Statistical Analysis Plan Addendum

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

Version: Final 1.0 (30 May 2022)

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

Syne qua non Study No: NOR18001

For Syne qua non Ltd – Lead Statistician

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List of Abbreviations

CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
FL	Follicular Lymphoma
MedDRA	Medical Dictionary for Regulatory Authorities
PT	Preferred Term
SAP	Statistical Analysis Plan
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures and Listings

Modification History

Version	Change History	Reason	Date
1.0	First Version	N/A	30MAY2002

1 Introduction

This addendum to the Statistical Analysis Plan (SAP) version 5.0 (dated 05APR2022) describes necessary clarifications to the Dose Limiting Toxicity (DLT) and Haematological Episodes analyses to be conducted for the LYMRIT-37-01 Phase I/IIa study (Part A). It also includes a small addition to the disease history analyses for Phase IIa Follicular Lymphoma (FL) patients.

This addendum must be read and applied in conjunction with the finalised and approved SAP version 5.0 (dated 05APR2022) for LYMRIT-37-01 Phase I/IIa (Part A) and the Table, Figure and Listing (TFL) Shells version 6.0 (dated 06APR2022).

2 Dose Limiting Toxicity

2.1 Existing Text

In section 3.13.2 of the SAP version 5.0 (dated 05APR2022), a DLT is defined as follows:

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

Haematological:

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

Non-haematological:

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

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

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

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

2.2 Reason and Justification for Addendum

The criteria definitions for DLT used within the SAP version 5.0 (dated 05APR2022) are in line with LYMRIT-37-01 protocol version 11.0 (dated 27OCT2017) onwards.

The Phase I/IIa (Part A) participants on the LYMRIT-37-01 study provided informed consent to earlier versions of the protocol. As the protocol versions have evolved over the years, the DLT criteria definitions have also been revised and amended.

A summary of the change in DLT definitions between the various versions of the protocol is summarised below:

LYMRIT-37-01 Protocol versions 4.0 to 7.0 inclusive
(4.0, 14Sep2012; 5.0, 25Mar2013; 6.0, 11Mar2014; 6.0B, 18Feb2015; 7.0, 26Nov2015)

Dose Limiting Toxicity was defined as:
Dose limited toxicity (DLT): Toxicity will be graded according to CTCAE version 4.

- Haematologic DLT is defined as grade 4 haematological toxicity that does not recover after 7 days, or grade 3 haematological toxicity that does not recover after 2 weeks.
- Non-haematologic DLT defined as grade 3 or more. However, the non-haematologic events will be evaluated by the safety review committee in the study and the decision will be taken by them to define whether the non-hematologic events are DLT or not.

LYMRIT-37-01 Protocol version 8.0, 04Jul2016

Dose limiting toxicity for Phase 1 arm 1 was defined as the following:
Toxicity will be graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (CTCAE; version 4).

- Haematologic DLT is haematology parameters defined as grade 4 that does not recover after 7 days, or grade 3 that does not recover after 2 weeks.
- Non-haematologic DLT defined as grade 3 or more, however, the non-haematologic events will be evaluated by the safety review committee in the study and decision will be taken by them to define whether the non-haematologic events are DLTs or not.

The safety review committee will make the recommendation whether to move to next dose level.

Dose limiting toxicity has been revised and is defined as the following for arms 2, 3, 4, 5 and phase II:
Haematology:
• Haematological grade 4 toxicity that does not recover to grade 3 within 7 days,
• or bleeding due to thrombocytopenia, or febrile neutropenia,
• or failure of platelets or neutrophils to recover to grade 1 by 12 weeks after treatment.
Non-haematological: grade 3 or more, final decision as to whether the non-haematological toxicity is a DLT will be made by the Safety Review Committee for this study.

LYMRIT-37-01 Protocol version 9.0, 28Nov2016 & version 10.0, 04Jul2017

Dose limiting toxicity was defined as the following:
Haematology:
• Haematological grade 4 toxicity that does not recover to grade 3 within 7 days,
• or bleeding due to thrombocytopenia, or febrile neutropenia,
• or failure of platelets or neutrophils to recover to grade 1 by 12 weeks after treatment.
Non-haematological: grade 3 or more, final decision as to whether the non-haematological toxicity is a DLT will be made by the Safety Review Committee for this study.

Plus clarification of the following: The DLT criteria that previously applied to Arms 2, 3, 4, 5 and phase II will also apply to Arm 1 phase I patients, to harmonise the assessment of the safety data of all enrolled patients/treatment arms.

NB all patients enrolled in LYMRIT-37-01 Part A (Phases I and IIa), were enrolled under Protocol versions 4.0 to 10.0 inclusive.

LYMRIT-37-01 Protocol version 11.0, 27Oct2017

Dose Limiting Toxicity was defined as:
• **Haematological**:
- Grade 4 toxicity that does not recover to grade 3 within 7 days
- or bleeding due to thrombocytopenia, or febrile neutropenia

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

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

2.3 Strategy for analysing DLTs

To account for the changes in the DLT definitions over the course of the study period for Phase I/IIa (Part A), the DLT definitions as outlined in Protocol Version 9.0 will be used for all participants irrespective of the Protocol version the participant was initially consented.

The Table below provides a summary of DLT criteria and related programming (NB this applies to time period from Day 1 to Week 12) for Phase I participants only:

Protocol Versions	DLT Criteria	Programming Requirements
4.0-7.0 Phase I Arm 1 Not applied due to re-evaluation under Version 9.0	• Grade 4 haematological toxicity* that does not recover after 7 days	• Grade 4 haematology lab value that lasts ≥7 days
	• Grade 3 haematological toxicity* that does not recover after 2 weeks. •	• Grade 3 haematology lab value that lasts ≥2 weeks
	• ≥Grade 3 non-haematological toxicity* with review/decision by SRC	• ≥Grade 3 biochemistry lab value • Any Grade ≥3 AE PT except the following: • AE PT THROMBOCYTOPENIA • AE PT PLATELET COUNT DECREASED • AEPT NEUTROPENIA • AE PT NEUTROPHIL COUNT DECRESAED • AE PT ANAEMIA • AE PT LYMPHOPENIA • AE PT LYMPHOCYTE COUNT DECREASED
8.0-10.0 Phase I Arms 2, 3, 4, 5 and Phase IIa Note: The Phase 1 Arm 1 patients were re-evaluated under Version 9.0 to these criteria	• Grade 4 haematological toxicity* that does not recover to grade 3 within 7 days	• Grade 4 haematology lab value that lasts ≥7 days
	• Bleeding due to thrombocytopenia	• Any one of the following AE PTs: • HAEMATURIA • EPISTAXIS

		• HAEMORRHAGE • PT containing BLEEDING • **<u>AND any one of the following concomitantly:</u>** • AE PT THROMBOCYTOPENIA • AE PT PLATELET COUNT DECREASED • Grade 1 to 4 platelet laboratory value
	• Febrile neutropenia	• AE PT FEBRILE NEUTROPENIA
	• Failure of platelets or neutrophils to recover to grade 1 by 12 weeks after treatment.	• Any ≥Grade 2 value during the first 12 weeks that is not Grade 0 or 1 at Week 12
	• ≥Grade 3 non-haematological toxicity* with review/decision by SRC	• ≥Grade 3 biochemistry lab value • Any Grade ≥3 AE PT
11.0 onwards (not applicable for Part A as all patients were enrolled under versions 4.0 to 10.0 inclusive. Applicable to Part B/C only.	• Grade 4 haematological toxicity* that does not recover to grade 3 within 7 days • Bleeding due to thrombocytopenia • Febrile neutropenia • ≥Grade 3 non-haematological toxicity* with review/decision by SRC	• As above

***Haematological toxicity = haemoglobin, neutrophils, lymphocytes and platelets only**

The definition of 'confirmed DLT' in the SAP version 5.0 (dated 05APR2022) is superseded by the definition of programmatically derived DLT in the SAP addendum. A Dose Limiting Toxicity (DLT) will be confirmed for a Phase I participant following a clinical review by the sponsor of the programmatically derived data.

Programmatically derived DLT AEs from study Day 1 to Day 92 (Month 3) will be listed by SOC and PT for Phase I participants only.

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

In cases, where the Safety Review Committee reviewed DLTs according to a version of the DLT definitions different from that present in the protocol version in place at the time the participant was initially consented, resulting discrepancies (if any) will be individually discussed in the Clinical Study Report for LYMRIT-37-01 Phase I/IIa (Part A).

In a change to the existing text in SAP version 5.0 (dated 05APR2022), all DLT AEs from study Day 1 to Day 92 (Month 3) will not be summarised by SOC and PT for Phase I only. This summary table is now to be omitted (reference: Table 14.3.2.1.1.A in the TFL shells version 5.0, dated 06APR2022) from the final outputs. As originally stated, all

programmatically derived DLTs will be listed for Phase I only (reference: Listing 16.2.7.3.1.A in the TFL shells version 5.0, dated 06APR2022) in the final outputs.

3 Haematological Episode

3.1 Existing Text

In section 3.13.3 of the SAP version 5.0 (dated 05APR2022), a haematological episode is defined as follows:

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

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

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

3.2 Reason and Justification for Addendum

Regarding haematological episodes for the Phase IIa participants, the same reasoning and justification for the addendum regarding DLTs for Phase I participants is also applicable i.e. in that from Protocol Version 9.0, they harmonised the assessment of the safety data of all enrolled patients/treatment arms.

Therefore, the definition for haematology/haematological DLTs in Protocol version 9.0 will be applied when defining the criteria for haematological episodes experienced by Phase IIa participants.

3.3 Strategy for analysing Haematological Episodes

As with the DLTs, to account for the changes in the DLT definitions over the course of the study period for Phase I/IIa (Part A), the DLT definitions as outlined in Protocol Version 9.0 will be used for all participants irrespective of the Protocol version the participant was initially consented.

Haematological Episodes will be programmatically derived using haematology laboratory parameters and the definitions for DLT. The Table below provides a summary of Haematological episodes criteria and related programming (NB this applies to time period from Day 1 to Week 12) for Phase IIa patients only:

Protocol Versions	**Haematological episodes**	**Programming Requirements**
8.0-10.0 **Phase I Arms 2, 3, 4, 5 and Phase IIa** **Note: The Phase 1 Arm 1 patients were re-evaluated under Version 9.0 to these criteria**	• Grade 4 haematological toxicity* that does not recover to grade 3 within 7 days	• Grade 4 haematology lab value that lasts ≥7 days
	• Bleeding due to thrombocytopenia	Any one of the following AE PTs: • HAEMATURIA • EPISTAXIS • HAEMORRHAGE • PT containing BLEEDING

		• **AND any one of the following concomitantly:** • AE PT THROMBOCYTOPENIA • AE PT PLATELET COUNT DECREASED • Grade 1 to 4 platelet laboratory value
	• Febrile neutropenia	• AE PT FEBRILE NEUTROPENIA

***Haematological toxicity = haemoglobin, neutrophils, lymphocytes and platelets, only**

The definition of 'confirmed' in the SAP version 5.0 (dated 05APR2022) is superseded by the definition of confirmed in the SAP addendum. A Haematological Episode will be confirmed for a Phase IIa participant following a clinical review by the sponsor of the programmatically derived data.

Programmatically derived Haematological Episode AEs from study Day 1 to Day 92 (Month 3) will be listed by SOC and PT for Phase IIa participants only.

In cases, where the Safety Review Committee reviewed haematological events according to a version of the haematological event definitions different from that present in the protocol version in place at the time the participant initially consented, resulting discrepancies (if any) will be individually discussed in the Clinical Study Report for LYMRIT-37-01 Phase I/IIa (Part A).

In a change to the existing text in SAP version 5.0 (dated 05APR2022), all programmatically derived Haematological Episodes from study Day 1 to Day 92 (Month 3) will not be summarised by SOC and PT. This summary table is to be omitted from the final outputs (reference: Table 14.3.2.1.2.A in the TFL shells version 5.0, dated 06APR2022). As originally stated, all programmatically derived haematological episodes will be listed for Phase IIa (reference: Listing 16.2.7.3.1.A in the TFL shells version 5.0, dated 06APR2022) in the final outputs.

4 Disease History

4.1 Existing Text

In section 3.7.3 of the SAP version 5.0 (dated 05APR2022), it states the following:

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

4.2 Reason and Justification for Addendum

For the disease history of the subgroup of Phase IIa FL participants, in addition to the initial diagnosis of NHL and current status of NHL being summarised for the subgroup of Phase IIa FL participants only, the Sponsor has also requested that the previous treatment for NHL and prior systemic therapies for NHL are also summarised for the subgroup of Phase IIa FL participants only.

4.3 Inclusion of additional Disease History Outputs

In a change to the existing TFL shells version 5.0 (dated 06APR2022) for the final outputs, two additional (repeated) tables will be included as follows:

- Table 14.1.5.1.A.4 Disease History - Previous Treatment for Non-Hodgkin Lymphoma (NHL) Information - Part A Phase IIa Patients with Follicular Lymphoma

- Table 14.1.5.2.A.4 Disease History - Prior Systemic Therapies for Non-Hodgkin Lymphoma (NHL) - Part A Phase IIa Patients with Follicular Lymphoma

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