“An open-label phase II single-centre study investigating the safety and efficacy of LTX-315 and adoptive T-cell therapy in patients with advanced/metastatic soft tissue sarcoma”

Statistical Analysis Plan

Version 1.0, February 18, 2022

NCT: 03725605

STATISTICAL ANALYSIS PLAN

An open-label phase II single-centre study investigating the safety and efficacy of LTX-315 and adoptive T-cell therapy in patients with advanced/metastatic soft tissue sarcoma

Sponsor Code: C17-315-04

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Sponsor: Lytix Biopharma AS

Evaluation: KLIFO GmbH, Munich

Final Version 1.0 of February 18, 2022

Previous Version(s): None

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DOCUMENT HISTORY

Version Number	Version Date	Main reason for new version	Summary of changes
1.0	18 Feb 2022	Initial Version	Not applicable

TABLE OF CONTENTS

ABBREVIATIONS

ACT	Adoptive T-cell Therapy
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CBR	Clinical Benefit Rate
CR	Complete Response
CT	Computed Axial Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DBL	Data Base Lock
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EoT	End of Treatment
FAS	Full Analysis Set
IHC	Immunohistochemical
IL-2	Interleukin 2
IMP	Investigational Medicinal Product
LLT	Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression Free Survival
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	All subjects screened Analysis Set
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TIL	Tumour Infiltrating Lymphocytes
W	Week

1 GENERAL

This Statistical Analysis Plan specifies the statistical methods to be applied in the analysis of this study. It was written by the responsible biostatistician prior to closure of the database according to SOPs of KLIFO GmbH. This SAP is based upon the Protocol Amendment (version 1.0 of 15th March 2018) and Protocol Amendment (version 2.0 of 31st March 2020) and contains a specification of the statistical methods described therein. The Study Protocol (version 1.0 of 19th December 2017) is not relevant for this SAP as no patient was screened or enrolled using this version.

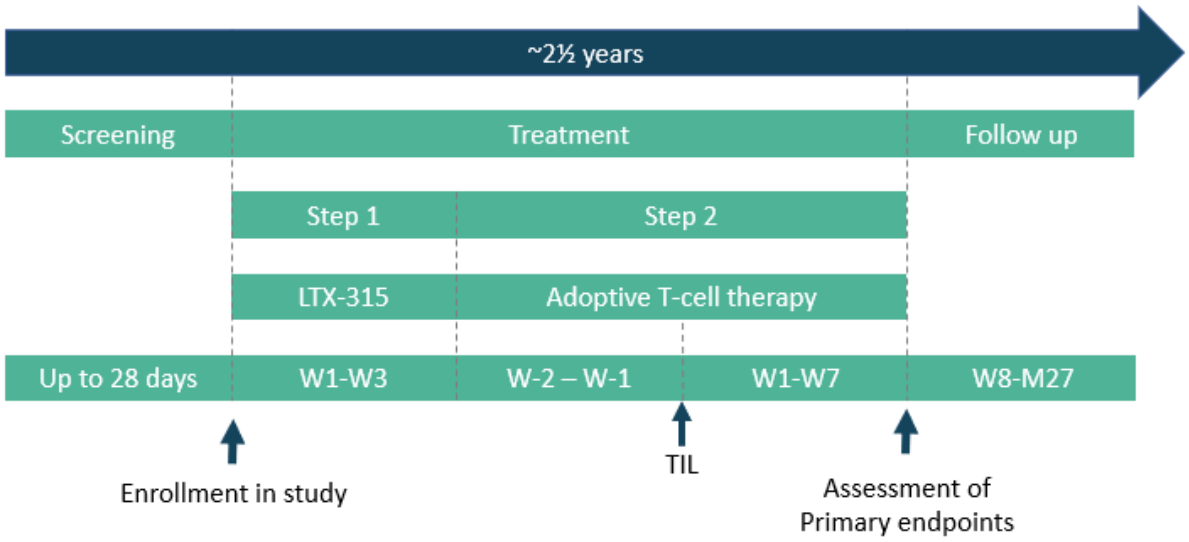
The primary objective of this phase II study is to determine the ability of LTX-315 to induce T-cell infiltration prior to TIL expansion in advanced/metastatic soft tissue sarcoma and to determine the safety of LTX-315 as part of adoptive T-cell therapy (ACT) in advanced/metastatic soft tissue sarcoma.

For this purpose, this trial has been designed as an open-label, single centre, phase II study.

All patients will have at least one tumour lesion available for injection with LTX-315 and 1 measurable lesion for disease assessment by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). An available lesion is defined as a lesion that can be injected and is not a non-injected bystander lesion.

The figure below shows the study design for Protocol Amendment 1.0.

Figure 1 Study design Protocol Amendment 1.0



W: Week

The course of treatment consists of 2 steps (Step 1 and Step 2) followed by clinical controls and evaluation-scans as follow-up:

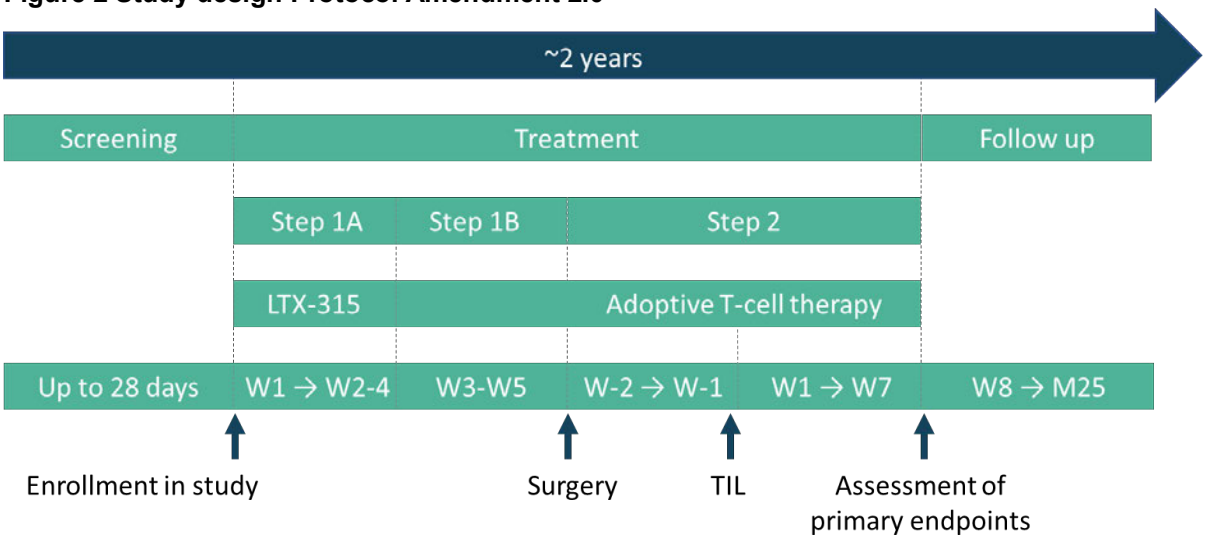
- Screening (28 days prior to Step 1): Visit 1; informed consent, check of eligibility and inclusion

- Step 1 (W1 to W3): Visit 2 to Visit 6; re-check of inclusion, baseline tumour biopsy, LTX-315 injections and surgical removal of the LTX-315 injected index tumour lesion followed by production and growth of TILs in the laboratory In case no T-cells can be expanded from the first index lesion, Step 1 can be repeated once.
- Step 2 (W-2 to W-1, W1 to W7): Visit 7 (which could be repeated once if Step 1 was repeated) and Visit 8 to Visit 25; check of eligibility for Step 2, treatment during hospitalisation with chemotherapy, TIL infusion and IL-2 administration, safety and efficacy of LTX-315/TIL treatment
- Follow-up: Visit 26 to Visit 34; safety and efficacy of LTX-315/TIL treatment for a follow-up period of 2 years

A total of 34 visits are scheduled with 6 additional repeat-visits, if applicable. For some visits, data will be collected at several timepoints, see section 7.1 of the Protocol Amendment Version 1.0 for details. Scheduled visits are varying between Protocol Amendments.

The figure below shows the study design for Protocol Amendment 2.0.

Figure 2 Study design Protocol Amendment 2.0



- Screening (28 days prior to Step 1): Visit 1; informed consent, check of eligibility and inclusion, identified adverse events (AEs) to be recorded in Medical History (Similar to Protocol Amendment 1.0)
- Step 1 (W1 to W3 – W5/W22): Visit 2 to Visit 6[1] for patients with progression disease (PD) at enrolment and Visit 2 to Visit 6, where Visit 6 consists of several Visits 6A to 6F, if a patient was enrolled with stable disease (SD); re-check of inclusion, baseline tumour biopsy, LTX-315 injections and surgical removal of the LTX-315 injected index tumour lesion followed by production and growth of TILs in the laboratory
- Step 2 (W-2 to W-1, W1 to W7): Visit 7 to Visit 25; check of eligibility for Step 2, treatment during hospitalisation with chemotherapy, TIL infusion and IL-2 administration, safety and efficacy of LTX-315/TIL treatment (Similar to Protocol Amendment 1.0). Follow-up: Visit 26 to Visit 30; safety and efficacy of LTX-315/TIL treatment for a follow-up period of 15 months. Only AEs considered related to LTX-315 or TIL to be reported

For Protocol Amendment 2.0 a total of 30 visits are scheduled with 6 additional visits, if applicable. Furthermore, for some visits, data will be collected at several timepoints, see section 7.1 of the Protocol Amendment Version 2.0 for details.

Before releasing data for final analysis, one or more data review and classification meetings will be held, if needed, to classify subjects with respect to analysis populations. The result of the classification meetings will be a detailed description of the analysis populations, and the number and nature of unresolved data queries will also be reported.

The SAP does not cover the exploratory endpoints mentioned in section 3.2 of the protocol.

2 EFFICACY AND SAFETY VARIABLES

2.1 General procedures

2.1.1 Time definitions and handling of visits

The total number of visits with investigations vary between Protocol Amendments as described in section 1.

In general, variables will be analysed according to the visit as documented in the eCRF. Details of the scheduled visits and time windows will be as described in section 7.1 of the respective Protocol Amendment.

2.1.2 Change from baseline

For continuous variables assessed at any visit after baseline, the absolute change from baseline will be calculated as [value at visit x] – [value at baseline]. Baseline value will be the last assessment with available data prior to the first administration of study medication. If a Baseline visit different from Screening will be used, this will be clarified in brackets for the respective analysis. If any of the two values (i.e. baseline value or value at the respective visit) is missing, the absolute change from baseline will be missing as well.

2.2 Primary Endpoints

The primary objective of this study is to determine the ability of LTX-315 to induce T-cell infiltration prior to Tumour Infiltrating Lymphocytes (TIL) expansion in advanced/metastatic soft tissue sarcoma and to determine the safety of LTX-315 as part of adoptive T-cell therapy in advanced/metastatic soft tissue sarcoma. Therefore, the primary efficacy endpoint is the change in total T-cell level in tumour tissues from Baseline (Step 1, Week 1, Day 1) to end of Step 1 (Step 1, Week 3). The primary safety endpoint is to detect AEs related to LTX-315 or to the combination of LTX-315 and adoptive T-cell therapy from Baseline (Step 1, Week 1, Day 1) to end of treatment (EoT) (Step 2, Week 7).

2.3 Secondary Endpoints

In addition to the primary endpoints described in Section 2.2 the following endpoints will be analysed:

- Change in CD3+ T-cell and CD3+CD8+ T-cell density in non-injected tumour tissues from Baseline (Step 1, Week 1, Day 1) to EoT (Step 2, Week 7) if the patient has a feasible bystander lesion and accept it to be biopsied.

- Total number of CD3+CD8+ T-cells and % CD3+CD8+T-cells of total CD3+ T-cells in final TIL infusion product.
- The anti-tumour effect assessed by:
    - Objective Response Rate (ORR) defined as proportion of patients who have achieved CR or PR at Step 2, Week 7 (EoT) and up to 15 months after EoT
    - Clinical Benefit Rate (CBR) defined as proportion of patients who have achieved CR, PR or SD at Step 2, Week 7 (EoT) and up to 15 months after EoT
    - Progression free survival (PFS) evaluated by time from Baseline until PD or death up to 15 months after EoT

2.4 Exploratory Endpoints

The SAP does not cover the exploratory endpoints mentioned in section 3.2 of the protocol.

3 STATISTICAL ANALYSIS SETS

The evaluation of efficacy and safety will be performed using the full analysis set (FAS). The Per-Protocol Set (PP), specified in the CSP, will not be used. This was planned for the analyses of specific summary tables. But as described in section 6.1 no summary tables will be provided.

In addition to FAS the all screened (SCR) analysis set is defined in section 3.1 and will be used for selected listings for completeness of presentation of all data documented in the eCRF.

The analyses and presentations will be performed for the FAS population unless otherwise specified.

3.1 All Subjects Screened (SCR)

The set of all subjects screened will include all patients with data documented at the screening visit. This set will be used for selected listings.

3.2 Full Analysis Set (FAS)

Patients will be included in the full analysis set (FAS) if they receive at least one injection of LTX-315. The FAS is by this definition also the safety analysis set. FAS will be used for evaluation of all efficacy and safety endpoints.

4 STATISTICAL EVALUATION

4.1 General

The statistical analysis will be performed using the software package SAS® version 9.4 or higher (SAS Institute Inc., Cary, NC 27513, USA).

Patient listings will be generated for all data items collected in the eCRF and for data provided by external laboratories. Relevant data of screening failures (i.e. of patients not eligible for treatment because of violations of in- or exclusion criteria) will also be listed.

Due to various reasons, which are described in section 6.1, no summary statistics will be calculated.

Any changes in the planned statistical methods will be documented in the study report.

4.2 Study Patients

4.2.1 Disposition of Patients

- Allocation to analysis sets, reason for exclusion from analysis sets and Protocol Version used for each patient
- Completion of Treatment - Step 1, reason for premature discontinuation of treatment
- Completion of full study, reason for premature discontinuation
- Study duration including the following:
    - Last visit during study: Last regular visit, where a visit date has been documented.
    - First dose of LTX-315: Date of first LTX-315 administration
    - Last dose of LTX-315: Date of last LTX-315 administration
    - Duration of step 1: Last regular visit during Step 1, where a visit date has been documented.
    - Number of days from surgery to ACT: Calculated as date of start of ACT (Step 2, Week 1, Day 0) - date of surgery
    - Duration of step 2: Last regular visit during Step 2, where a visit date has been documented.
    - Duration of Follow-up: Last regular visit during Follow-up, where a visit date has been documented.
    - Number of days from start of LTX-315 treatment to surgery: Calculated as date of surgery - date of first LTX-315 treatment
    - Withdrawal date
- Difference between visits including the following:
    - Difference between the dates of Screening visit and Step 1, Day 1 (in days)
    - Difference between the dates of Step 1, Day 1 and of the subsequent visits 2 to visit 6/6C (in days or weeks, as applicable)
    - Difference between the dates of Step 2, Day 0, Time 12 hours and of Visit 7, Visit 25 to Visit 30 (in days weeks or months, as applicable)

4.2.2 Protocol Deviations

Deviations from the study protocol, especially the prescription of doses not scheduled in the study protocol, other modes of administration, other indications, and longer treatment periods are not permissible (except in an emergency).

Before data base lock (DBL) all protocol deviations will be evaluated. Other protocol deviations than the above mentioned may be regarded as major. The decisions will be documented.

All protocol deviations and the additional aspect of violations of any eligibility criteria will be listed.

4.2.3 Demographic and Other Baseline Characteristics

The following demography data, medical history, disease characteristics and baseline

characteristics will be shown for FAS:

- Demographic data at Screening:
  - Sex,
  - Age (years)
  - Ethnicity (Hispanic or Latino, not Hispanic or not Latino)
  - Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White)
  - Height (cm)
  - Weight (kg with one decimal)
- History of cancer disease, current status of cancer disease, prior cancer therapy, prior cancer radiation and prior cancer surgeries
- Medical history:
  Medical history including Common Terminology Criteria for Adverse Event (CTCAE) grade is collected and coded by Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 and will be classified by System Organ Class (SOC), Preferred Term (PT) and Lowest Level Term (LLT). Medical history will be listed including CTCAE grade by subject.
- Hospital admission and hospital discharge

4.2.4 Treatment Compliance

The number of injections and the total dose (mg) of LTX-315 injected will be entered in the eCRF at each treatment visit.

All data related to injections with LTX-315 and with other IMPs (TILs, Sendoxan, Fludara and Proleukin) will be listed using FAS.

4.2.5 Concomitant Treatment

Concomitant therapies will be coded in WHODrug version Sep 2018 and listed by the first and the second level of the ATC classification.

All concomitant medication and therapies used within 28 days prior to day 1 (screening) and up to the end of treatment visit will be recorded in the eCRF.

In the follow-up period and until study completion the following will be recorded in the eCRF:

- concomitant medication and therapies used for soft tissue sarcoma or which may alter the course of the disease
- concomitant medication and therapies used for events related to the LTX-315 and adoptive T-cell therapy

The drug name or generic name, reason for the treatment, and the start and stop dates of administration are to be noted if possible. Any changes in the dose or frequency of administration of concomitant medications should be recorded in the eCRF.

All concomitant medication will be listed using the FAS.

4.3 Efficacy Evaluation

The evaluation of efficacy will be performed for the FAS.

4.3.1 Primary Efficacy Evaluation

The primary efficacy endpoint is change in total T-cell level in tumour tissues from baseline (Step 1, Week 1, Day 1) to end of Step 1. In Step 1 the total T-cell level is measured at baseline and end of Step 1.

Absolute values and change from baseline (Step 1, Week 1, Day 1) for T-cell level will be listed for the FAS. Change from baseline will be listed as absolute change.

For subjects repeating Step 1, measurements of T-cell level from end of Step 1B will be used for calculation of the change.

Individual plot of T-cell level against actual time will be presented including measurements from possible repeats of Step 1 for the FAS.

All data will be listed including both Step 1 and Step 1B if applicable.

4.3.2 Secondary Efficacy Evaluation

The secondary endpoints are listed in 2.3 and will be analyzed using the FAS.

4.3.2.1 Change in CD3+ T-cell level and CD3+CD8+ T-cell density in non-injected tumour tissues

CD3+ T-cell level and CD3+CD8+ T-cell density are measured at baseline (Step 1, Week 1, Day 1) and at end of treatment (Step 2, Week 7) in non-injected bystander lesion.

For subjects repeating Step 1 the T-cell level from Step 1B will be used for calculation of the change.

Absolute values and change from baseline (Step 1, Week 1, Day 1) for CD3+ T-cell level and CD3+CD8+ T-cell density will be listed for the FAS. Change from baseline will be listed as absolute change. All data will be listed including values from all repeats of Step 1 if applicable.

Individual plot of CD3+ T-cell level and CD3+CD8+ T-cell density against actual time will be presented for the FAS.

4.3.2.2 Total number of CD3+CD8+ T-cells and % CD3+CD8+ T-cells of total CD3+

Total CD3+CD8+ T-cell level and % CD3+CD8+ T-cell of total CD3+ in final TIL infusion product will be listed using FAS.

4.3.2.3 Anti-tumour effect

Full tumour assessment by CT/MRI scan will be done at screening, during Step 1 at Week 6, Week 14, and Week 22, if applicable, and during Step 2 at Week -2 and at Step 2, Week 7 and at all visits through the follow-up period. Overall response using RECIST 1.1 is assessed at all visits, at which a CT/MRI scan is scheduled, except screening. Overall response using RECIST will be listed using FAS.

The tumour response according to RECIST criteria is listed below in order with the best response first and the worst last

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)

4.3.2.3.1 Objective Response Rate

ORR is defined as proportion of patients who according to RECIST 1.1 criteria (see CSP Appendix) have achieved CR or PR at Step 2, Week 7 (EoT) and up to 15 months after EoT.

The objective tumour response (CR, PR, SD, PD) according to RECIST 1.1 criteria verified by imaging technique will be listed using FAS.

In addition, the best overall tumour response according to RECIST 1.1 criteria from screening until PD, death, or 15 months after EoT, whichever comes first will be listed using FAS.

The best overall tumor response for each visit at which RECIST is specified, will be documented in the eCRF. The best overall response for the time window from screening until PD, death, or 15 months after EoT, whichever comes first will be calculated as specified in the following table:

	At least 1 occurrence of				
Best Overall Response	CR	PR	SD	PD	Missing data
CR	Yes	No	No	No	No
PR	Any	Yes	No	No	No
SD	Any	Any	Yes	No	No
PD	Any	Any	Any	Yes	Any
Not evaluable	Any	Any	Any	No	Yes

4.3.2.3.2 Clinical Benefit Rate

CBR is defined as proportion of patients who according to RECIST 1.1 criteria have achieved CR, PR or SD. RECIST data for patients who have achieved clinical benefit will not be listed and can be read out of the listing showing all RECIST data.

4.3.2.3.3 Progression Free Survival

PFS is defined as the time in days from baseline until PD or death.

A patient who leaves the study without evidence of progression or death will be censored at the last tumour assessment date. Progression free patients will be censored 15 months after EoT.

In any case of censoring, the date of censoring will be the last time point documenting survival status.

Progression free survival will not be estimated using the Kaplan-Meier method, but overall survival data, including censoring information, will be listed using FAS.

A scatterplot of PFS (in days) against %CD3+CD8+ T-cells in TIL product will be presented.

4.4 Safety Evaluation

The safety evaluation will include analyses of the primary endpoint described in section 2.2 and other safety relevant data. The safety evaluation will be based on the full analysis set.

4.4.1 Primary Safety Evaluation

The primary safety endpoint is adverse events related to LTX-315 or to the combination of LTX-315 and adoptive T-cell therapy from baseline (Step 1, Week 1, Day 1) to end of treatment (Step 2, Week 7).

Adverse events are events occurring during or after administration of the investigational medicinal product (IMP). AEs will be coded using MedDRA version 21.1 and will be classified by SOC, PT and LLT.

Adverse events related to LTX-315 are events where causality to LTX-315 is marked on the adverse events page.

Adverse events related to the combination of LTX-315 and adoptive T-cell therapy are events where both causality to LTX-315 and at least one of the other IMPs (TILs, sendoxan, fludara and proleukin) are marked on the adverse event page.

All data will be listed using FAS.

4.4.2 Other Safety Evaluation

4.4.2.1 Adverse Events

Adverse events are events occurring during or after administration of IMP. Adverse events will be coded using the MedDRA version 21.1 and will be classified by SOC, PT and LLT.

Additionally, AEs will be categorized as

- pre-treatment,
- treatment-emergent.

Treatment emergent AEs (TEAEs) are defined as AEs/Serious Adverse Events (SAEs) occurring during or after administration of the IMP. AEs occurring before administration of the IMP are considered as non-treatment emergent, which are recorded and listed as Medical history. Non-treatment emergent AEs/SAEs which are worsened after treatment with IMP will be added as new event and assessed as treatment emergent.

Adverse events in the follow-up period will only be reported in the eCRF if they are related to either LTX-315 or TIL treatment.

All AEs will be listed using FAS. Separate listings will be made for:

- AEs
- TEAEs
- Serious Adverse Events and deaths
- TEAEs leading to withdrawal of IMP

- AEs occurring in the follow-up period

4.4.2.2 Vital signs, Laboratory, Tumour Assessment and other Safety Evaluation

All data related to the following topics will be listed using FAS:

- Vital signs (blood pressure, heart rate, body temperature); The listings will include change from baseline.
- 12-lead Electrocardiogram (ECG)
- Physical examination
- Height and weight; The listings will include change from baseline for body weight.
- Laboratory parameters (Blood and urine clinical safety laboratory tests, Coagulation, Serology); The listings will include all measurements and change from baseline, except Serology. Furthermore, values outside normal ranges will be flagged.
- Eastern Cooperative Oncology Group (EOCG) performance
- Lesions to be injected
- Injected lesion biopsies
- Non injected lesion biopsies
- Surgical removal of LTX-315 injected lesion
- Full tumour assessment for each lesion (target and new lesion)
- Full tumour assessment - Tumor burden and percentage change from screening
- Renal function evaluation (creatinine clearance)
- Overall survival; Overall survival is defined as the time in days from baseline until death. A patient that leaves the study will be censored at the last visit date. Overall survival will be censored 15 month after end of treatment. In any case of censoring, the date of censoring will be the last time point documenting survival status.

4.5 Evaluation of Other Variables

Flow cytometry data and Immunohistochemical (IHC) data will be listed using FAS.

4.6 Missing Values

No imputation of missing data will be performed. Missing data for time to event endpoints is handled using censoring.

5 INTERIM ANALYSIS

No interim analysis is planned.

6 CHANGES FROM PROTOCOL

6.1 Planned Deviations from Protocol

The analyses planned in this analysis plan are not consistent with the provisions in the clinical

study protocol.

At the time this SAP is written, the study has ended with a total of 6 patients. Three of these patients have been included using the Protocol Amendment 1.0 and three patients have been included using the Protocol Amendment 2.0. In addition to other changes (see Summary of key changes in Protocol Amendment 2.0) the two versions differ in amount and timepoints of visits and IMP administrations. Moreover, Protocol Amendment 2.0 also allowed inclusion of subjects that were in stable disease at baseline. This is the reason why the data from patients cannot be compared between the Amendments. Furthermore, a stratified analysis for the two Amendments cannot be considered due to the low number of patients in each group. Therefore, no summary tables are planned in this SAP and no survival analysis will be performed. All patient data will be listed indicating the respective Protocol Amendment used and plots will be provided as described.

6.2 Other Changes from Protocol

The following changes from protocol were made:

- Analysis set SCR was added. This will guarantee complete data listings of all data documented in the eCRF.
- Analysis set PP will not be created and will not be used for analysis. This change is related to section 6.1 and the reason, that no summary tables, for which this would have been used, will be provided.
- The BAS Test was performed, but not documented in the eCRF, thus no data will be listed. PD was documented.
- Exploratory endpoints mentioned in section 3.2 in the protocol were not described in this document and will not be analysed within this analysis.

7 SUMMARY TABLES AND DATA LISTINGS

7.1 Summary Tables

No summary tables will be planned as stated in section 6.1.

7.2 Data Listings

The data listings planned are listed in Appendix A.

Data listings will include all treated patients, the disposition listing as well as the inclusion and exclusion criteria listing will include all screened patients. FAS analysis set will be used except of the disposition and the inclusion and exclusion criteria listing where SCR analysis set will be used.

In general, data listings will be sorted by screening number of the patients and visit, if applicable. Flags will be provided in the listings indicating which Protocol Amendment was used for each patient.

7.3 Figures

Figures planned are listed in Appendix B.

8 SIGNATURES

Sponsor:

Vibeke Sundvold

Lytix Biopharma AS, Norway

21 February 2022
Date

[redacted]

Signatures (continued)

Biostatistician:

Jana Neumann

KLIFO GmbH, Germany

[redacted]

18.02.2022
Date

9 APPENDICES

A List of Data Listings

B List of Figures

List of Data Listings

Analysis Sets:
SCR = All Patients Screened
FAS = Full Analysis Set
NOTE: The wording may be adapted in the final output, also some listings may be split into two or more parts if they do not fit on the page, and several listings may be combined where reasonable depending on size.

No.	Title/Content	Analysis Set	Variables to be included/Variables of the following form in the eCRF and corresponding derived variables
1. Patient Disposition and Baseline Characteristics			
1 - 1.1	Patient disposition - Allocation to analysis sets, reason for exclusion from analysis set and Protocol Version used for each patient	SCR	SCR; FAS; exclusion from FAS; Protocol Version; Date of informed consent
1 - 1.2.1	Completion of Treatment - Step 1	FAS	Form 'End of treatment'
1 - 1.2.2	Completion of full study	FAS	Completion/discontinuation status (Form 'End of study'))
1 - 1.3	Study duration	FAS	Last visit during study; First dose of LTX-315; Last dose of LTX-315; Duration of step 1, step 2, follow-up; Number of days from start of LTX-315 treatment to surgery; Number of days from surgery to ACT; Withdrawal date
1 - 1.4	Visit dates and differences between visit dates	FAS	Treatment Phase; Visit; Visit Date; Differences between visit days (in days, weeks or months, as applicable)
1 - 1.5.1	Protocol deviations - overall	FAS	Form 'Protocol deviations'
1 - 1.5.2	Protocol deviations - log	FAS	PD-log
1 - 1.6	Inclusion and exclusion criteria	SCR	Form 'Eligibility criteria' (for Step 1 and Step 2)
1 - 2.1	Demographic data I	FAS	Form 'Demographics'
1 - 2.2	Demographic data II: Women related information	FAS	Form 'Pregnancy Test'
1 - 2.3	History of cancer disease and current status of cancer disease	FAS	Forms 'History of cancer disease' and 'Current status of cancer disease'
1 - 2.4	Prior cancer therapy	FAS	Respective Forms
1 - 2.5	Prior cancer radiation	FAS	Respective Forms
1 - 2.6	Prior cancer surgeries	FAS	Respective Forms
1 - 2.7	Medical history	FAS	Respective Forms

1 - 3.1	IMP administration	FAS	Form 'LTX-315 ADMINISTRATION'
1 - 3.2	Cyclophosphamide infusion	FAS	Form 'Cyclophosphamide infusion'
1 - 3.3	Fludarabine phosphate infusion	FAS	Form 'Fludarabine phosphate infusion'
1 - 3.4	TIL infusion	FAS	Form 'TIL infusion'
1 - 3.5	Interleukin-2 injection	FAS	Form 'Interleukin-2 injection'
1 - 3.6	IL-2 Self-administration	FAS	Form 'IL-2 Self-administration'
1 - 4	Concomitant Medication	FAS	Form 'Concomitant medication'
1 - 5	Hospital admission and hospital discharge	FAS	Forms 'Hospital admission' and 'Hospital discharge'
1 - 6	Formal fields - Immunological blood sample	FAS	Immunological blood sample (for PBMC) and Immunological blood sample (for serum)
2. Efficacy Evaluation and Other Variables			
2 - 1	Primary efficacy endpoint - Change in total T-cell level from baseline to end of step 1	FAS	Value absolute and change
2 - 2.1	Change in CD3+ T-cell and CD3+CD8+ T-cell density in non-injected tumour tissues from baseline to end of treatment	FAS	Value absolute and change
2 - 2.2	Total number of CD3+CD8+ T-cells and % CD3+CD8+ T-cells of total CD3+ T-cells in final TIL infusion product	FAS	Value absolute and relative
2 - 2.3.1	Anti-Tumor effect - Objective tumore response	FAS	Form 'Scan / IRRC' and RECIST data
2 - 2.3.2	Anti-Tumor effect - Best overall tumour response from screening until PD, death, or 15 months after EoT	FAS	All related Variables
2 - 2.3.3	Anti-Tumor effect - Progression free survival	FAS	All data related; censoring
2 - 3	Flow cytometry data	FAS	Data from Center for Cancer Immune Therapy
2 - 4	Immunohistochemical (IHC)	FAS	IHC data from Veracyte
3. Safety			
3 - 1.1.1	Primary safety endpoint - AEs related to LTX-315 from Baseline to EoT	FAS	Variables from AE form and corresponding derived variables (if applicable)
3 - 1.1.2	Primary safety endpoint - AEs related to the combination of LTX-315 and adoptive T-cell therapy from Baseline to EoT	FAS	see Listing 3 - 1.1.1
3 - 1.2	Adverse events	FAS	see Listing 3 - 1.1.1
3 - 1.3	Treatment emergent adverse events	FAS	see Listing 3 - 1.1.1
3 - 1.4	Serious adverse events and deaths	FAS	see Listing 3 - 1.1.1

3 - 1.5	Treatment emergent adverse events leading to withdrawal of IMP	FAS	see Listing 3 - 1.1.1
3 - 1.6	Adverse events occuring in the follow-up phase	FAS	see Listing 3 - 1.1.1
3 - 2	12-lead ECG	FAS	Form '12-lead ECG' and '12-lead ECG repeated'
3 - 3.1	Vital signs - heart rate and body temperature	FAS	Form 'Vital signs' incl. change from baseline
3 - 3.2	Vital signs - blood pressure monitoring		Form 'Blood pressure monitoring' and 'Additional blood pressure monitoring' incl. change from baseline
3 - 4	Physical examination	FAS	Form 'Physical examination'
3 - 5	Height and weight	FAS	Form 'Height' and 'Weight' incl. change from baseline
3 - 6.1.1	Safety laboratory assessment - Formal fields, sample date and time	FAS	All formal fields related to safety laboratory data
3 - 6.2.1 - 3 - 6.2.26	Safety laboratory assessments - Blood test: Haemoglobin Thrombocytes Leukocytes Differential-count Haematocrit Erythrocyte count Creatinine Sodium Potassium Ionized calcium Phosphate Magnesium Chloride Serum glucose ALAT ASAT ALP Bilirubin Albumin LDH Urea CRP	FAS	All respective data incl. change from baseline
3 - 6.3.1 - 3 - 6.3.2	Safety laboratory assessment - Coagulation: APTT P-Coagulation factors II-VII-X (INR)	FAS	All respective data incl. change from baseline

3 - 6.4	Safety laboratory assessment - Serology: HIV Hepatitis B: HBVsAg, HBVsAb, HBVcAb Hepatitis C: HCVAb HTLV: HTLV-IgG Epstein-Barr: P-EBV Syphilis: Treponema	FAS	All respective data
3 - 6.5.1 - 3 - 6.5.4	Safety laboratory assessment - Urine analysis: Protein Glucose Erythrocytes Leukocytes	FAS	All respective data incl. change from baseline
3 - 7	Eastern Cooperative Oncology Group performance status (ECOG)	FAS	Form ' ECOG performance status'
3 - 8.1	Lesion to be injected	FAS	Form 'Lesion to be injected'
3 - 8.2	Injected lesion biopsies	FAS	Form 'Injected lesion biopsies'
3 - 8.3	Non injected lesion biopsies	FAS	Form 'Non injected lesion biopsies'
3 - 9	Surgical removal of LTX-315 injected lesion	FAS	respective Form
3 - 10.1	Full tumour assessment for each lesion (target and new lesion)	FAS	Form 'Lesion assessment' and 'New lesion'
3 - 10.2	Full tumour assessment - Tumor burden and percentage change from Screening	FAS	Form 'Tumor burden'
3 - 11	Renal function evaluation (creatinine clearance)	FAS	Form 'Renal function'
3 - 12	Overall survival	FAS	All related variables

List of Figures

Analysis Sets:
FAS = Full Analysis Set

No.	Title	Type	Set
Efficacy Evaluation and Other Variables			
2 – 1	T-cell level in tumour tissues – Subject profile by actual time	Line charts	FAS
2 – 2	PFS (in days) against %CD3+CD8+ T-cells in TIL product	Scatterplot	FAS