted and eligibility is not confirmed within 28 days prior to first dose of rituximab, the medical monitor should be contacted to determine if the screening procedures should be repeated prior to dosing.

- Informed consent.
- Demographic information.
- Concomitant medications and procedures.
- Previous treatments of NHLs.
- Medical history (to include DLBCL history).
- CD37 expression (the result of the assay is not required for enrolment into the study)
- Inclusion/exclusion checks.
- Clinical assessments including:
    - Full physical examination including lymph node examination.
    - Weight.
    - Vital signs.
    - Temperature.
    - 12-lead electrocardiography (ECG).
    - Eastern Cooperative Oncology Group (ECOG) performance status.

- Laboratory tests including: serum biochemistry; haematology; coagulation; urinalysis; lymphocyte subset, immunoglobulin, immunogenicity testing (local and central); hepatitis B test (HBsAg and anti-HBc), HIV test, serum pregnancy test (if applicable) and protein electrophoresis.
- CT scans with contrast medium.
- Fluorodeoxyglucose (FDG) PET/CT scan.
- Bone marrow biopsy (a biopsy taken up to 8 weeks prior to the administration of rituximab is permitted).
- FACT-LYM, QoL assessment

Serious Adverse Events (SAEs) with onset after obtaining informed consent.

4.7.2 Rituximab Administration (-14 days +/- 2 days)

An intravenous infusion of 375 mg/m^2 rituximab will be given 14 days prior to administration of Betalutin (Day -14) ±2 days.

- Premedication (see Section 6.1.2 for details).
- Rituximab administration (see Section 6.1.2 for details).
- Information about AEs after rituximab administration.
- Information about rituximab administration.
- Concomitant medication and procedures.

4.7.3 Pre-Betalutin assessments, lilotomab infusion and Betalutin administration (Day -1 or 0)

A visit window of ±2 days is permitted for the Day 0 visit. The dose of radioactivity will be based on the actual administration date.

For logistical reasons, the pre-Betalutin assessments may be conducted the day before administration of Betalutin (Day -1) or prior to Betalutin administration on Day 0.

- Clinical assessments including:
    - Full physical examination including lymph node examination.
    - Weight.
    - Vital signs.
    - Temperature.
    - ECG (resting 12-lead).
    - ECOG performance status.

- Clinical chemistry, haematology, urinalysis; the haematology results need to be clinically evaluated prior to Betalutin administration.
- Serum pregnancy test (if applicable).
- Any AEs before Betalutin administration.
- Concomitant medication and procedures.

4.7.3.1 Pre-dosing with lilotomab (Day 0)

An intravenous infusion of 60 mg/m^2 or 100 mg/m^2 lilotomab will be given within 4 hours prior to administration of Betalutin on Day 0.

4.7.3.2 Betalutin administration (Day 0)

- Biodistribution (sub-study).
- Information on study drug administration.

4.7.3.3 Post-Betalutin administration (Day 0)

- Vital signs and temperature, 2 hours after administration.
- Any AEs regardless of causality.
- Concomitant medication and procedures.

4.7.4 Post-Betalutin Assessments

4.7.4.1 To Month 3 (Week 12)

<u>At Weeks 1, 2, 3, 5, 6, 7, 9, 10 and 11 the following will be collected:</u>

- Physical examination.
- Vital signs and temperature.
- Haematology.
- Serum biochemistry.
- Urinalysis.
- AEs regardless of causality.
- Concomitant medication and procedures.

<u>At Month 1, 2 and 3 (Weeks 4, 8 and 12) the following will be performed:</u>

- Physical examination.

- Lymph node examination.
- Vital signs and temperature.
- ECOG performance status.
- Haematology.
- Serum biochemistry.
- Urinalysis.
- Immunogenicity, (Week 4 and 12 only)
- ECG (resting 12-lead) (Week 4 and 12 only)
- AEs regardless of causality.
- Concomitant medication and procedures.

In addition, the following will be measured and collected at Month 3 (Week 12):

- Blood samples for lymphocyte subset and immunoglobulin levels.
- CT scan with contrast medium of regions involved with lymphoma at screening and baseline.
- FDG PET/CT scan.
- FACT-LYM, QoL assessment.

4.7.4.2 **Months 4, 5 and 6**

- Patient status (survival), cause of death and date of death.
- Disease progression and any cancer related medication and procedures
- Clinical assessments including:
    - Physical examination.
    - Lymph node examination.
    - Vital signs.
    - Temperature.
    - ECOG performance status.
- Haematology.
- Serum biochemistry.
- Urinalysis.
- Lymphocyte subset.
- Immunoglobulin.

- Immunogenicity, (at month 6 only).
- CT scan with contrast medium of regions involved with lymphoma at baseline (at month 6 only).
- FDG PET/CT scan (at month 6 only).
- Possible long term toxicity.
- Treatment-related adverse reactions (ARs) only.

4.7.4.3 **Months 9 to 24**

The following information will be collected at 3-monthly visits until Month 24:

- Patient status (survival), cause of death and date of death.
- Disease progression and any cancer related medication and procedures
- Clinical assessments including:
    - Physical examination.
    - Lymph node examination (at months 9 and 12 only)
    - Vital signs.
    - Temperature.
    - ECOG performance status.
- Haematology.
- Urinalysis (at months 9 and 12 only)
- Lymphocyte subset analysis (at months 9 and 12 only)
- Immunoglobulin levels (at months 9 and 12 only)
- Serum biochemistry.
- Immunogenicity (at Month 12).
- Long term toxicity.
- Treatment-related adverse reactions (ARs) only.
- CT scan with contrast medium of regions involved with lymphoma at baseline (at Month 12, 18, and 24).
- FACT-LYM, QoL assessment (Month 12 only).

4.7.5 Withdrawal

- Clinical assessments including:
    - Physical examination.

- Vital signs.
- Temperature.
- ECOG performance status.

- Haematology.
- Serum biochemistry.

If a patient has failed to attend scheduled assessments in the study, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

4.7.6 Relapse

The following information will be collected at relapse:

- CT scan with contrast.
- Optional CD37 expression.

4.7.7 After Withdrawal

Patients who have withdrawn from the study will be contacted every 3 months for up to 2 years, to check their disease status and commencement of next anticancer treatment, if patient has agreed:

- Date of progression.
- Survival check.
- Details of next treatment for DLBCL and start date.

5 STUDY POPULATION

5.1 Inclusion Criteria

Eligible patients must meet the following criteria at the time of enrolment:

1. Male or female aged ≥18 years.
2. Histologically confirmed DLBCL (WHO classification).
3. Received at least one prior line of therapy including immuno-chemotherapy.
4. In first or subsequent relapse, or refractory to the last treatment (defined as less than a complete metabolic response to the last treatment, or disease progression within 6 months from the last treatment).

5. Not suitable for, or declined/unwilling to undergo intensive therapy, including high dose chemotherapy and autologous stem cell transplantation (ASCT). The decision of whether a patient is unsuitable or not for ASCT should be made by the investigator following a thorough review of the patient. For guidance, possible reasons patients may be unsuitable for ASCT may include but are not limited to; excessively elderly or frail patients, those with an increased bilirubin or creatinine level (to be eligible for this study patients must still meet inclusion criteria 11), low cardiac ejection fraction, forced expiratory volume in 1 second and/or lower than predicted carbon monoxide diffusion test.
6. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (at least one objectively bi-dimensionally measurable (nodal) lesion (>1.5 cm in its largest dimension by CT scan).
7. Negative human anti-mouse antibody (HAMA) test.
8. Life expectancy of at least 3 months.
9. Bone marrow tumour infiltration <25% tumour cells (in biopsy taken from a site not previously irradiated).
10. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.
11. Normal organ and marrow (normocellular) 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 ≤2.5 x upper limit of normal (ULN) (except patients with documented Gilbert's syndrome);
    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 ≤1.5 mg/dL or a creatinine clearance >60 mL/min;
    g. Normal coagulation parameters (elevated international normalized ratio (INR), prothrombin time or activated partial thromboplastin time (APTT) ≤1.3 ULN range acceptable).
12. Women of childbearing potential, defined as neither post-menopausal nor permanently sterile must agree to the contraceptive requirements below. Permanent sterilisation methods may include hysterectomy, bilateral salpingectomy and bilateral oophorectomy and postmenopausal is defined as no menses for 12 months without an alternative medical cause.

    Women of childbearing potential must:
    a. understand that the study medication may have a teratogenic risk

b. have a negative serum pregnancy test at screening and before Betalutin injection
c. commit to continued abstinence from heterosexual intercourse (excluding periodic abstinence or the withdrawal method) or begin two effective methods of birth control with a Pearl-Index ≤ 1%. 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 amenorrhoea. Apart from abstinence, effective methods of birth control are:
    - Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
        - oral
        - intravaginal
        - transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation
        - oral
        - injectable
        - implantable
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomised partner

13. Male patients must agree to use condoms during intercourse throughout study drug therapy and the following 12 months
14. Ability to give written, informed consent prior to any study-specific screening procedures, with the understanding that the consent may be withdrawn by the patient at any time without prejudice.
15. Capable of understanding the protocol requirements, is willing and able to comply with the study protocol procedures and has signed the informed consent document.
16. A negative Hepatitis B test during screening (HBsAg and anti-HBc) and negative HIV test during screening.

5.2 Exclusion Criteria

Eligible patients must not meet/have the following criteria:

1. Prior hematopoietic allogenic stem cell transplantation.
2. Prior autologous stem cell transplantation.
3. Previous total body irradiation.

4. Prior anti-lymphoma therapy (chemotherapy, immunotherapy or other investigational agent), excluding corticosteroids within 4 weeks prior to start of study treatment (i.e. rituximab) (G-CSF or GM-CSF are permitted up to 2 weeks prior to start of study treatment.).
5. Patients who are receiving any other investigational agents.
6. Patients with known or suspected central nervous system involvement of lymphoma.
7. 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. localized 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 complete remission;
8. Pregnant or breastfeeding women.
9. Exposure to another CD37 targeting drug.
10. Allergy to X ray contrast agents
11. A known hypersensitivity to rituximab, lilotomab, Betalutin or murine proteins or any excipient used in rituximab, lilotomab or Betalutin.
12. Has received a live attenuated vaccine within 30 days prior to enrolling in the study.
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.

5.3 Withdrawal and Termination Criteria

5.3.1 Patient Withdrawal

In accordance with the Declaration of Helsinki, each subject 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 co-operation.

Should a patient decide to withdraw after administration of the investigational product(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 Case Report Form (CRF). 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.

The Investigator may withdraw a patient from the study and discontinue study treatment and assessments at any time. Example reasons for discontinuing a patient from this study are:

- Disease progression.
- Other toxicities or events, unrelated to Betalutin, that would, in the Investigator's opinion, prevent the patient from continuing this trial.
- Protocol non-compliance. (All documentation concerning the patient must be as complete as possible. Withdrawals due to non-attendance of study visits must be followed-up by the Investigator to obtain the reason for where possible).
- Patient withdraws consent to participate in the study.

The Sponsor reserves the right to request the withdrawal of a patient due to protocol violation or other significant reason.

5.3.2 Procedures for Discontinuation

When a patient withdraws from the study, the reason for withdrawal should be sought where possible and recorded in the patient file and the electronic case report form (eCRF). Every effort will be made to complete the Final Study Visit.

5.3.3 Study Treatment Discontinuation

All patients enrolled into the study should receive their planned study medication including rituximab at Day -14 (+/- 2 days) and lilotomab on Day 0 and Betalutin unless one of the following occurs:

- A positive pregnancy test for female patients (see Section 7.10)
- A severe hypersensitivity reaction to rituximab, lilotomab or Betalutin.
- The patient experiences an AE prior to or during the administration of study medication which in the opinion of the investigator should result in study treatment discontinuation.
- Patient withdraws consent for further treatment (see Section 5.3.1).

All efforts should be made to continue to follow-up the patient if study treatment is discontinued (See Table 2).

5.3.4 Study or Site Termination

If the Sponsor or their representatives, Investigator, or Competent Authority (CA) discover conditions during the study that indicate that the study or site involvement should be terminated, this action may be taken after appropriate consultation with the Sponsor and the Investigator. Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, unacceptable risk to patients enrolled in the study.
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug.
- Difficulties in the recruitment of patients

Conditions that may warrant termination of a study site include, but are not limited to:

- Failure of an Investigator to comply with pertinent clinical trial regulations.
- Submission of knowingly false information from the research facility to the Sponsor, study monitor, or CA.
- Insufficient adherence to protocol requirements.

Study termination and follow-up will be performed in accordance with applicable local regulations.

6 TREATMENT PLAN

6.1 Investigational Medicinal Products

The IMPs, rituximab, lilotomab and Betalutin, can be administered on an outpatient basis. The patient should be under surveillance at the hospital for at least 2 hours after administration (unless local regulations require a longer surveillance period). Adequate resuscitation equipment needs to be available for patients in the event of an emergency.

A drug handling plan including supply, packaging, handling, storage, accountability, labelling, preparation and administration, will be given to the personnel prior to patient inclusion. See also Investigator's Brochure.

6.1.1 Betalutin

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

The total radioactivity of the Betalutin vial at the reference date will depend on the patient body weight. When administered on a day other than the reference day, the volume should be corrected according to the physical decay table included in the IMP manual.

6.1.1.1 Supply and packaging

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

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

Each vial should be used for one patient only.

6.1.1.2 Handling and storage

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

6.1.1.3 Preparation and administration

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

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

The syringe should be shielded to protect the operator from exposure to radiation during preparation and administration of the patient doses. Each patient will receive one dose in accordance with the treatment schedule. Betalutin will be given as a slow bolus injection. After administration, the equipment used in connection with the preparation and administration of drug, is to be treated as radioactive waste and should be disposed in accordance with hospital procedure for handling of radioactive material.

6.1.1.4 Drug accountability

The nuclear medicine specialist at the centre is responsible for drug accountability. The study drug should be kept in a secure place and must be administered only to patients in the study. An appointed individual is responsible for maintaining accurate records of the study drug. A list of study drug 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 for the handling of radioactive material, provided they have been stored for a minimum of 3 months (>10 half-lives for lutetium-177) before disposal.

6.1.1.5 Patient protection

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

6.1.2 Rituximab

Rituximab will be ordered through the standard procedure at the study centre. Patients will be pre-treated with rituximab delivered by infusion at a dose of 375 mg/m^2 14 days before Betalutin administration (Day -14 +/- 2 days).

The product should be administered according to the approved product information (prescribing information) for rituximab. Premedication consisting of an anti-pyretic and an antihistamine, e.g. paracetamol and dexchlorpheniramine or cetrizine, should always be administered before rituximab infusion. The types of pre-medication used prior to rituximab infusion will follow institutional guidelines, including any use of corticosteroids. The prepared rituximab solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus. The institutional guideline for infusion of rituximab will be followed. If an AE occurs the infusion will be stopped. When the symptoms have disappeared, the infusion will be re-started with 50% decreased infusion rate.

6.1.3 Lilotomab

Lilotomab will be supplied in vials containing lilotomab 5 mg/ml concentrate for solution for infusion and will be prepared aseptically at the institution and made ready for infusion using the same procedure as for rituximab. Pre-medication consisting of an antipyretic and antihistamine medication should be administered before infusion of lilotomab.

Lilotomab will be infused within 4 hours of the Betalutin administration. Lilotomab at a dose of 60 mg/m^2 or 100 mg/m^2 (up to a maximum of 2.7m^2) will be infused over 60 minutes. Body surface area should be calculated using the duBois calculation. The infusion rate may be adjusted depending on how well it is tolerated. If the patient experiences AEs as drop in blood pressure, chills, fever and dyspnoea the infusion will be stopped. When the symptoms disappear, the infusion will start again with 50% reduced infusion rate.

The patient will be under surveillance during infusion. Blood pressure and pulse rate are measured before infusion, each 15 minutes during infusion and about 1 hour after the end of infusion. Any AEs will be recorded in the eCRFs.

6.1.4 Investigational Product Complaints

Pharmaceutical technical complaints associated with the investigational product must be reported to the sponsor immediately. The same reporting timelines as for SAEs apply.

6.2 Treatment Allocation

A patient number will be assigned when a patient signs the informed consent form and is evaluated for inclusion into the study.

The Investigator will contact the CRA. after the completion of all the screening evaluations to confirm the patient eligibility

6.3 Permitted and Restricted Concomitant Medications/Treatments

All prescription, non-prescription, or over-the-counter medications including herbal remedies, dietary and nutritional supplements and complementary and alternative therapies given to or taken by the patient at study entry (including Screening) and during the study must be clearly documented on the eCRF.

Any medication considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator(s).

For treatment of DLT or any other clinically significant events, any available standard therapy may be used as required. In the case of anaemia, transfusions with packed red blood cells (pRBC) can be administered. See Section 6.5 (Supportive Care Guidelines) for further details.

Start of possible new cancer treatment after Betalutin administration will be recorded in the eCRF.

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

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

6.4 Pre-Medication Guidelines

Pre-medication guidelines may be introduced or recommended where clinically significant injection site reactions or other study-related events e.g. histamine release, are seen on study. These guidelines will be reviewed by the Safety Review Committee.

6.5 Supportive Care Guidelines

6.5.1 Severe thrombocytopenia (platelets <20x10^9/L)

Patients will be transfused with platelets to maintain a platelet count >20x10^9/L or higher if clinically indicated to control bleeding.

6.5.2 Injection site irritation

Local irritation at the injection site may be treated according to local treatment guidelines.

6.5.3 Persistent neutropenia (neutrophils/granulocytes <0.5x10^9/L) without fever

Patients with persistent neutropenia will be started on granulocyte-colony stimulating factor (G-CSF) 5 µg/kg/daily given subcutaneously until the neutrophil count has reached the local hospital's reference range.

6.5.4 Neutropenia with fever (neutrophils/granulocytes <1x10^9/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.

6.5.5 Severe anaemia (haemoglobin <8.0 g/dL)

Patients will be transfused with packed red cells to maintain haemoglobin level >8.0g/dL, at the discretion of the investigator.

6.5.6 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 rituximab, lilotomab or Betalutin.

6.5.7 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.

6.5.8 Precautions during administration of lilotomab:

Premedication should be given. The premedication should be the same as standard site specific premedication for rituximab administration.

If an adverse event occurs, such as drop in blood pressure, chills, fever and/or dyspnoea, 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.

The patient will be under surveillance during infusion. Blood pressure and pulse rate are measured before infusion, each 15 minutes during infusion and about 1 hour after the end of infusion. Temperature of the patient will be measured before and after infusion.

Medication and supportive care measures should always be available during an infusion.

For administration of rituximab, please refer to the product's Summary of Product Characteristics.

6.6 Treatment Compliance

Patients will receive infusions of rituximab in the ward under surveillance by trained personnel used to handle infusions with rituximab. The volume to be given will be prepared by the pharmacy and the infusion bags will be delivered to the ward as ready to use solutions.

Patients will receive the Betalutin treatment under supervision of a nuclear medicine specialist or licensed radiation oncologist. Site personnel will check the administration volume and total radioactivity injected and will record the activity dose and volume injected in the patient's source documents and eCRF.

7 SAFETY ASSESSMENTS

The following safety data will be collected and evaluated:

- AEs.
- Physical examination, including ECOG performance status.
- Lymph node examination.
- Vital signs (systolic/diastolic blood pressure, heart rate).
- Body temperature.
- 12-lead ECG.
- Laboratory variables.
- Immunogenicity assessment.
- Bone marrow biopsy.
- Long term toxicity.

The time points for assessments are shown in Table 4.

7.1 Adverse Events

7.1.1 Definitions

7.1.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence (i.e., any unfavourable and unintended sign) in a patient administered a medicinal product.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

7.1.1.2 Definition of Adverse Reaction

An AR is all untoward and unintended responses to an investigational medicinal product related to any dose administered.

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

7.1.1.3 Definition of Serious Adverse Event or Serious Adverse Reaction

An SAE or serious AR are any untoward medical occurrence or effect that at any dose:

- results in death;
- is life-threatening;
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- medically important, or
- is a congenital anomaly/birth defect.

Life-threatening in the definition of a SAE or serious AR 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/AR is serious in other situations. Important AEs/reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Hospitalization 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).

7.1.1.4 Definition of Unexpected Adverse Reaction

An unexpected AR is an AR of which the nature or severity is not consistent with the applicable product information (e.g., IB for an unapproved investigational product or summary of product characteristics for an authorized product). When the outcome of the AR is not consistent with the applicable product information this AR should be considered as unexpected.

7.1.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

All suspected ARs that are considered related to study drug 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 7.1.5.

7.1.1.6 Definition of Adverse Events of Special Interest (AESI)

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

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

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

7.1.2 Responsibility

7.1.2.1 Investigator's Responsibilities

The Investigator shall report all SAEs independent immediately (within 24 hours of the Investigator becoming aware of the event) to the Sponsor's representative except for those that the protocol or IB identifies as not requiring immediate reporting. The immediate report shall be followed by detailed written report(s).

AEs and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the Sponsor according to the reporting requirements and within the time periods specified in the protocol.

For reporting death of a patient, the Investigator shall supply the Sponsor and the Ethic committee with any additional information requested.

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

7.1.2.2 Sponsor's Responsibilities

The Sponsor is responsible for the ongoing safety evaluation of the investigational medicinal product.

The Sponsor is responsible for the prompt notification to all concerned Investigators, the ethics committees (ECs)/ Institutional Review Board (IRBs) and Regulatory 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 and the Code of Federal Regulations Title 21.

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 Regulatory 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 investigational medicinal product and/or concomitant therapy. The Sponsor will assess whether or not the AE is unexpected.

7.1.3 Assessments of Adverse Events: Seriousness, Causality, Severity and Expectedness

7.1.3.1 Seriousness

Seriousness will be determined according to the definition, see Section 7.1.13.

7.1.3.2 Causality

Causality will be determined based on the definition in Section 7.1.2 All AEs judged by the Investigator or the Sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as ARs. The Sponsor will not overrule the causality assessment given by the Investigator. If the Sponsor disagrees with the Investigator's causality assessment, both the opinion of the Investigator and the Sponsor will be provided with the report.

All toxicities/AEs will be graded according to CTCAE version 4. In the eCRF the Investigator's opinion of the relationship of the AE(s) to the investigational drug, will be categorized 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 test drug administration cannot be ruled out.

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

In addition to the Investigator's own description of the AE, each AE will be encoded by Sponsor's representative, according to a dictionary of medical codes (Medical Dictionary for Regulatory Activities [MedDRA]).

7.1.3.3 Severity

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

The severity of all events will be graded according to the CTCAE by the Investigator. For events not listed in the toxicity table, severity should be recorded as:

Grade 1: Mild AE: the event causes discomfort without disruption of normal daily activities.

Grade 2: Moderate AE: the event causes discomfort that affects normal daily activities.

Grade 3: Severe, undesirable or disabling AE: the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status and/or causes a substantial disruption of a person's ability to conduct normal life functions

Grade 4: Life-threatening or disabling AE: the patient was at risk of death at the time of the event or the event caused death.

Grade 5: Death related to AE

7.1.3.4 Expectedness

Expectedness is defined in Section 7.1.4 Reports have to be considered as unexpected if they add significant information on the specificity or severity of an expected AR. The expectedness

of an AE/AR will be determined by the Sponsor. The event is unexpected if it is not consistent with the applicable product information, i.e. the IB for Betalutin or the approved product information (prescribing information) for rituximab.

7.1.4 Reporting of Adverse Events Regardless of Causality

Any AEs that occur after patient has received study drug (i.e. after rituximab infusion) and within 12 weeks after study drug administration must be reported, whether or not considered related to the study drug. All AEs will be reported in the patient eCRFs provided. If more than one AE occurs, each event should be recorded separately. All AEs will be followed up until resolved or as clinically required.

AEs that occur from 12 weeks after study drug administration that are judged to be related to the study drug will be reported when they come to the Investigator's attention. Specific information about patient's possible diseases such as leukaemia, myelodysplastic syndrome and aplastic anaemia or any other secondary malignancy, will be collected up to 2 years after study drug administration or until further anticancer treatment is given, including information about treatment given to the patient due to NHL.

7.1.4.1 Death

Death is not defined as an AE but as an outcome of an AE. It is important that the event leading to the death is reported. It will be reported as an AE up to 12 weeks after Betalutin injection. Thereafter, death it will be collected in the eCRFs as survival information. It will be reported as outcome of an AR when it is judged as related to study drug.

7.1.4.2 Progression of disease

Progression of disease will not be recorded as an AE but captured on the tumour assessment form in the eCRF, unless it is clinical progressive disease then the symptom associated with clinical progressive disease will be recorded.

7.1.4.3 Adverse events due to rituximab injection

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

AEs may be reported spontaneously by the patient or elicited through open (non-leading) questioning during each visit to the centre 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 the CTCAE), relationship to treatment (unrelated, possible, probable), according to the need of other specific therapy, and outcome. All information will be recorded in the Adverse Event eCRF page.

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

7.1.5 Reporting of Serious Adverse Events

SAEs will be reported in the following time periods:

- SAEs will be collected from signing the informed consent to ensure that any protocol-related SAEs are collected and up to 12 weeks after the last injection of the study drug, whether or not considered related to the study drug.
- Any SAE that occurs after 12 weeks from the last injection of the study drug when it comes to the Investigator's attention and is judged to be related to the subject's participation in the study or related to the treatment.

All SAEs must be reported to Sponsor's representative as follows:

Within 24 hours of discovery of the event the SAE form should be completed and forwarded by fax or e-mail to the sponsors representative.

The SAE must be documented in the hospital records.

It is the responsibility of the investigator to follow up on all SAEs until the patient is recovered, stabilized or recovered with sequelae and to provide the information using the same procedures and timelines as those for the initial report.

It is important to send "as complete as possible" report. 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. Follow-up information may qualify for new assessments in case of SUSAR it might be both degraded to SAE and upgraded to SUSAR depending on the information given. The SAE/SUSAR will be evaluated by the sponsor. The Safety Review Committee will review safety data and SUSARs regularly.

The Sponsor or assigned designee is responsible for reporting all the relevant safety information to the regulatory authorities and to the IRB/ECs concerned. Where applicable as per local requirements, the Investigator will inform the IRB/EC and/or the regulatory authority of the SAE.

Sponsor will inform all Investigators concerned of relevant information about **SUSAR**s.

7.2 Physical Examination

An abbreviated physical examination consisting of the heart, lung, abdomen, skin, oral cavity, general and other significant findings will be performed at the time points specified in the Schedule of Study Assessments in Table 4.

A physical examination consisting of palpation of the lymph nodes will be performed at certain time points.

Any physical examination findings that are 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.

7.3 Bone Marrow Biopsy

Bone marrow biopsy will be taken from a site not previously irradiated at screening to ensure less than 25% tumour cells in the marrow.

7.4 ECOG Performance Status

The Investigator will also assess the ECOG performance status at time points shown in the Schedule of Study Assessments (Table 4). ECOG performance status will be classified as shown in Table 6.

Table 6 Classification 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 selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

From Oken et al., 1982 (43).

Performance status response and progression will be evaluated as:

- Improvement or worsening, respectively, by 1-point or more on the ECOG scale from the baseline value.

7.5 Vital Signs

Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate and body temperature) will be measured as described in the Schedule of Study Assessments (Table 4) after the patient has been resting supine for a minimum of 5 minutes. On the day of Betalutin administration, vital signs will be assessed pre-dose and up to 2 hours after the Betalutin injection. Patient status will be monitored during Betalutin administration and repeat vital signs will be taken if needed. Measurement of blood pressure will be done on the arm contralateral to the site of investigational product administration, and the exact blood pressure recorded e.g. it should not be rounded to the nearest 5 mmHg.

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. Abnormalities in vital signs may be AEs/SAEs. 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 CRF page. Any notable abnormal vital signs, finding or related AE must be followed until outcome is known.

7.6 12-lead ECG

12-lead ECG will be obtained at screening as noted in the Schedule of Assessments (Table 4) during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. A 12-lead ECG will be performed by qualified personnel at the site after at least a five-minute rest with the subject in a semi-recumbent or supine position.

All efforts should be made to ensure that an identical ECG machine is used to collect traces for individual patients. If any clinically significant findings are observed on the ECG, the Investigator will record it as part of the medical history prior to start of dosing and as an AE post-dose, where the finding represent a clinically significant change from baseline.

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

7.7 Clinical Laboratory Parameters

Blood and urine samples for determination of clinical chemistry, haematology, coagulation and urinalysis parameters will be taken at the times shown in the Schedule of Study Assessments (Table 4) and as clinically indicated. The date and time of collection will be recorded in the source data and on the eCRF.

Clinical chemistry, haematology, coagulation analysis and urinalysis will be performed at each site's local laboratory or other local laboratories as appropriate. The approximate blood volumes for clinical chemistry and haematology (including coagulation) testing are 3.5 mL and 4 mL, respectively.

Copies of laboratory accreditation certificates and reference ranges will be provided prior to the analysis of the first patient sample.

The local laboratory parameters to be measured are shown in Table 7.

Table 7 Laboratory parameters

Clinical chemistry	**Haematology, including coagulation screen**
Calcium	Red blood cell count
Albumin	Haemoglobin
Bilirubin, total	Haematocrit
Alanine transaminase (ALT, ALAT, SGPT)	Absolute reticulocyte count
Aspartate transaminase (AST, ASAT, SGOT)	Platelet count
Alkaline phosphatase (total ALP)	White blood cells count
Glucose (random)	Leucocyte differential count
Lactate dehydrogenase (LDH)	Neutrophils
Gamma glutamyl transferase (GGT)	Lymphocytes
Sodium	Monocytes
Potassium	Eosinophils
Magnesium	Basophils
Urea (BUN)	Activated partial thromboplastin time (APTT)*
Creatinine	International normalized ratio (INR) or prothrombin time*
Uric acid	Lymphocyte subsets**
Pregnancy test as required	
Protein electrophoresis*	
Quantitative serum immunoglobulins**	
Human anti-mouse antibody (HAMA)*	
Hepatitis B test (HBsAg and anti-HBc)*	
HIV test	
Urinalysis	
Glucose	
Protein	
Bilirubin	
Ketones	
Blood	
pH	
Specific gravity & microscopic examination when indicated	

* At screening only; ** At certain time points specified in the Schedule of Assessments (Table 4).

Reference ranges from the site laboratory will be provided to Sponsor's delegate. If during the study, ranges should be changed, the Investigator is requested to provide updated laboratory normal values.

Each parameter will be evaluated whether it is significant or not. When the CTC AE grade exists for a parameter, the grade should be recorded in the eCRF.

Laboratory values outside reference range recorded in the CTCAE, will be graded 1 to 5 according to the CTCAE criteria Laboratory values with CTCAE grade 3 or higher have to be reported as an AE. The laboratory values might be an SAE in accordance to the SAE definition. During the long term follow-up period only changes in laboratory values judged to be related to the study drug will be reported.

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.

Approximate volume of blood to be drawn from each patient

The total volume of blood that will be drawn from each patient in this study will vary depending on how long the patient stays in the study. Table 8 indicates the range for patients during the initial assessment period to Week 12.

Table 8 Approximate volume of blood to be drawn from each patient during the initial assessment period to Week 12

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Serum biochemistry/haematology/lymphocytes subset	7	Max 14	98
Immunogenicity	9	4	36
Immunoglobulin levels	5	1	5
Total (maximum volume to be drawn)			139

Max = maximum number of samples to be taken.

Additional blood will be taken for the patients included in the pharmacokinetic sub-study.

7.8 Immunogenicity Assessment ~~(~~HAMA~~)~~

Blood samples will be obtained at the times shown in the Schedule of Study Assessments (Table 4) for the assessment of immunogenicity

Approximately 9 mL of blood will be collected at each time point for preparation of serum samples. Full instructions for sample preparation, handling procedures, aliquoting of samples, storage and shipping of these serum samples will be provided in the Laboratory Manual for this study. At screening only, HAMA test can be obtained by local assessment for eligibility

confirmation purposes and in parallel submitted to central laboratory per Laboratory Manual. HAMA will be measured by ImmunSTRIP HAMA IgG, an ELISA test system for human antibodies to mouse IgG. In addition, patient blood samples will be biobanked under appropriate storage conditions, for further immunogenicity assessments to monitor the full spectrum of the ADA response after dosing with lilotomab and Betalutin. These additional assessments will be performed at a central laboratory.

There has been no report of development of a HAMA response for patients included so far in cohorts 1-3 of this Study (See Table 9).

Table 9 Monitoring of the HAMA response in LYMRIT 37-05

Subject ID	Cohort	Lilotomab dose	Betalutin dose	Month 1	Month 3	Month 6	Month 12
7240081001	1	60 mg/m^2	10 MBq/kg	Negative	Negative	NA	NA
8260021002	1	60 mg/m^2	10 MBq/kg	Negative	NA	NA	NA
8260021003	1	60 mg/m^2	10 MBq/kg	NA	NA	NA	NA
8400072006	2	100 mg/m^2	10 MBq/kg	Negative	Negative	NA	NA
8260012007	2	100 mg/m^2	10 MBq/kg	ND	ND	NA	NA
3800042008	2	100 mg/m^2	10 MBq/kg	NA	NA	NA	NA
7240083002	3	100 mg/m^2	15 MBq/kg	Negative	Negative	NA	NA
8260023003	3	100 mg/m^2	15 MBq/kg	ND	NA	NA	NA
7240083006	3	100 mg/m^2	15 MBq/kg	NA	NA	NA	NA

NA: Not applicable, patient withdrawn; ND: Not done; A negative result is considered in the range of 0-74 ng/ml (all negative results reported in the table above resulted as <6 ng/ml and were therefore considered negative).

7.9 Potential Long Term Toxicity

At the follow-up visits the Investigator will follow the patients closely to examine if they suffered from any new primary cancers and bone marrow changes (acute myelogenous leukaemia, myelodysplastic syndrome, and aplastic anaemia). In addition, physical examination will be performed and blood samples for haematology and biochemistry taken.

7.10 Pregnancy

In principle, pregnancy and the lactation period, are exclusion criteria for clinical studies involving investigational drugs. In the event of a pregnancy occurring during the course of this study, Nordic Nanovector must be notified immediately. If the pregnancy involves a patient

enrolled to the trial, the patient should be immediately withdrawn from study. The pregnant patient or the patient's partner should be followed-up during the entire course of the pregnancy and postpartum period.

Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. Off-spring should be followed up for at least 8 weeks after delivery. Longer observation periods may be determined by the sponsor if an adverse outcome of the pregnancy was observed.

Pregnancies occurring during the study up to 90 days after final dose of IMP must be reported to the sponsor's represent within one working day of becoming aware of them using a Clinical Trial Pregnancy Reporting Form. A pregnancy is not a SAE unless the outcome of the pregnancy meets serious criteria as defined in Section 7.1.5. When a "pregnancy is detected without an adverse outcome", the Investigator should complete the Pregnancy Form and send this to the sponsor's safety department as per the above. It should be clearly stated that no AE was observed. If the outcome of the pregnancy meets the criteria of a SAE (i.e. congenital anomaly, stillbirth, neonatal death), then it should be reported as described in Section 7.1.5.

7.11 Misuse and overdose

Drug misuse and drug overdose should be reported in the same format and within the same timelines as an SAE even if they may not result in an adverse outcome. For monitoring purposes, any case of overdose must be reported on an overdose form. When an "overdose" of the investigational product occurs without an AE, the Investigator should complete the Overdose Form and send this to the sponsor's represent. It should be clearly stated that no AE occurred. If the pharmacy discovers that an overdose has or may have been administered they should contact the Investigator and study coordinator.

8 EFFICACY ASSESSMENTS

8.1 Tumour Response

Contrast enhanced CT and PET/CT scans will be evaluated at the study centre(s). Tumour response and progression will be evaluated by use of the Cheson 2014 criteria (1).

8.1.1 Contrast Enhanced CT Examination

Baseline CT image must be taken within 4 weeks prior to rituximab infusion. The schedule of assessments (Table 4) shows the frequency of CT examinations per patient.

A CT volume scan re-constructed in 3 mm slices with use of intravenously injected contrast agent will be performed per examination. The target lesions will be selected and measured at baseline and followed at each efficacy assessment. The longest perpendicular diameters (major and minor axis) will be recorded in the eCRF.

8.1.2 PET/CT Examination

PET should be performed along with low dose non-diagnostic CT (PET/CT) for anatomic co-registration and attenuation correction. PET/CT scan will be done at baseline, 3 (Week 12) and 6 months after Betalutin administration for all patients. Baseline imaging should be done within 4 weeks prior to administration rituximab 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 FDG. Anti-diabetic drugs cannot be taken on the day of PET/CT examination.

PET/CT examination will be performed by a commercial combined PET/CT scanner. All scans should be performed on the same camera. PET/CT imaging will be performed about 60 to 70 minutes after intravenous administration of 5-10 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 when both modalities are to be done on the same day.

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

Guidelines for baseline CT examination:

1) Target lesions on the CT scans do not need to match those evaluated on the PET scan
2) Target lesions should be chosen according to Cheson criteria, 2014
3) Approximately 6 target lesions should be selected; there must be at least one target lesion
4) The largest target lesions should be selected
5) Lesions should be from disparate regions of the body if possible
6) Mediastinal and peritoneal lesions should be included in target lesions
7) None of the lesions should be < 10 mm

Guidelines for baseline PET examination:

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

Deauville criteria - PET/CT scoring

PET scans are scored on a 5 point scale, and follow-up will be assessed as described beneath. In addition, SUV max will be recorded. Further details will be described in the imaging manual.

Images will be evaluated and scored according to a 5-point scale (Table 10).

Table 10 Uptake score with the use of Deauville criteria

Negative	Positive
1. no uptake	4. moderately increased uptake compared to liver at any site
2. uptake ≤ mediastinum*	5. markedly increased uptake compared to liver at any site, new sites of involvement
3. uptake > mediastinum but ≤ liver*	X. new areas of uptake unlikely to be related to lymphoma

*Mediastinal and liver uptake is defined as SUVmax +/-10%.; Binary response scale for extranodal involvement yes/no or +/-: 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).

8.1.3 Overall Tumour Response Evaluation

The Cheson criteria, 2014 (1) are a combined score taking into consideration, positive or negative scored PET scan, the contrast enhanced CT images and bone marrow biopsies when available (see Table 11).

Table 11 Overall tumour response evaluation

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS†. It is recognized 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† with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm 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-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 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 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 target nodes/nodal masses Extranodal lesions	Score 4 or 5 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	PPD progression 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 preexisting non-measured lesions

Response and Site	PET-CT-Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g. infection, inflammation). If uncertain regarding etiology 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

From Cheson et al. (1)
Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.
*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal, and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g. liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g. GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (e.g. with marrow activation as a result of chemotherapy or myeloid growth factors).
†PET 5PS: 1, no uptake above background; 2, ≤ uptake mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Overall Response Rate (ORR)

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

Best ORR will also be evaluated, taking the best response rate achieved independent of time point for image evaluation.

Duration of Response will be evaluated and is defined as the time from when the response criteria are met to the time of relapse or progression.

Progression free survival (PFS)

Defined as the interval from Betalutin administration to date of

- relapse (new or enlarged lesions after CR);

- progression (new or enlarged lesions after PR or SD), or
- death from any cause.

If none of the above events are observed, PFS will be censored at the date of the last assessment (i.e. last CT scan).

Overall survival (OS), defined as the duration in weeks from the date of study entry until the date of death of any cause. Patients lost to follow-up are censored at the last date they were known to be alive. Patients still alive are censored at the last known date alive as captured in the survival follow-up.

8.2 Clinical Benefit

Clinical benefit endpoints include:

- Performance status defined as improvement or worsening, respectively, by 1-point or more on the ECOG scale from the baseline value (see Section 7.4).

The Investigator will assess the ECOG performance status at time points shown in the Schedule of Study Assessments (Table 4). The patient will be asked to complete the FACT-LYM questionnaire at time points shown in the Schedule of Study Assessments (Table 4).

8.3 Quality of Life

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

9 PHARMACOKINETICS, BIODISTRIBUTION AND DOSIMETRY

A separate pharmacokinetics, biodistribution and dosimetry manual will be prepared prior to study start, summarizing the necessary information regarding the equipment, acquisition, image processing and dosimetry.

9.1 Pharmacokinetics

Adaption of the sampling times may be necessary based on the results. The radioactivity in whole blood will be determined from each sample at the study centre if a gamma counter is available, otherwise samples will be shipped to a central laboratory assessment. The raw data print outs will be saved in the Trial Master File (TMF). Sampling times will be recorded in the eCRF

9.1.1 Blood clearance

A few patients at selected sites will participate in a biodistribution sub-study and will have blood samples collected and measured for

- total radioactivity (or total payload) in peripheral blood to measure the total radioactivity per ml and to assess the presence of Betalutin, ^{177}Lu-satetraxetan chelate, ^{177}Lu-DTPA chelate and ^{177}Lu
- total lilotomab antibodies in serum by quantitatively determining levels of total circulating antibodies (lilotomab, lilotomab satetraxetan, and Betalutin)

Measurements at the following time points after the lilotomab administration on Day 0: 0 (pre-dose), 5, 30, 60 and 120 minutes, and then at these time points following Betalutin administration: 0 (pre-dose), 15 minutes, 1, 2, 4 and 24 hours post-dose, plus Days 2, 3, 4, 7 (±1), 14 (±2) and 21 (±2). The time points mentioned are approximate time points. The exact time point the sample is taken need to be recorded in the eCRF.

9.1.2 Urine clearance

Every effort should be made to collect urine during the first 24 hours after Betalutin injection. The first void should be collected separately, and then from 0 to 2-4 hours to the whole body (WB) scan and from 2-4 hours WB scan to 24 hours WB scan (see Table 5).

9.2 Biodistribution and Dosimetry

The purpose of the biodistribution and dosimetry study is to provide estimates for the absorbed dose delivered to normal body structures as well as to tumours that can be identified in the images. In order to perform such estimates, it is necessary to measure, in absolute terms, organ/tissue activity at different time points after injection. Such time series enable one to estimate the cumulated activity in each organ displaying uptake.

The injected activity of Betalutin will be measured by an activity calibrator at the study center.

A SPECT/CT scanner with two heads equipped with medium energy collimators should be used. This equipment will be used for CT, SPECT and planar whole body scanning. Lutetium-177 emits two photons suitable for imaging, with energy peaks at 113 keV and 208 keV (6% and 10.4% per disintegration respectively). Both windows are acquired, and two sets of reconstructions are made; one for visual interpretation (combined energy window) and one for dosimetry (single 208keV window).

The primary method of estimating the cumulated activity in a source organ is using planar WB images at several time points to determine the biokinetics for source organs, combined with SPECT/CT acquisitions for quantification. SPECT/CT obtained activity estimates are used to normalize planar WB activity estimates at different imaging time points.

The intention is to use planar scans as the basic means for following the activity as a function of time for selected organs, and SPECT studies for 3D delineations. Serial planar WB scans will be obtained at ~2-4 hours on Day 0 and on Days 1, 4 and 7, including SPECT/CT images at Days 0, 1, 4 and 7 if sites have the equipment and experience to perform WB scans. At sites not participating in the biodistribution sub-study, a Day 4 SPECT/CT scan is optional. A visit window of ±1 day is permitted for the Day 4 SPECT/CT scan.

For the full details of the dosimetry sub-study please refer to the Dosimetry protocol.

10 BIOMARKER AND PHARMACODYNAMIC ASSESSMENTS

10.1 Archived Biopsy

Patients with available archived tumour biopsy will be asked to provide consent for access to some of this sample, alternatively a fresh sample is required for CD37 analysis. The result of the assay is not required for enrolment into the study. A sample will be biobanked for future analysis of DNA, RNA, protein and other biomarkers.

10.2 Fresh Biopsy

All patients will be asked to provide consent for access to archived tumour tissue where available, and for sending samples to a centralised lab for CD37 analysis. If needed, fresh biopsies will be taken pre-dose where informed consent has been given. A sample will be biobanked for future analysis of DNA, RNA, protein and other biomarkers.

11 STATISTICAL METHODS AND PLANNED ANALYSES

11.1 Sample Size

The purpose of this study is to escalate dosing of lilotomab and/or Betalutin to achieve a maximum tolerated dose for future studies in relapsed/refractory DLBCL. Using the 3+3 design, it is possible that as many as 24 subjects will be treated and assessed during the escalation phase. Approximately 50% of these patients are expected to have relapsed > 6 months after their last line of therapy, and the remaining 50% are anticipated to be refractory to their last line of therapy. Because there is some expectation that non-refractory relapsed patients may benefit more from this treatment regimen, it is desirable to have sufficient numbers in both patient subgroups to allow for adequate estimation of ORR. Since the DLT is not anticipated to be different in the subgroups, an attempt to balance will occur in the expansion phase for the recommended dosing regimen, by enrolling 10 relapsed patients, not refractory to last treatment and 10 patients refractory to last therapy. The final total should target approximately 40 patients treated with approximately 20 treated from each subgroup.

11.2 Analysis Populations

Two populations will be used for analysis, the safety population and the evaluable population, as defined below:

Safety population: All patients who receive rituximab.

Evaluable population: All patients who receive Betalutin and have at least one post-baseline assessment of disease response.

11.3 End of Study and Study Completion

"End of Study" for the purpose of locking the database and generating the main clinical study report (CSR) will be defined as last follow-up Month 6 study assessment (with a Final Study Visit for those patients who have withdrawn from the study prior to Month 6). "Study Completion" will be defined as the point when all patients have had the opportunity to be followed up for up to 2 years from Day 0. Additional data from the patient(s) continuing to be followed up after Month 6 will be presented as an Addendum to the CSR upon reaching the Study Completion.

11.4 Database lock

The clinical database lock will occur after all data are reconciled (i.e. "cleaned") for all patients who participate in the study. A single CSR will be generated for this study consisting of a report on patient follow-up to Month 6, plus an addendum to this report to describe long-term follow-up. The Statistical Analysis Plan (SAP) will be finalized and signed before the database lock for the main CSR.

11.5 Statistical Considerations

Detailed statistical analysis information will be provided separately in the Statistical Analysis Plan (SAP). The SAP will detail all data handling rules, including the management of missing values and the handling of data for withdrawn patients. The SAP will also outline protocol violation criteria along with any specific analysis population definitions. Any deviations to the planned analyses specified or populations defined within the SAP will be justified in writing and presented within the final CSR.

There will be no formal statistical analysis. Data will be summarized using descriptive statistics.

11.5.1 Analysis of Demographic and Pre-treatment Characteristics

Demographic data and other pre-treatment characteristics (including medical history, disease-related characteristics and prior anti-cancer therapies) will be summarized using descriptive

statistics. Administration of the investigational medicinal products (Betalutin, lilotomab and rituximab) will be listed by patient and summarized.

11.5.2 Analysis of Safety Data

All safety and tolerability assessments will be based on the safety analysis set, which is defined as all patients who have received at least one dose of rituximab.

Safety parameters (see Section 7) will be summarized using descriptive statistics. Categorical data will be presented as percentages and frequency tabulations. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance. The number of subjects reporting AEs, and the number of AEs reported will be presented. AEs will be coded using MedDRA. The events will be tabulated by body system, preferred term, intensity, CTCAE grading, severity and relationship to study medication. Duration of AEs will also be tabulated. SAEs and AEs leading to withdrawal will be presented in separate tabulations.

For laboratory data, in addition to summary statistics, the number of abnormal and clinically significant observations will be tabulated by time of measurement. The laboratory values will also be graded according to toxicity graded as CTCAE.

Toxicity will be graded using CTCAE v4.0 and reported for all AEs.

11.5.3 Analysis of Tumour Response

Tumour assessment will follow the response criteria for malignant lymphoma according to Cheson et al, 2014 (1).

Anti-tumour and clinical benefit variables will be summarized descriptively. Where appropriate, variables will be presented in terms of absolute and relative change from baseline. Categorical data will be presented as percentages and frequency tabulations. Response rates (such as PFS and CR) will be presented as point estimates with 95% CIs. Time to event endpoints such as PFS will be presented in Kaplan-Meier graphs along with the median time to event with 95% CIs.

11.5.4 Pharmacokinetic, Biodistribution and Dosimetry Analysis

Data will be listed by patient, dose level and time point using descriptive statistics, as appropriate. Individual PK data will be tabulated and PK assessments vs. time curves presented. The following PK parameters will be determined using non-compartmental analyses: Cmax, Tmax, area under curve (AUC), clearance, apparent volume of distribution and half-life. Additional PK parameters may be calculated as appropriate.

A separate manual will be made available for the biodistribution and dosimetry handling and analysis of data. A separate study report will be written for this sub-study.

11.5.5 Handling of Drop-outs and/or Missing Data

No missing data will be estimated.

11.5.6 Sub-group Analysis

No formal sub-group analyses are planned. Data for the relapsed and refractory patients will be summarized separately using descriptive statistics.

12 DATA HANDLING

12.1 Patient Data Protection

Patient number will identify the patients in the eCRF.

The Investigator is responsible for keeping a list of all enrolled patients including patient numbers, full names and date of birth. In addition, the Investigator will prepare a list of patients who were screened for participation of the study but were not enrolled and the reason for non-eligibility. A note will be made in the hospital medical records that the subject is participating in a clinical study. The patients' written informed consent forms will be kept at the hospital in strict confidence.

The patients will be informed in writing that the results will be stored and analysed electronically according to national laws, as applicable, and that patient confidentiality will be maintained.

The patients will also be informed in writing about the need for source data verification (SDV), audits and inspections. The audit/inspection and SDV will be performed by at least one of the following parties; authorized representatives of the Sponsor, authorized monitors, hospital IRB/ECs or regulatory authority. In these cases, a relevant part of the patient records will be required and reviewed.

In accordance with the General Data Protection Regulation (GDPR), the patient will be informed of the following:

- Nordic Nanovector ASA is responsible their personal data collected as a participant in this clinical trial or study.
- The personal data collected as part this study may be kept for 25 years in accordance with clinical trial rules.
- The use of their personal data for the purposes described in the informed consent form is based on their consent, legal requirements that cover the conduct of research studies and public interest.
- If the patient previously agreed that his/her personal data may be used for other scientific purposes that are additional to the study, they may have a right to object to

the use of their personal data for this additional research for reasons specific to them. If they wish to object to such use, to contact their study doctor or Data Protection Officer at the study site.
- The patient can ask to see the information that has been collected about them or ask that we send their personal data to another person or company. If they think any of the information is incorrect, they can ask their study doctor in writing if it can be changed or removed. If they change their mind about taking part, we will not collect any further personal data from them. However, we are not able remove the personal data that was collected for this research study before they stopped. They can also ask that we restrict the use of your personal data.
- If the patient has questions about how we use their personal data or wish to exercise any of their rights, they will be asked to contact their study doctor or Data Protection Officer at the study site. If they are not happy with the response they receive, the patient may make a complaint to their local data protection authority.

12.2 Electronic Case Report Forms (eCRFs)

All data will be collected using an eCRF within a fully validated and CFR 21 Part 11 compliant Electronic Data Capture (EDC) system. All data will be entered into the CRF by the Site Staff. These data will then be source data verified and reviewed by the study monitor before data cleaning by Data Management is performed. All queries will be raised and resolved within the EDC system. During entry programmatic checking of the data will be performed and once saved into the database more complex programmatic checks will also be performed. During the conduct of the study all system users will have real time access to the data, the level of access to the data and study privileges will be determined by their user role.

After all queries have been resolved, the SAP approved and signed, and any summary/analysis populations approved, the database will be locked, and the data released for summary and analysis.

12.3 Data Management

Data management will be carried out as described in the sponsor's subcontractor's Standard Operating Procedure (SOPs) for clinical studies.

All eCRFs will be entered electronically by site staff into a validated database. Data entry will be SDV by a sponsor representative. Comprehensive edit checks will be used to clean the data, and data queries will be generated and resolved by the investigator(s) or assigned designee. Patient data will be entered continuously. All changes to the data and the database structure will be recorded in an audit trail.

All changes to the data and the database structure will be fully audit trailed either electronically within the clinical database or via a paper trail.

Data queries will be generated at data entry or if questions arise during the data validation or detected during a manual review (safety data). The queries are entered into the eCRF and resolved according to the electronic data capture manual.

AEs and SAEs will be handled in the same way as the other data reported in the eCRF. However, in addition the SAEs will be coded and medical assessed for reporting to authorities according to national regulatory requirements. Before the database is locked (i.e. Clean File declared), reconciliation of the data will be performed. Coding of AEs and medical history will be performed according to MedDRA and coding of concomitant medications will be performed according to WHO-Drug dictionary.

A quality check of a random sample of the data will be performed to ensure that the consistency between the database and the eCRFs are at least on the pre-defined level described in SOPs of the sponsor's subcontractor and in the data validation plan.

Clean File will be declared when all data has been entered, the data entry verified, the data validated, and the database defined as clean by the Clinical Data Manager. After declaration of Clean File, the data will be exported from the database to SAS datasets and both the database and the SAS datasets will be locked and protected from changes. Subsequently then the inclusion of patients into the three analysis sets will be done in such a way that it is ensured that all rules have been applied equally on all patients. All statistical analyses will be performed on the locked SAS-datasets.

12.4 Retention of Documents

The following information must be retained for at least 5 years after completion or discontinuation of the study or longer if required by local regulations. If the data from this study is used to support a marketing authorisation the data must be retained for at least 15 years after completion or discontinuation of the trial or for at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region; or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product: source data, source documents, eCRFs, protocol and amendments, drug accountability forms, correspondence, subject identification list, informed consent forms, and any other essential documents.

It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained according to ICH guidelines [Good Clinical Practice (GCP)]. The eCRFs will be archived by the Sponsor for the lifetime of the product. No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. In accordance with data protection legislation, the subject identification list should be destroyed when it is no longer needed. Should the Investigator wish to assign the study

records to another party or move them to another location, advance written notice should be given to the Sponsor.

13 SPECIAL REQUIREMENTS AND PROCEDURES

13.1 Independent Ethics Committee/Institutional Review Board

The study protocol, including the patient information and informed consent to be used, must be approved by the centre's IEC, IRB and/or regional Ethics Committee (EC). A written approval must be obtained before enrolment of any patients into the study. It is the responsibility of the Investigator to supply the sponsor with a copy of the members of the hospital IEC, IRB or regional EC and the Letter of Approval defining the version of each document approved.

The investigator will ensure that this study is conducted in accordance with ICH GCP, Seoul (2008) amendment to Declaration of Helsinki 1964 (64th WMA General Assembly, Fortaleza, Brazil, October 2013), 21 Code of Federal Regulations (CFR) Part 50, including notes of clarification up to Tokyo (2004), the EU Clinical Trials Directive 2001/20/EC, the GCP Directive 2005/28/EC, the requirements of local IRB/IECs, and with national laws and regulations for clinical research.

The Investigator is responsible for informing the ethics committees and regulatory authorities of any SAEs and/or major amendments to the protocol as per national requirements. The Investigator should file all correspondence and a copy should be sent to Sponsor.

Either the Investigator or the Sponsor must submit progress reports to the IEC/IRB according to local regulations and guidelines.

13.2 Protocol Amendments and Discontinuation

Any changes to the protocol or discontinuation of the study require a written protocol amendment or statement, respectively. The Investigators, IEC/IRB in some cases and Sponsor must approve the protocol amendment or statement. The Principal Investigator(s) and the Sponsor's authorised representative will sign the protocol amendment. Any significant deviation from the protocol when no approved amendment exists will be regarded as a protocol violation and will be addressed as such during the reporting of the study.

National authorities and hospital IEC, hospital IRB or regional EC will be notified about all protocol amendments or discontinuation of the study. If the protocol amendment results in major changes, affecting patients' safety, the objective(s) or the scientific quality of the study, it must be approved by the hospital/regional IEC/IRB of all participating centres as per local regulations, as well as by the national regulatory authorities.

The Sponsor will have the right to terminate the study at any time in case of safety issue or if special circumstances concerning the study substance or the company itself should occur, making further patient treatment impossible. The sponsor will inform the Investigators about the reasons for study termination.

13.3 Investigator's Overall Responsibility

The investigator will ensure that this study is conducted in full conformance with the latest amendment to the Declaration of Helsinki 1964 (64th WMA General Assembly, Fortaleza, Brazil, October 2013), 21 CFR part 50, and with national laws and regulations for clinical research.

The Investigator is responsible for performing the study in accordance with this protocol, the ICH guidelines on GCP and local regulations, and for collecting, recording, and reporting the data accurately and properly. Agreement of the Investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the Sponsor and other forms as required by national authorities in the country where the study centre is located.

The Investigator is responsible for giving information and training about the study to all staff members involved in the study or in any element of subject management, both before starting the practical performance of the study and during the course of the study (e.g., when new staff become involved).

The Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

The Investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study. The Investigator must be familiar with the background and requirements of the study and with the properties of the investigational product as described in the Investigator's Brochure.

The Investigator is responsible for destroying the subject identification list when it no longer needs to be retained according to ICH guidelines.

The Investigator at each centre has the overall responsibility for the conduct and administration of the study at that centre, and for contacts with study centre management, the IRB/EC, and with local authorities.

13.4 Patient Informed Consent

Written and verbal information about the study in a language understandable by the patient will be given to all patients. Written informed consent will be obtained from each patient before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential

hazards, and insurance arrangements in force are explained. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. The Investigator will keep the original consent forms and copies will be given to the patients.

13.5 Direct Access to Source Data/Documents

The monitor(s), auditor(s), authorized personnel of the Sponsor, and health authority inspector(s) or their agents will be given direct access to source data and documentation (e.g., medical charts/records, laboratory results, printouts, etc.) for SDV, provided that patient confidentiality is maintained in accordance with local requirements.

13.6 Confidentiality Regarding Study Patients

The Investigator must assure that the privacy of the patients, including their personal identity and all other personal medical information, will be maintained at all times. In the eCRF and other documents or image material (including materials from all imaging modalities) submitted to the Sponsor, patients will not be identified by their names, but by an identification code (e.g., initials and allocation number). Personal medical information may be scrutinized for the purpose of verifying data recorded in the eCRF. This may be done by the monitor(s), properly authorized persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

13.7 Study Monitoring

Monitoring is a Sponsor's process for tracking a clinical study to ensure its scientific integrity, the data-quality, safety and well-being of the patients and compliance with the Declaration of Helsinki and other regulatory and/or Sponsor regulations.

To ensure compliance with GCP, the monitor or Sponsor's representative is responsible for ensuring that the study is conducted according to the protocol, and other written instructions.

The monitor is the primary association between the Sponsor and the Investigator. The main responsibilities of the monitor are to assure adherence to the protocol, accurate and complete data recording and reporting in the eCRFs, and that informed consent is obtained and recorded for all patients before their participation in the study.

The monitor will contact and visit the Investigator at regular intervals throughout the study. To assure the accuracy and completeness of the data recorded in the study, the monitor will be allowed to compare eCRFs with medical records and other relevant documentation during the

on-site monitoring visits to ensure the completeness, consistency, and accuracy of the data being recorded.

The monitor is responsible for explaining the protocol and study related procedures to all study staff, including the Investigator. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the Investigator or the monitor.

As part of the supervision of the study progress other Sponsor personnel may, on request, accompany the monitor on visits to the study centre. The Investigator and assisting staff must agree to cooperate with the monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits.

13.8 Audit and Inspection

According to ICH Guidelines on GCP, the Sponsor may audit the investigational site to compare raw data, source data, and associated records with the interim or final report of the study to assure that data have been accurately reported. The Investigator must accept that regulatory authorities, EC or an IRB may conduct an inspection to verify compliance of the study with protocol, GCP, ICH guidelines and any applicable regulatory requirements. If the Investigator is contacted with a request for an inspection, the Investigator must inform the Sponsor immediately.

13.9 Laboratory Accreditation

Any clinical laboratory facility used for analysis of samples obtained under this protocol must demonstrate adequate licensure and accreditation. Reference ranges of test results must be provided to the Sponsor.

The study centre must have the appropriate license for any procedure involving the administration of radioactive substances supplied by the Sponsor.

13.10 Patient Insurance and Indemnity

This study is covered under the sponsor's liability insurance policy. A certificate of insurance can be provided upon request.

14 INVESTIGATOR AGREEMENT

14.1 Financial Disclosure

According to the FDA 21 CFR, part 54, the Sponsor is required to completely and accurately disclose or certify information to the FDA concerning the financial interests of a clinical Investigator who is not a full-time or part-time employee. Therefore, the Investigator must

provide the Sponsor with sufficient, accurate financial certification that no financial arrangements (further defined in 21 CFR 54.2) exist with the Sponsor, or fully disclose the nature of the arrangement.

14.2 Study Agreement and Payment of Grant

A separate financial agreement (Clinical Study Agreement) including budget will be signed between the Sponsor and the Investigator and/or the institution involved. The budget will be itemised on a per patient basis and the payee name(s) and tax identification number(s). Additionally, the Investigator should not begin the study until the Sponsor has confirmed the agreed final budget in writing. The Investigator must comply with all the terms, conditions and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, the study agreement shall prevail.

15 CONFIDENTIALITY AND REPORTING AND PUBLICATION OF RESULTS

All information concerning Betalutin and the Sponsor's research and product development including patent applications and manufacturing processes not previously published are considered confidential and shall remain the sole property of the Sponsor.

15.1 Statistical and Clinical Reports

The Sponsor is responsible for preparing a CSR, in cooperation with the principal Investigator. The report will be added to the Sponsor's data file and may be used for regulatory purposes and/or in company publications.

If the study is terminated prematurely for any reason an abbreviated report will be prepared.

15.2 Regulatory Use of Data

By signing the protocol, the Investigator agrees that the results of this study may be used for submission to national and/or international regulatory and supervising authorities. The authorities will be informed of the Investigator's name, address, qualifications and extent of involvement.

15.3 Publication of Results

All publications will be prepared and published in collaboration between investigators and Sponsor.

Manuscripts based on this protocol will follow the recommendations from the International Committee of Medical Journal Editors (ICJME) Uniform Requirements for Manuscripts

Submitted to Medical Journals (www.icmje.org). Authorship will be based on the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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