STATISTICAL ANALYSIS PLAN

A PHASE 3, SINGLE-ARM, OPEN-LABEL, MULTICENTRE STUDY TO ASSESS THE EFFICACY AND SAFETY OF DEEP SUBCUTANEOUS INJECTIONS OF LANREOTIDE AUTOGEL® 120 MG ADMINISTERED EVERY 28 DAYS IN CHINESE PARTICIPANTS WITH UNRESECTABLE, LOCALLY ADVANCED OR METASTATIC GRADE 1 OR 2 GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS (GEP-NETS)

[D-CN-52030-411]

This statistical analysis plan is based on:

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PROTOCOL TITLE:	**A PHASE 3, SINGLE-ARM, OPEN-LABEL, MULTICENTRE STUDY TO ASSESS THE EFFICACY AND SAFETY OF DEEP SUBCUTANEOUS INJECTIONS OF LANREOTIDE AUTOGEL® 120 MG ADMINISTERED EVERY 28 DAYS IN CHINESE PARTICIPANTS WITH UNRESECTABLE, LOCALLY ADVANCED OR METASTATIC GRADE 1 OR 2 GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS (GEP-NETS)**
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The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan:

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HISTORY OF CHANGES

Version Number	Date	Description/Rational for change
1.0	21MAY2021	Not Applicable
1.1	30MAY2022	Update the SD decimal place in part 5.1; Deleted the description related to estimand, TFLs about PCSA; Added remapping rule about delayed visits for tumour assessment, several TFLs due to COVID-19.
1.2	17JUN2022	Update the remapping rule, subgroups and add the imputation rule.
2.0	01AUG2022	Delete Listing of participants with treatment discontinuation or study withdrawal due to COVID-19; add the data handling logic for laboratory values or concentration data. Add Intention-To-Treat (ITT) Set (without COVID impacts) and Modified Intention-To-Treat (ITT) Set (without COVID impacts). Update the definition of CBR.
2.1	05JAN2023	Add a section of Analysis of COVID impacts on efficacy endpoints, and delete the definition of Intention-To-Treat (ITT) Set (without COVID impacts) and Modified Intention-To-Treat (ITT) Set (without COVID impacts).
2.2	14FEB2023	Delete visit “Week 48 (Visit 14)” in section 5.1.1.3.
3.0	17FEB2023	Add the definition of subsequent treatment and the description of summary of subsequent treatment.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
ADA	Anti-Drug Antibodies
ADaM	Analysis Dataset Model
AE	Adverse Event
ATC	Anatomic Therapeutic Class
BICR	Blinded independent central review
C	Concomitant
CBR	Clinical benefit rate
CgA	Chromogranin A
CI	Confidence interval
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOSI	End of Study Intervention
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients
FDA	Food and Drug Administration
GEP-NET	Gastroenteropancreatic neuroendocrine tumours
ICE	Intercurrent Event
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
MTK	Multi-target tyrosine kinase
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival

ABBREVIATION	Wording Definition
P	Prior
PD	Progressive Disease
PFS	Progression free survival
PK	Pharmacokinetic
PN	Preferred Name
PP	Per Protocol
PR interval	Prolonged Release Interval
PRRT	Peptide Receptor Radionuclide Therapy
Confirmed PR	Confirmed Partial Response
PT	Preferred Term
QoL	Quality of life
QRS	Time interval for ventricular depolarization
QT	Time interval for ventricular depolarisation and repolarisation
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	Time between QRS complexes
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SI	International System of Units
SOC	System Organic Class
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
TTP	Time to progression
ULN	Upper Limit of Normal

1 INTRODUCTION

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol D-CN-52030-411. It describes the rules and conventions to be used in the analysis and presentation of data, the data to be summarised and analysed, including specificities of the statistical analyses to be performed.

Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CSR.

The SAP is to be finalised before first participant in. A separate shell will be provided for tables, figures and listings.

Any deviations from the SAP after database lock will be documented in the CSR (section 9.8 "Changes in the conduct of the study or planned analyses" as per International Conference on Harmonisation (ICH) E3).

This analysis plan does not cover pharmacokinetics (PK) and biomarker analysis which will be described in a separate document.

2 PROTOCOL OVERVIEW

2.1 Study Objectives and Hypotheses

2.1.1 Primary objective

The primary objective of the study is to evaluate the efficacy of repeated deep s.c. injection of lanreotide Autogel 120 mg every 28 days for 24 weeks in Chinese participants with unresectable, locally advanced or metastatic GEP-NETs.

2.1.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the efficacy of lanreotide Autogel 120 mg administered every 28 days for 48 weeks.
- To evaluate the safety of lanreotide Autogel 120 mg administered every 28 days for 48 weeks.

2.1.3 Exploratory Objective

- To evaluate independent injection of lanreotide Autogel 120 mg administered every 28 days for 24 weeks during the independent injection period (independent injection cohort).

2.1.4 Statistical Hypotheses

The null hypothesis H0: P$\leqslant$40% versus the alternative hypothesis H1: P>40%, where P is the CBR at the end of 24 weeks of study intervention. The threshold CBR at W24 was defined as 40%.

2.2 Overall Study Design and Investigational Plan

This is a prospective, multicentre, single-arm, nonrandomised, open-label, interventional, phase 3 study in Chinese adult participants with unresectable, well differentiated locally advanced or metastatic GEP-NETs (gastric, pancreas, midgut, hindgut), Grade 1 or 2, nonfunctioning and functioning. The study design is illustrated in Figure 1.

The main study will include a screening period of up to 4 weeks followed by a 48-week intervention period. During the intervention period, 43 participants will receive deep subcutaneous injection of lanreotide Autogel 120 mg every 28 days (i.e. 4 weeks; a total of 12

injections). The main study will include 14 visits (one screening visit, 13 visits, one every 4 weeks (Day 1, W4 to W48 (EOSI)) during the 48-week intervention period.

After completion of the main study period, approximately five participants (assuming 10 to 25% eligible participants after 48 weeks of intervention in the main study) will enter an independent (self/partner) injection period with lanreotide Autogel 120 mg every 28 days for 24 weeks (a total of six independent injections). To be eligible, the participant must provide additional informed consent to continue, have a positive benefit/risk ratio of continuing study intervention (no disease progression at W48 and good tolerability during the main study period) and be a suitable candidate for independent injection (considered able to independently administer lanreotide following training and likely to benefit from independent administration e.g. reducing the burden of frequent hospital visits) in the opinion of the investigator. For the independent injection period there will be up to six additional visits (W52 to W68 (optional) and W72 (EOSI)). Visits for study assessments will be performed at W48, W52 (optional) and W56 (optional); with EOSI assessments at W72. At the W48 visit, the first injection will be performed independently at the study site (under medical supervision) for training purposes. At W52 and W56, the second and third injections may also be performed at the study site for training purposes or may be performed at home if no further training is needed, in the opinion of the investigator. At W60, W64 and W68, the fourth, fifth and sixth injections will be performed at home or at the study site. Participants will be contacted by telephone at W52, W56, W60, W64 and W68 (if no study site visit is performed) for safety purposes.

The primary efficacy endpoint is clinical benefit rate (CBR) of tumour response assessed using Response Evaluation Criteria in Solid Tumours RECIST Version 1.1 [Eisenhauer 2009] and confirmed by blinded independent central review (BICR) after 24 weeks of study intervention. Secondary efficacy endpoints will be assessed during the intervention period, including PFS, overall survival (OS), time to progression (TTP), proportion of participants alive and without progressive tumour, CBR after 48 weeks of intervention, overall response rate (ORR), disease control rate (DCR), NET-related clinical symptoms, circulating chromogranin A (CgA), 5-hydroxyindoleacetic acid (5-HIAA) and other biomarkers and QoL. Safety data including AEs, clinical safety laboratory tests, electrocardiograms (ECG), physical examination, vital signs and gallbladder echography will also be evaluated. Exploratory endpoints will be assessed in the five participants continuing in the independent injection period (proportion of participants preferring independent injection over HCP injections, participant-reported indirect costs and work productivity, plus tumour response, NET-related clinical symptoms, QoL, biomarkers and safety).

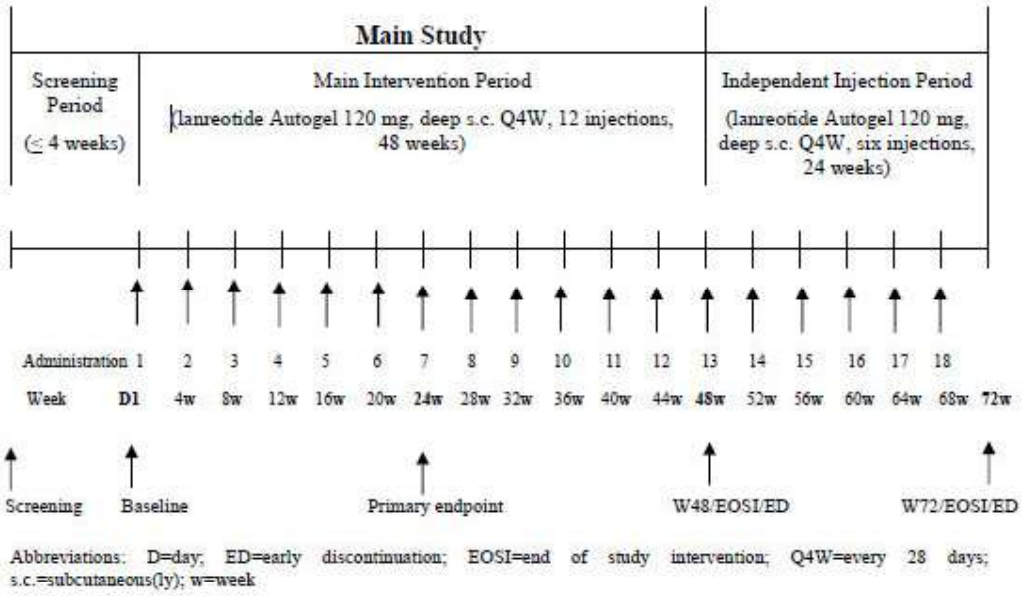
The maximum duration of the study is approximately 24 months (main study: approximately 18 months).

Maximum duration of the study per participant:

- Screening period: up to 4 weeks
- Main study period: 48 weeks
- Independent injection period for the independent injection cohort only: additional 24 weeks

After the end of study assessments, participants will enter a remote post-intervention survival follow-up period and a telephone call will be used to collect survival status and subsequent therapies. This follow-up will be performed for all participants (irrespective of whether they participate in the independent injection period or not) within 4 weeks after the last participant enrolled in the study reaches W48 or W72(for independent injection period only) or until the day of discontinuation.

Figure 1 Study Schema



Abbreviations: D=day; ED=early discontinuation; EOSI=end of study intervention; Q4W=every 28 days; s.c.=subcutaneous(ly); w=week

Note: W48/EOSI=end of main study (after 48 weeks of intervention period) for all participants; W72/EOSI=end of independent injection period only for independent injection period

After finishing the intervention in the main study period or the independent injection period, the investigator will record overall survival status within 4 weeks after the last participant last visit in either period reaches W48 or W72, respectively, or the day of discontinuation, irrespective of subsequent therapy

2.3 Sample Size Determination and Power

Approximately 51 participants will be enrolled to achieve 43 receiving study intervention in the main study period and 36 participants evaluable for CBR at W24. Based on Chinese epidemiology, it is expected to have the relevant representation of all types of GEP-NETs in the Chinese population, including Pan-NET and GI-NET.

Note: "Enrolled" means a participant's, or their legally authorised representative's, agreement to participate in a clinical study following completion of the informed consent process.

The expected CBR at W24 was set to 64% based on the results from Japanese Study ITM-014N-001 and global pivotal Study 2-55-52030-726 (CLARINET; NCT00353496). The threshold CBR at W24 was defined as 40% based on Japanese Study ITM-014N-001 and medical expert's opinions. When a statistical test was performed for a null hypothesis with one-sided type I error of 2.5%, a minimum sample size required to yield a power of at least 80% would be 36 participants. Considering a 15% drop-off rate, 43 participants would be necessary for the primary efficacy evaluation of CBR at W24.

To provide clinical experience of independent injection in Chinese participants, approximately five qualified participants (having a positive benefit/risk ratio) will have independent injection of lanreotide Autogel during the 24 weeks of the independent injection period (assuming 10 to 25% eligible participants after 48 weeks of intervention in the main study will continue to receive independent injection). The aim is to achieve five participants that have been trained to perform independent injections and are considered able to independently administer lanreotide from the investigator.

2.4 Randomisation and Blinding (if applicable)

This is a non-randomised, open-label study.

2.5 Schedule of Assessments

Schedule of assessments is presented in section 1.3 from the protocol.

2.6 Change from Statistical Section of the Protocol

There is no change in SAP from statistical section of the protocol.

3 PLANNED ANALYSES

3.1 Data Monitoring

No independent DMC will be used in this study.

3.2 Interim Analysis / Primary Analysis

No interim analysis will be performed. Two analyses will be performed according to the following data cut-offs in the main study period.

The first analysis will be performed when all participants complete the first 24 weeks of the main study period. The cut-off date considered for this analysis is the date of the last W24 visit for the last participant. All available data at the time of this data cut-off date will be included in this analysis. The purpose of this analysis is the final analysis of the primary efficacy endpoint, as well as efficacy and safety analyses of the first 24 weeks of the main study period. This analysis will not be considered as an interim analysis because the first 24 weeks of main study period is of primary interest.

The second analysis will be performed when all participants have had the opportunity to complete the main study (W48). The reporting database will include all main study data for all participants enrolled into the study.

3.3 Final Analysis

The third and final analysis will be performed when the last participant completes the independent injection period. The reporting database will include all independent injection period study data.

4 ANALYSIS SETS

Enrolled Set

The enrolled set will contain all participants who sign the ICF.

Safety Set

The safety set will contain all participants who receive at least one dose of study intervention. If there is any doubt whether a participant was treated or not, they will be assumed treated for the purposes of analysis.

Intention-To-Treat (ITT) Set

The ITT set will contain all participants who receive at least one dose of study intervention.

Modified Intention-To-Treat (mITT) Set

The mITT set will contain all participants in the ITT having at least W24 data recorded for the primary efficacy endpoint.

Per Protocol Set

The per-protocol set (PP) will contain all participants in the mITT who did not experience any major protocol deviations that may interfere with the efficacy evaluation. Please refer to section 5.3 for details regarding the management of deviations.

Immunogenicity Set

The immunogenicity set will contain all participants in the ITT who have baseline and at least one postbaseline anti-lanreotide antibody result.

Independent Injection Set

The independent injection set will contain all participants who receive the study intervention by independent injection.

5 STATISTICAL METHODS/ANALYSES

The statistical analyses will be performed in accordance with ICH E9 guideline and guidelines presented in section 8.

TigerMed will perform the statistical analysis of this study under the supervision of the data management/statistical department of IPSEN.

5.1 General Considerations

The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures, and derived listings. Unless otherwise specified, min and max values will be reported with the same decimal as the units of measure; the mean, median and SD will be reported to 1 greater decimal place, all of them will not be greater than 4 decimal places. Any values that require transformation to standard units (metric or International System [SI]) will be converted with the appropriate corresponding precision.

Percentages of categorical variables will be presented to 1 decimal place unless otherwise specified.

All statistical analyses will be performed using the SAS® software version 9.4.

5.1.1 Outputs Presentation

5.1.1.1 Tables Header

Since this is a single-arm study, all summary tables will be presented by treatment group.

5.1.1.2 Presentation of Treatment Group

Tables, Figures and Listings (TFLs) will be displayed using the following treatment group labels:

Lanreotide Autogel 120mg

5.1.1.3 Presentation of Visits / Timepoints

Summaries by visit will be presented using visit number as collected in the Electronic Case Report Form (eCRF).

Visits in the TFLs will be presented as follows and in the following order:

Long Visit Name	Short Name
Screening (Visit 1)	Scr
Baseline (Visit XX)	Bsl
Week 4 (Visit 3)	W4
Week 8 (Visit 4)	W8
Week 12 (Visit 5)	W12
Week 16 (Visit 6)	W16
Week 20 (Visit 7)	W20
Week 24 (Visit 8)	W24

Week 28 (Visit 9)	W28
Week 32 (Visit 10)	W32
Week 36 (Visit 11)	W36
Week 40 (Visit 12)	W40
Week 44 (Visit 13)	W44
Week 52 (Visit 15)	W52
Week 56 (Visit 16)	W56
Week 60 (Visit 17)	W60
Week 64 (Visit 18)	W64
Week 68 (Visit 19)	W68
End of Study Intervention in Main Intervention Period	EOSIM
End of Study Intervention in Independent Injection Period	EOSII
Early Discontinuation in Main Intervention Period	EDM
Early Discontinuation in Independent Injection Period	EDI
Remote Follow-up	FU

Note: The baseline visit name in tables will be displayed as “Baseline”, and in the listings the baseline flag may correspond to values from Visit 1, Visit 2 or sometimes unscheduled visit.

5.1.2 Descriptive Statistics

All raw and derived variables will be listed and described using summary statistics. For categorical variables, summary statistics will be displayed using descriptive statistics by frequency count and percentages by category. The missing category will be presented if there is at least one missing category for at least one treatment group. Except otherwise specified, participants with missing data will be included in the calculation of percentages. For quantitative variables, summary statistics will be displayed using descriptive statistics by number of observations, mean, standard deviation (SD), first quartile, median, third quartile, minimum and maximum. Frequency and proportion of missing data will be displayed.

5.1.3 Baseline value

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to first Investigational Medicinal Product (IMP) administration (including unscheduled assessments). If the assessment time and/or IMP administration time is not collected, the assessment performed on the same day as the first IMP administration will be considered as baseline.

5.1.4 Reference Start Date and Study Day

Reference start date is defined as the day of the first IMP administration.

The day of the first IMP administration will be Day 1. Study day will be calculated as:

- The difference between the event date and the reference date plus one day, if the event is on or after the reference date.

- The difference between the event date and the reference date, if the date of event is prior to the reference date.

Study day will appear in any listings where an assessment date or event date appears.

In case of partial or missing event date, study day will appear missing while any associated durations will be presented based on the imputations described in appendix A2.

5.2 Disposition and Analysis Sets

Following disposition summaries and listings will be provided:

- Summary table with the number and percentages of treated participants per site on the ITT set,
- Summary table with the number and percentage of participants screened, screen failed, reason for screen failures, treated, completed, withdrawn and reason for withdrawal on the enrolled set,
- Summary table on duration of participant participation in the study. The definition of the duration of participant participation is from date of consent to the last study visit on the ITT set,
- Summary of the number and percentage of participants with treatment discontinuation or study withdrawal due to COVID-19,
- Summary of the number and percentage of participants with study disruption due to COVID-19,
- Listing of dates of visit including duration of participant participation on the ITT set,
- Listing of screen failure participants on the enrolled set,
- Listing of withdrawal participants on the ITT set,
- Listing of participants impacted by COVID-19,
- Listing of participants with study disruption, including missed tumour assessment and dose delay due to COVID-19.

Following summaries and listings will be provided on the ITT set:

- Listing of participants not meeting at least one inclusion criteria,
- Listing of participants fulfilling at least one exclusion criteria,
- Summary of the number and percentage of participants in each analysis set by treatment group, based on all treated participants with reasons for exclusion from each analysis set,
- Listing including flag for each analysis set and reason for exclusion from each set.

5.3 Protocol Deviations

An exhaustive list of major protocol deviations that may occur during the course of the study and any action to be taken regarding exclusion of participants from the PP set is defined in protocol deviation log. Major protocol deviations will be determined before database lock of the study, finalised during the blind data review and documented in a separate document.

Following protocol deviation summary and listing will be provided on the ITT set:

- Number and percentage of participants with major protocol deviations by deviation category (see DV section of Standard Study Data Tabulation Model (SDTM) user guide).
- Number and percentage of participants with major protocol deviations related to COVID-19 by deviation category
- A Listing of major protocol deviations.
- A listing of all protocol deviations by deviation class (e.g. minor/major)
- A listing of protocol deviations related to COVID-19 by deviation class (e.g. minor/major)

5.4 Demography and Other baseline characteristics

All demographic and baseline characteristics summaries and listings will be provided for the ITT set and mITT set.

Following summaries will be provided on:

- Demographic variables (age, age categories (from 18 to 64 years/from 65 to 84 years/85 years and over), sex, ethnicity, race, height),
- Other baseline characteristics (weight, BMI, tobacco use, alcohol use),
- Disease characteristics:

  type of GEP-NET (functioning/non-functioning);

  NET grade;

  mitotic count;

  proliferation index Ki67;

  time since initial diagnosis;

  primary NET site;

  menopausal (yes/no);

  has the assessment of Somatostatin receptor been performed (yes, no, unknown);

  the outcome of Somatostatin receptor (Positive, Negative)

  the method of performing Somatostatin receptor (Imaging, Immunohistochemistry)

  presence or absence of NET-related symptoms;

  sum of diameters for target lesions;

  presence or absence of progression;

  follicle stimulating hormone result;

  ECOG performance score.

Listings will also be provided for all the summaries listed above.

5.5 Medical history, non-drug therapies, medications and surgical procedures

Medical and surgical history, non-drug therapies, surgical procedures and clinical symptoms will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) in effect within IPSEN at the time of database lock. Medications will be coded using the latest version of World Health Organization-Drug dictionary in effect within IPSEN at the time of database lock.

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the first IMP administration and the last IMP administration to allow classification as either Prior only, Prior and Concomitant, Concomitant only, or Subsequent only:

Prior (P)	Start and stop dates prior to the date of the first IMP administration.
Prior and Concomitant (PC)	Start date before the date of the first IMP administration and stop date on or after the date of the first IMP administration.
Concomitant (C)	Start date on or after the date of first IMP administration.
Subsequent	Start date after the date of last IMP administration.

Summary tables on prior medications/non-drug therapies/surgical procedures will include “P” only, summary tables on concomitant medications/non-drug therapies/surgical procedures will include “C” and “PC”.

See detailed rules in appendix A2 for classification of prior and concomitant medication/non-drug therapies, surgical procedures in case of partial/missing date.

The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code, that is, corresponding to the first 3 figures.

Following summaries, presenting count and percentages of participants will be provided on the ITT set:

- Medical and surgical history by primary system organ class (SOC) and preferred term (PT),
- Prior medications (P) for the study indication by ATC class (ATC level 2) and preferred Name PN,
- Concomitant medications (PC, C) for the study indication by ATC class (ATC level 2) and Preferred Name PN,
- Prior non-drug therapies (P) by primary SOC and PT,
- Concomitant non-drug therapies (PC, C) by primary SOC and PT,
- Prior surgical procedures (P) by primary SOC and PT,
- Concomitant surgical procedures (PC, P) by primary SOC and PT,
- Prior radiotherapies (P) by primary SOC and PT,
- Concomitant radiotherapies (PC, C) by primary SOC and PT,
- Subsequent medications for the study indication by ATC class (ATC level 2) and preferred Name PN,
- Subsequent surgical procedures by primary SOC and PT,
- Subsequent radiotherapies by primary SOC and PT.

Listings will be provided for all the summaries listed above. These listings should include a flag indicating the category (P, PC, C) as described in the table above.

A prohibited medication or therapy or procedure listing be provided including the following drugs and procedures:

- Interferon, PRRT (other than that used for imaging or SSTR scintigraphy), chemotherapy or chemoembolisation, radiofrequency ablation or cryoablation
- Any somatostatin analogues other than study intervention
- GH antagonist
- Cyclosporin
- mTOR inhibitor, MTK inhibitors
- Tumour resection

5.6 Compliance

Compliance will be calculated by period as: number of actual injections/number of planned injections in main intervention period or in independent injection period.

Following summary and listing will be provided on the safety set:

- Descriptive statistics of compliance including number of percentage of participants by class of compliance and period (e.g. <80%, >=80%).

- A listing of treatment compliance including whether each subject is affected by COVID-19.

5.7 Efficacy

5.7.1 General Considerations

The primary efficacy evaluation will be performed on the intention-to-treat (ITT) set.

Sensitivity analysis of the primary efficacy evaluation will be based on the modified intention-to-treat (mITT) set and the per protocol set (PP). Secondary analyses will be performed on the ITT set.

A listing of all efficacy data (raw and derived) should be provided (see listing detail conventions in Appendix A4). Descriptive statistics will be provided for all endpoints.

5.7.1.1 Significance Testing and Estimations

All statistical tests will be two-sided at the 5% level of significance. Confidence intervals will be 95%, unless otherwise specified in the description of the analyses.

5.7.1.2 Handling of Dropouts and missing data

The imputation of missing single item values in the quality-of-life questionnaires (EORTC QLQ-C30 and QLQ-GI.NET21) within one visit will be made following the recommendations for these questionnaires [Fayers PM, 2021]. If for a patient at least half of the items from the respective scale have been answered, the missing items will be imputed with the average value of those items which are present. For all other variables, no adjustments will be made for missing data in the analysis.

5.7.1.3 Statistical/analytical issues

Adjustments for Covariates

No covariate adjustment analysis is planned in this study.

Interim Analyses and Data Monitoring

No interim analysis will be performed. Please refer to section 3.

Multicentre Studies

No by-centre displays or adjustments for centre are planned for this study.

Multiple Comparisons/Multiplicity

Multiplicity will not be adjusted.

5.7.2 Analysis of Primary Efficacy Endpoint

5.7.2.1 Endpoint and Treatment Effect Definition

The primary efficacy endpoint is CBR of tumour response assessed using RECIST (Version 1.1) and confirmed by BICR at W24.

CBR is defined as the proportion of participants with a best overall response of confirmed CR, confirmed PR, or continued SD until the time of assessment.

Unconfirmed PR or CR preceding SD or following SD are treated as SD. Thus, in the data analysis this situation will be regarded as continued SD.

5.7.2.2 Primary Analysis

For the primary efficacy endpoint CBR at W24, the summary statistics of number and percentage of participants and point estimates and exact 95% CIs based on the Clopper-Pearson method will be calculated based on ITT.

The SAS code to be used could be presented in Appendix A1.

A listing will be provided including all participants with missing values for the primary endpoint. For these participants, the listing will provide all observed data related to the primary endpoint i.e. all measurements recorded prior to the missing value, any measurements recorded after the missing value, important baseline characteristics, the reason and timing for study discontinuation. The listing will also provide the imputed value(s) (if applicable) used in the primary analysis and any sensitivity analyses.

5.7.2.3 Sensitivity Analysis

Sensitivity analyses will be conducted to further explore the primary efficacy endpoint with the same statistical method on the mITT set.

A PP set will also be used to explore the primary efficacy endpoint with the same statistical method.

5.7.2.4 Supplementary Analysis

No supplementary analyses will be performed.

5.7.2.5 Subgroup Analysis

Descriptive subgroup analyses of the primary efficacy variable will be performed on the following factors. The subgroups include:

- Age: ⩽65 years or >65 years
- Sex: Male or Female
- Progression at baseline: Yes or No
- Previous treatment for NET (drug or other treatment method): Yes or No
- Progression at baseline, Previous treatment for NET (drug or other treatment method): (Yes, Yes) or (Yes, No) or (No, Yes) or (No, No)
- Classification of site of primary tumour: gastric, pancreas, midgut, hindgut, other
- GEP-NET Grading: 1, 2
- Somatostatin receptors: (Yes or No or Unknown)
- COVID-19 impact on treatment or not: (Yes or No)

5.7.3 Analysis of Key Secondary Efficacy Endpoints

5.7.3.1 Endpoint and Treatment Effect Definition

Secondary efficacy endpoints and evaluations are summarised in table 1.

Table 1 Secondary Endpoints and the related definition

Endpoint	Variable	Definition
PFS within 24 and 48 weeks after the first administration of study intervention	PFS	Time from the first administration of study intervention to the date of the first documented PD measured using RECIST (Version 1.1) and confirmed by BICR, or

		death from any cause, whichever comes first.
OS at the end of the main study	OS	The time from the first administration of study intervention to the date of death from any cause
TTP within 48 weeks after the first administration of study intervention	TTP	The time from the first administration of study intervention to the date of the first documented PD, or clinical progression confirmed by the investigator
Proportion of participants alive and without tumour progressive at W24 and W48	Proportion of participants alive and without tumour progressive	The number and proportion of participants alive and without progressive disease at W24 and W48
CBR at W48	CBR	The proportion of participants with a best overall response of confirmed CR, confirmed PR, or confirmed SD until the time of assessment
ORR at W24 and W48	ORR	The proportion of participants with a best a best overall response of confirmed CR, confirmed PR
DCR at W24 and W48	DCR	The proportion of participants with a best overall response of confirmed CR, confirmed PR or SD
Change from baseline in NET-related clinical symptoms at W24 and W48	Change from baseline in NET-related clinical symptoms	NET-related clinical symptoms (eg: flushing, diarrhea, abdominal pain, weakness, heartburn, nausea, vomit, sweating, tremor, palpitation, or erythema)
Change from baseline in plasma CgA, 5-HIAA and other biomarkers in the circulation at W12, W24, W36 and W48	Change from baseline in plasma CgA, 5-HIAA and other biomarkers	Other biomarkers include: Gastrin, Glucagon and Insulin.
Change from baseline in QoL assessment at each visit	Change from baseline in QoL assessment	See section 7

5.7.3.2 Main Secondary Analysis

For time-to-event endpoints (PFS, TTP and OS), the survival curve will be estimated by the Kaplan-Meier estimate, the proportion of subjects with event or censored and the median survival and its 95% CI, and Kaplan-Meier estimated probabilities with corresponding 95% CIs

at W24 and W48 will be provided based on ITT. The listing of PFS, TTP and OS will also be provided.

Censoring rules for the PFS and TTP endpoints are shown in table 2.

Table 2 Censoring Rules for PFS and TTP Endpoints

Situation	Date of Progression or Censoring	Outcome
No baseline radiological assessments	The day of first administration	Censored
Confirmed (documented) PD during the study	Date of radiological assessment showing PD	Event
No death or confirmed PD	Date of last adequate radiological assessment	Censored
Study intervention discontinuation for clinical (unconfirmed) progression	Date of last adequate radiological assessment	Censored
Study intervention discontinuation for toxicity or reason other than confirmed PD, clinical progression or death	Date of last adequate radiological assessment	Censored
New anticancer treatment for GEP-NET started with no confirmed PD beforehand	Date of last adequate radiological assessment before start of new treatment	Censored
Death during the study before confirmed PD	Date of death (PFS)/Date of last adequate radiological assessment (TTP)	Event (PFS)/Censored (TTP)
Confirmed PD after two or more missed radiological assessments	Date of last adequate radiological assessment before missed assessments	Censored
Study intervention discontinuation for other than confirmed PD or death, and no postbaseline radiological assessments	The day of first administration	Censored

The OS will be assessed once the data from the last participant completing the main study are available. Participants who are not known to have died at the time of the analysis will be censored. Where possible, post-intervention survival status will be confirmed for all participants that are alive at the last assessment. Any participant who is confirmed to be alive will be censored at this time. Any participant who could not be contacted at this time will be censored at the time that the participant was last confirmed to be alive.

The below secondary endpoint will be assessed by Kaplan-Meier method based on ITT.

- A summary of number and percentage of participants who are alive and without tumour progression at W24 and W48 and their 95% CI will be calculated by the Kaplan-Meier method.

The below secondary endpoints will be assessed by the same statistical method as the primary efficacy endpoint based on ITT.

- A summary of number and percentage of participants with CBR at W48
- A summary of number and percentage of participants with ORR at W24 and W48
- A summary of number and percentage of participants with DCR at W24 and W48

The below secondary endpoints will be assessed by the descriptive statistics based on ITT:

- A summary of change from baseline in NET-related clinical symptoms at W24 and W48
- A summary of change from baseline in QoL assessment at W12/W24/W36/W48 using the EORTC QLQ-C30
- A summary of change from baseline in CgA, 5-HIAA and other biomarker(s) in the circulation at W24 and W48.

5.7.3.3 Subgroup Analysis

No subgroup analysis for main secondary efficacy endpoints.

5.7.4 Analysis of Exploratory Endpoints

Descriptive statistics will be used to summarise the exploratory efficacy endpoints on independent injection set:

- A summary of proportion of participants preferring independent injection over HCP injections at W72
- A summary of participant-reported indirect costs (e.g. transport costs) at W48 and W72
- A summary of participant-reported work productivity at W48 and W72
- The antitumour effect CBR (assessed by imaging) at W72
- A summary of change from baseline in NET-related symptoms control at W72 (if applicable)
- A summary of change from baseline in CgA, 5-HIAA and other biomarkers in the circulation at W72
- A summary of change from baseline in QoL at W72.

5.7.5 Analysis of COVID-19 impacts on efficacy endpoints

Primary Efficacy Endpoint

For the primary efficacy endpoint CBR at W24, the summary statistics of number and percentage of participants and point estimates and exact 95% CIs based on the Clopper-Pearson method will be calculated based on ITT without missed or delayed study intervention due to the COVID-19 up to W24.

Further analyses will be conducted to explore the primary efficacy endpoint with the same statistical method on the subsets of ITT. The subsets of ITT include:

- ITT with dose delayed due to COVID-19 up to W24,
- ITT with 1 dose missing due to COVID-19 up to W24,
- ITT with 2 or more doses missing due to COVID-19 up to W24.

Secondary Efficacy Endpoints

For the secondary efficacy endpoints (OS and PFS), the survival curve will be estimated by the Kaplan-Meier estimate, the proportion of subjects with event or censored and the median survival and its 95% CI, and Kaplan-Meier estimated probabilities with corresponding 95% CIs at W48 will be provided based on ITT without missed or delayed study intervention due to the COVID-19 up to W48.

Note: Due to the possible impact of COVID-19, the evaluation for the primary efficacy endpoint at scheduled visits after the first dose may be delayed. After performing the remapping step (see

the note in visit window section), if the tumour evaluation at a scheduled visit after the first dose is delayed and there is no record of unscheduled visit before the next scheduled visit, the missing tumour evaluation results at scheduled visits will be imputed by the results of delayed evaluation at the next scheduled visit.

5.8 Safety

5.8.1 General Consideration

All safety summaries and analyses will be based upon the safety set. All safety data will be included in participant data listings (see listing detail conventions in Appendix A4).

Baseline value definition is given in section 5.1.3. Rules to handle multiple observations of the same parameter that occurred for the same visit/timepoint are explained in section 5.1.1.3. If conversion factors are used, they should be presented either in the relevant section or a link to section 7 should be added.

All AEs will be recorded and graded according to the current version of the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

5.8.2 Extent of exposure

Duration of exposure will be defined in weeks as:

Weeks of exposure = (Date of last study drug administration – Date of first study drug administration + 28)/7.

The following extent of exposure summaries will be presented in each period:

- Summary of the duration of exposure to treatment, by treatment group. Provide the mean, median, and the count and percentage of participants exposed for specified periods.
- Summary of the actual dose by treatment group. Provide the mean, median, sum and the count and percentage of participants.
- Summary of number of injections,
- Summary of dose intensity (dose intensity = cumulative dose/planned total dose *100%.),
- Listing of exposure data.

5.8.3 Adverse Event

All adverse events (AEs) recorded in the eCRF will be coded using the latest version of MedDRA dictionary in effect within IPSEN at the time of the database lock. AEs will be classified as treatment-emergent AEs (TEAEs) during main intervention period and TEAEs during independent injection period according to the rules below:

- Within each period, events with start date on or after the date of first IMP administration and up to EOS or 4 weeks after date of last dose of treatment,
- Within each period, events whose CTCAE grade worsens on or after the date of first IMP administration,
- Refer to appendix Partial/Missing Date Convention' for handling of partial date.
- In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the most conservative case; i.e. treatment emergent.

The following summaries will be presented by treatment group and by period:

- An overview table summarizing the

  - number and percentage of participants with at least one of the following AEs: any AE, any TEAE, Serious Adverse Event (SAE), serious TEAE, drug-related TEAE, drug-related serious TEAE, non-serious TEAE, TEAE leading to treatment discontinuation, TEAE leading to discontinuation from the study, CTCAE Grade >=3 TEAE, TEAE leading to death, serious TEAE leading to death, drug-related serious TEAE Leading to Death, serious TEAE leading to treatment discontinuation, serious TEAE leading to discontinuation from the study,
  - corresponding number of events for each of the AE categories listed above (these should be distinguished from counts and rates of participants e.g. marked by square brackets [])

- A summary of the number and percentage of participants reporting an AE by treatment group, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by treatment group, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by treatment group and PT,
- A summary of the number and percentage of participants reporting a TEAE by treatment group, CTCAE grade, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by treatment group, causality, SOC and PT,
- A summary of the number and percentage of participants reporting a drug-related TEAE by treatment group, CTCAE grade, SOC and PT,
- A summary of non-serious TEAE by treatment group, SOC and PT,
- A summary of the number and percentage of participants reporting a serious TEAE related to COVID-19 by treatment group, SOC and PT.

AEs summaries will be ordered in term of decreasing frequency for SOC and PT within SOC, and then alphabetically for SOC and PT within SOC. AEs summaries by PT will be ordered in term of decreasing frequency of PT, and then alphabetically for PT.

AEs will be counted as follows:

- Participants with more than one AE within a particular SOC are counted only once for that SOC. Similarly, participants with more than one AE within a particular PT are counted only once for that PT;
- Participants reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case CTCAE grade (grade order: 5>4>3>2>1>missing) will be used in the corresponding CTCAE grade summaries;
- Participants reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case relationship to study medication (order: related > not related > missing) will be used in the corresponding relationship summaries;
- If the CTCAE grade is missing for a TEAE, it will be considered as missing in the summary tables;
- Summary by CTCAE grade will be presented (in the same order as above);
- If the causality is missing for a TEAE, it will be considered related in the summary tables;

- The non-serious TEAEs table should include a specific row "any non-serious TEAE above 10%;

In addition, a listing with all AEs data will be listed by treatment group and period including non-TEAEs, Treatment-emergence status will be flagged in the listing.

The following listing will be provided by period:

- A listing of all deaths that occurred during the study,
- A listing of all SAEs,
- A listing of all adverse events leading to discontinuation of study treatment,
- A listing of participants reporting a serious TEAE related to COVID-19

Deaths, SAEs, and Other Significant Adverse Events (AE)

The following summary tables will be provided by period:

- A summary of the number and percentage of on-treatment deaths (including SAEs with fatal outcome and deaths as PT), by treatment group,
- A summary of the number and percentage of deaths (including SAEs with fatal outcome and deaths as PT), by treatment group,
- A summary of the number and percentage of subjects reporting a serious TEAE, by treatment group, SOC and PT,
- A summary of the number and percentage of subjects with AEs leading to discontinuation of study treatment, by treatment group, SOC and PT.

Injection site related reactions

The following summary tables will be provided by period:

- A summary of the number and percentage of participants reporting an injection site related reaction, by treatment group, SOC and PT,

The following listing will be provided by period:

- A listing of all injection site related reactions that occurred during the study.

5.8.4 Laboratory Data

All laboratory data will be presented in the units of International System of Units (SI). The tests detailed in table 3 will be performed by the local laboratory.

Table 3 Protocol-Required Clinical Safety Laboratory Tests

Test	Parameters Assessed
Pregnancy testing	Highly sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential)
Other screening tests	FSH (as needed in women of non-childbearing potential only)
Haematology	Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell

	count, and differential white blood count (neutrophil, eosinophil basophil, monocyte and lymphocyte)	
Biochemistry	Liver function	Total protein, albumin, total and direct bilirubin, ALP, ALT, AST, GGT
	Renal function	Blood urea nitrogen, creatinine
	Pancreatic function	Amylase, lipase
	Lipid profile	LDL cholesterol, HDL cholesterol, triglyceride
	Electrolytes	Sodium, potassium, chloride
	Minerals	Calcium, inorganic phosphate,
	Miscellaneous	Fasting glucose, HbA1c, lactate dehydrogenase
Endocrinology	FT3, FT4, TSH, and prolactin	
Coagulation	aPTT, PT, INR	
Urinalysis	Protein, glucose, urobilinogen and occult blood	

Describe the summaries that are to be provided. These may include the following summaries:

- A summary of the actual and change from baseline in each laboratory parameter by treatment group and timepoint,
- A shift from baseline of the number and percentage of participants experiencing Abnormalities.
- A summary of the number and percentage of participants experiencing treatment-emergent clinically significant laboratory abnormalities, by laboratory parameter and treatment group,
- A shift from baseline to worst post-dose (i.e. highest grade) in CTCAE Grade of laboratory results.

For shift tables, the denominator should be the number of participants with both a baseline and a post-baseline assessment at a given timepoint.

In addition, the following listings are to be provided:

- A listing of all laboratory data. Out-of-reference-range values will be flagged as high (H) or low (L),
- Laboratory reference ranges,
- A listing of Abnormalities. All data for a laboratory parameter will be displayed for a participant having at least one post-baseline Abnormality(with flag indicating Abnormality),
- A listing of CTCAE grade 3 and higher values. All data for a laboratory parameter will be displayed for a participant who has any post-baseline value with CTCAE grade greater than or equal to 3 for the parameter.

5.8.5 Vital Signs

Weight, temperature, pulse rate, respiratory rate, and systolic/diastolic blood pressure will be assessed. Describe the summaries that are to be provided. These may include:

- A summary of the actual and change from baseline in each vital sign parameter by treatment group and timepoint,

The following listing are to be provided:

- A listing of vital sign data by treatment group, with abnormal value highlighted.

5.8.6 Electrocardiogram (ECG)

The following quantitative ECG measurements will be taken during the study:

- Normal Sinus Rhythm (yes/no),
- heart rate (bpm),
- PR interval (msec),
- QRS duration (msec),
- QT interval (msec),
  Bazett corrected QT (QTcB) interval (msec) = QT/$\sqrt{RR}$;
  Fridericia corrected QT (QTcF) interval (msec) = QT/$\sqrt[3]{RR}$);
- Corrected QT Interval (msec).

An overall Investigator assessment of ECG will be provided as "normal", "abnormal, not clinically significant" and "abnormal, clinically significant".

The following summaries of ECG data will be provided:

- A summary of the actual and change from baseline in each ECG parameter by treatment group and timepoint,
- A Shift from baseline (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) to each post-baseline visit.

The following listing are to be provided:

- A listing of ECG data by treatment group, with abnormal value highlighted.

5.8.7 Physical Examination

The following summary and listings will be provided:

- A shift from baseline (normal vs abnormal) to each post-baseline visit
- A listing of physical examination data,
- A listing with any participants with at least one physical examination abnormality.

5.8.8 Other (if applicable)

Pregnancy data will be shown in a data listing.

For gallbladder ultrasonography data, a shift from baseline (normal vs abnormal) to each post-baseline visit is needed and also the related listing should be provided.

5.9 PK (if applicable)

Not applicable.

5.10 Anti-drug Antibodies (if applicable)

Serum lanreotide levels and antidrug antibodies (ADA) assessments will be performed by a bioanalytical CRO (LabCorp) under Ipsen REED/DMPK department's supervision using a validated method. The analysis for ADA will be based on immunogenicity set.

A listing of antibodies sampling times and any deviations from the scheduled times will be provided.

Concerning ADA sample results, the following definitions will be considered:

- Seroconverters are subjects with negative ADA at baseline and positive ADA post-treatment.
- Seroreverters are subjects with positive ADA at baseline and negative ADA post-treatment.
- Incidence is defined as the proportion of seroconverters.

The following conventions will be considered:

- Percentage of seroconverters and incidence should be calculated using the number of subjects with a baseline assessment and at least one ADA assessment posttreatment.
- Percentages of seroreverters should be calculated using the number of subjects with positive ADA at baseline and at least one ADA assessment posttreatment.

The following summaries of ADA data will be provided:

- An overall summary of ADA status with:
- Number and percentage of positive baseline results;
- Number and percentage of seroconverters;
- Number and percentage of seroreverters.
- A listing of individual antibodies results will also be provided as well as two tables including:
- The percentage of subjects developing anti-lanreotide antibodies at each ADA time point; and
- Descriptive statistics on anti-lanreotide antibodies titer.

6 DATA HANDLING

6.1 Visit window

All data will be organized and analysed according to the scheduled visits outlined in the protocol. As defined by the protocol, screening has to be performed within 4 weeks before fist treatment. And all participants will receive a fixed dose of lanreotide Autogel 120 mg by deep subcutaneous injection every 28 days during the study. There is an allowed window of ±3 days for each injection.

Participants who discontinue study intervention but have not withdrawn from the study must be followed for survival data until death or within 4 weeks after the last W48 visit of the last participant in the main intervention period or within 4 weeks after the last W72 visit of the last participant in the independent injection period (unless the participant has specifically withdrawn consent for any further contact).

Note: Due to the possible impact of COVID-19, the tumour evaluation at scheduled visits after the first dose may be delayed. If the tumour evaluation at a scheduled visit after the first dose is delayed and there is a valid evaluation record at unscheduled visit before the next scheduled visit, the missing tumour evaluation results at scheduled visits will be remapped by the results of delayed evaluation at unscheduled visit before the next scheduled visit. If there are more than two consecutive scheduled visits delayed and there is a valid evaluation record at unscheduled visit before the next scheduled visit, the last missing tumour evaluation result at scheduled visits will be not remapped by the results of delayed evaluation at unscheduled visit before the next scheduled visit.

If the tumour evaluation at a scheduled visit after the first dose is delayed and there is no record of unscheduled visit before the next scheduled visit, the missing tumour evaluation results at scheduled visits will be not remapped.

6.2 Unscheduled Visits, Retest, Withdrawal Visit,

All listings will include retests and unscheduled visits, while for the description by visit in the tables, only the scheduled visits according to the protocol will be described.

Unscheduled visit and retest measurements will be used to provide a measurement for a baseline data or endpoint value (e.g. worst value), if appropriate according to their definition. These measurements will also be used to determine abnormal laboratory, vital signs values or ECG.

If a value requires a retest (for laboratory values, vital signs and ECG) the closest non-missing reliable value to the scheduled visit will be used in the summary tables.

Participants who have withdrawn early from the study have their last assessment entered as visit 90 in the eCRF.

6.3 Laboratory Values or Concentration Data

For laboratory values or concentration data below the lower limit of quantification (LLOQ) like "<xxx" or "<=xxx", or above the upper limit of quantification (ULOQ) like ">xxx" or ">=xxx", LLOQ or ULOQ (xxx) will be used for calculation of descriptive statistics. The original laboratory values or concentration data ("<xxx", "<=xxx", ">xxx" or ">=xxx") are presented in the listing.

7 DERIVED DATA (IF APPLICABLE)

When applicable, below derivation rules should be followed:

- **Change from baseline**

Change from baseline at a given visit will be calculated as a difference from baseline.

- **Age**

Age (years) will be calculated as follows and truncated to the largest integer that is less than or equal to the calculated result:

Age = (date of informed consent date - birth date)/365.25.

- **BMI**

BMI (kg/m2) will be derived as Weight (kg)/[Height(cm)/100]**2 measured at each visit and rounded to the nearest decimal.

- **Quality of Life Questionnaire EORTC QLQ-C30 (Version 3.0)**

The EORTC QLQ-C30 questionnaire contains 30 single items (Q1 – Q30). Q1 – Q28 range from 1 to 4 with 1 being the most favourable answer and 4 the worst case (1 = Not at all, 2 = A little, 3 = Quite a bit, 4 = Very much). Q29 and Q30 range from 1 (= Very poor) to 7 (= Excellent) with 1 being the worst case and 7 the most favourable answer.

Subscores will be derived according to the rules contained within the EORTC Scoring Manual [12]. The subscores will include five functional scales, three symptom scales, a global health status / QoL scale, and six single items (see the below table). Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

Table: EORTC QLQ-C30 definition of subscores

EORTC QLQ-C30	
Subscores Single questions	**Subscores Single questions**
Global health status / QoL (QL)	Q29, Q30
Physical functioning (PF)	Q1, Q2, Q3, Q4, Q5
Role functioning (RF)	Q6, Q7
Emotional functioning (EF)	Q21, Q22, Q23, Q24

Cognitive functioning (CF)	Q20, Q25
Social functioning (SF)	Q26, Q27
Fatigue (FA)	Q10, Q12, Q18
Nausea and vomiting (NV)	Q14, Q15
Pain (PA)	Q9, Q19
Dyspnoea (DY)	Q8
Insomnia (SL)	Q11
Appetite loss (AP)	Q13
Constipation (CO)	Q16
Diarrhoea (DI)	Q17
Financial difficulties (FI)	Q28

All of the subscores range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high /healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

The principle for scoring these scales is the same in all cases:

i) Estimate the average of the items (I1, I2, ..In) that contribute to the scale; this is the raw score.

$$\text{Raw score} = RS = (I1 + I2 + \ldots + I_n) / n$$

ii) Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

For functional scales: $\text{Score} = \{1 - [(RS - 1) / \text{range}]\} \times 100$

For symptom scales and global health status / QOL:

$$\text{Score} = \{(RS - 1) / \text{range}\} \times 100$$

where range is the difference between the maximum possible value of RS and the minimum possible value of RS.

8 REFERENCES

Reference to ICH regulatory guidelines:

- ICH E3: Structure and Content of Clinical Study Reports
- ICH E6 (R2): Good Clinical Practice
- ICH E9: Statistical Principles for Clinical Trials
- ICH E9 (R1) Addendum: Estimands and Sensitivity Analysis in Clinical Trials

Reference to NMPA regulatory guidelines:

- Biostatistics Guidelines for Drug Clinical Trials
- Good Clinical Practice
- Guidelines for Principles of Structure and Content of Clinical Study Report of Drugs
- Guidelines for Data Management and Statistical Analysis Plan and Report of Drug Clinical Trials

Reference to EMA or point to consider guidelines:

- Adjustment for baseline covariates in clinical trials

- Choice of a non-inferiority margin
- Clinical trials in small populations
- Data monitoring committees
- Investigation of subgroups in confirmatory clinical trials
- Missing data in confirmatory clinical trials
- Application with Meta Analyses, One pivotal study
- Multiplicity issues in clinical trials

Switching between superiority and non-inferiority

Reference to FDA guidelines:

- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (December 2018)

Standard Ipsen SDTM user guide

Standard ADaMs user guide

Ipsen Global Style guide

References for all statistical methods are listed below:

- Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by European Organisation for Research and Treatment of Cancer, Brussels 2001.

9 APPENDICES

A1. SAS code

- The code to get exact 95% CIs based on the Clopper-Pearson:

CCI

A2.Partial/Missing Date Convention

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / partial, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or the stop date indicates differently.
- Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the first IMP administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be "≥xx" according to the start and last visit dates).

Algorithm for Prior/ Concomitant/Subsequent

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the first IMP administration and the last IMP administration to allow classification as either Prior only, Prior and Concomitant, Concomitant only, or *Subsequent only*.

In case of partial start and/or stop medication/ non-drug therapies/surgical procedures dates, imputation will be done to determine the classification:

- If a partial start date, the first day of the month will be imputed for missing day and January for missing month,
- If a partial stop date, the last day of the month will be imputed for missing days and December will be imputed for missing month.

In case incomplete start or stop date does not allow the classification, will be classified as concomitant.

Algorithm for TEAE

For deriving the TEAE flag the following process of temporary date imputation is done. The date imputation algorithm for incomplete adverse event start dates is described in Table 4. Classification of adverse event according to its treatment-emergent status is then done using the imputed date.

In the following table, all dates are presented using an YYYY-MM-DD format. As an example, suppose First IMP administration = 2002-08-11 and several AEs have incomplete start dates.

Table 4: Data imputation algorithm for AE start date

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day is missing			
YYYY-MM < YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-07-XX	2002-07-01

YYYY-MM = YYYY-MM of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-08-XX	Min (2002-08-11, AE end date)
YYYY-MM > YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-09-XX	2002-09-01
Day and month are missing			
YYYY < YYYY OF [First IMP admin.]	YYYY-01-01	2001-XX-XX	2001-01-01
YYYY = YYYY OF [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-11, AE end date)
YYYY > YYYY OF [First IMP admin.]	YYYY-01-01	2003-XX-XX	2003-01-01
Day, month, and year are missing			
XXXX-XX-XX	Min ([First IMP admin.], AE end date)		Min (2002-08-11, AE end date)

YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

For studies with injection cycle:

If an AE onset date is partial or missing, the event will be allocated to the first IMP administration where onset could have occurred (taking into account date and time stopped).

If AE end date is partial, imputation could be done assuming the latest possible date (i.e. last day of month if day unknown, or 31st of December if day and month are unknown).

A3. Programming Convention for Outputs

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified.

The mean, median, lower quartile, upper quartile, SD and standard errors (SE) of the mean 95% confidence interval values will be reported to one decimal place greater than the raw data recorded in the database.

The minimum and maximum values will be reported with the same number of decimal places as the raw data recorded in the database.

In general, the maximum number of decimal places reported should be four for any summary statistic.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentage will be calculated using n as denominator. The denominator n will be specified in a footnote for clarification if necessary. If sample sizes are small, the data displays will show the percentages, but in the CSR only frequency counts should be described.

P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such.

Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

A4. Listings conventions

Any listings will contain at least the following data: participant identifier, age and gender. When dates are presented, the associated study days should be included. They should be sorted by treatment group then participant identifier. For multicentre studies, listings should be broken down by centre and treatment group.

Note: In this study (D-CN-52030-411), any listings will contain at least the following data: participant identifier, age and gender. All listings should be sorted by participant identifier.

A5. EudraCT categories for age

For EudraCT results summaries, in addition to quantitative descriptive statistics of age, demographic tables should include presentation of age using the following EudraCT categories (as applicable):

Adults (18-64 years)
From 65 to 84 years
85 years and over