Document Name: dfr52014245 16.1.9 statistical analysis plan 20230130

Clinical	PPD 06-Feb-2023 13:46:06 GMT+0000
Clinical	PPD 06-Feb-2023 17:53:52 GMT+0000
Clinical	PPD 09-Feb-2023 13:33:49 GMT+0000

Approved

STATISTICAL ANALYSIS PLAN

An open-label, multicentre, single arm study to assess the efficacy and safety of triptorelin 6-month formulation administered subcutaneously in participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue

D-FR-52014-245

This statistical analysis plan is based on:
PROTOCOL VERSION AND DATE: VERSION 2.0 – 13 SEPTEMBER 2022

SAP Version	Date
Final Version 1.0	30 January 2023

APPROVAL PAGE

STUDY NUMBER:	D-FR-52014-245
PROTOCOL TITLE:	An open-label, multicentre, single arm study to assess the efficacy and safety of triptorelin 6-month formulation administered subcutaneously in participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue
SAP VERSION:	Final Version 1.0
SAP DATE:	30 January 2023

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan:

Name	Company	Function	Date	Signature
PPD	IPSEN	Statistics Study Lead		esignature
	IPSEN	Medical Monitor		esignature
	SP (PAREXEL)	Senior Statistician		esignature

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Class
BMI	Body Mass Index
C	Concomitant
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ED	Early discontinuation
EMA	European Medicines Agency
EoS	End of study
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone
ICE	Intercurrent Event
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTC	National Cancer Institute – Common Toxicity Criteria
P	Prior

ABBREVIATION	Wording Definition
PC	Prior and Concomitant
PCSA	Potentially Clinically Significant Abnormalities
PK	Pharmacokinetic
PN	Preferred Name
PP	Per Protocol
PR	Time interval from the start of atrial depolarization to start of ventricular depolarization
PSA	Prostate-Specific Antigen
PT	Preferred Term
QRS	Time interval for ventricular depolarization
QT	Time interval for ventricular depolarisation and repolarisation
QTcF	Corrected QT interval by Fredericia
RR	Time between QRS complexes
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures and Listings
TNM	TNM Classification of Malignant Tumors

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol D-FR-52014-245. 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 included in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not included in this SAP will be clearly identified in the respective CSR.

The SAP was planned to be finalised prior to the first participant being enrolled, and the finalization was delayed to accommodate protocol amendment. A separate shell will be provided for tables, figures and listings (TFLs).

Any deviations from the SAP will be documented in the CSR (section 9.8 “Changes in the conduct of the study or planned analyses” as per International Council for Harmonisation (ICH) E3).

This SAP does not cover pharmacokinetics (PK) analysis which will be described in a separate document, if PK analysis is required.

2 PROTOCOL OVERVIEW

2.1 Study Objectives and Hypotheses

The aim of the study is to assess the effects of triptorelin when given every 6-months under the skin to adult males with cancer in the prostate. Triptorelin is an agonist analogue of natural gonadotropin-releasing hormone (GnRH). The principal modification consists of substitution of natural glycine in position 6 by a D-amino acid (D-tryptophan). Clinical and animal studies have provided positive results of triptorelin's action in hormone-dependent disorders such as prostate cancer, endometriosis, central precocious puberty, uterine fibromyomas, in vitro fertilisation and breast cancer.

- **Study objectives and Endpoints**

Study objectives and endpoints are outlined in Table 1 below.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously in maintaining serum testosterone castrate levels in participants with advanced prostate cancer previously treated and castrated with a GnRH analogue	• Percentage of participants maintaining castrate levels of serum testosterone during the study (maintenance of castration defined as testosterone <1.735 nmol/L (50 ng/dL) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337)
Secondary	
• To evaluate the efficacy of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously on castration	• Percentage of participants castrated at each timepoint on Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337 (castration defined as testosterone <1.735 nmol/L (50 ng/dL))
• To evaluate the efficacy of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously on testosterone levels <0.694 nmol/L (20 ng/dL)	• Percentage of participants with a serum testosterone level <0.694 nmol/L (20 ng/dL) during the study • Percentage of participants with a serum testosterone level <0.69 nmol/L (20 ng/dL) at each timepoint on Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337
• To demonstrate the effect of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously to suppress the 'acute-on-chronic' effect following the administration of the second dose	• Percentage of participants castrated on Day 3 and Day 7 after each injection administered on Day 1 and Day 169 (castration defined as testosterone <1.735 nmol/L (50 ng/dL))
• To demonstrate the effect of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously in the maintenance of PSA	• Percent change in PSA from baseline (prior to injection) at Day 169 and Day 337 (Percent change in PSA defined as the absolute value of difference between the PSA values at Day 169 and Day 337 and the baseline value divided by the baseline value)

Objectives	Endpoints
• To demonstrate the safety profile of triptorelin embonate 22.5mg 6-month formulation administered subcutaneously	• Incidence of TEAEs (including local tolerability) throughout the study i.e. up to Day 337 • Change from baseline in clinical safety laboratory parameters (blood chemistry and haematology) at Day 337 • Change from baseline in physical examination at Day 169 and Day 337 • Change from baseline in ECG at Day 337 • Change from baseline in vital signs (blood pressure and heart rate) at each visit up to Day 337

AE=adverse event; ECG=electrocardiogram; PSA=prostate-specific antigen; TEAE=treatment-emergent adverse event
Note: A list of laboratory parameters to be assessed during the study are presented in Protocol Appendix 10.2.

- **Hypotheses**

Hypotheses for this study are defined below.

The primary objective of this study is to evaluate the efficacy triptorelin embonate 22.5 mg (6-month formulation) administered subcutaneously in maintaining serum testosterone castrate levels during the study (maintenance of castration defined as testosterone <1.735 nmol/L (50 ng/dL) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337) with two complete study intervention administrations. Thus, the null hypothesis to be tested is as follows:

Null hypothesis: percentage of participants castrated (serum level of testosterone <1.735 nmol/L) from date of first dose to Day 337 is less than or equal to 90%.

Alternative hypothesis: percentage of participants castrated (serum level of testosterone <1.735 nmol/L) from date of first dose to Day 337 is greater than 90%.

2.2 Overall Study Design and Investigational Plan

This is a phase III, multicentre, open-label, non-comparative, repeat dose study to evaluate the efficacy and safety of triptorelin 6-month formulation (22.5 mg) administered subcutaneously in participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue.

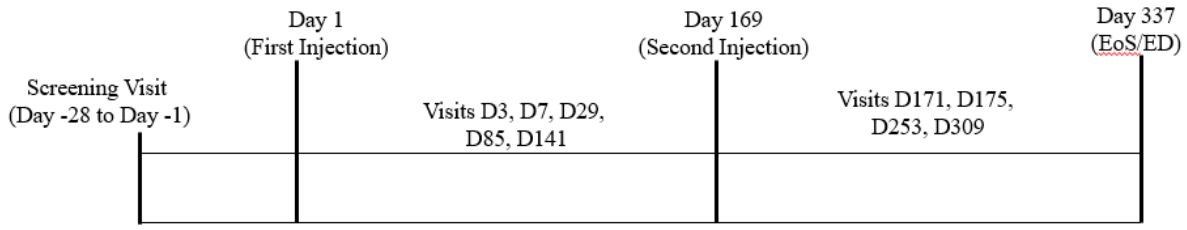
Approximately 145 participants will be assigned to triptorelin embonate 22.5 mg (6-month formulation) to be administered on Day 1 and Day 169. Note: participants must receive study intervention on Day 1 in accordance with the treatment schedule of their previously received GnRH analogue therapy.

The study will consist of a 4-week screening period, during which participants with prostate cancer will be screened for eligibility. On Day 1, all eligible participants will receive a single open-label administration of study intervention. Following treatment on Day 1, visits will occur on Day 3, Day 7, Day 29, Day 85, Day 141, Day 169 (second administration), Day 171, Day 175, Day 253, Day 309 and Day 337. (Note: if necessary, participants can request home visits, except for visits where study intervention is to be administered).

Participants will be considered to have completed the study when final procedures and assessments have been performed at the Day 337 visit. Participants who withdraw from the study before the completion of the Day 337 visit will have early discontinuation procedures and assessments performed at their final visit.

The study design is illustrated in Figure 1.

Figure 1 Study Schema



D=day; ED=early discontinuation; EoS=end of study

Participants will receive a subcutaneous injection of triptorelin embonate 22.5 mg (6-month formulation) on Day 1 and Day 169.

2.3 Sample Size Determination and Power

This single-arm study is designed to demonstrate that the percentage of participants remaining castrated (maintenance of castration defined as testosterone <1.735 nmol/L (50 ng/dL) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337) during the study is greater than 90%. Considering an observed castration maintenance in 97% of participants, 130 eligible participants are required to demonstrate the efficacy of the triptorelin 6-month formulation with approximately 90% power and a one-sided alpha of 0.025 using an exact binomial test. The objective will be achieved if the lower bound of the 95% confidence interval (CI) of the observed rate is greater than 90%.

Considering a drop-out rate of 10%, 145 participants will be included in the study.

2.4 Randomisation and Blinding

This is a non-randomised, open-label study. Therefore, no procedure for blinding is applicable.

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 from the statistical section of the protocol.

3 PLANNED ANALYSES

3.1 Data Monitoring

No independent Data Monitoring Committee will be used in this study.

3.2 Interim Analysis / Primary Analysis

No interim analysis will be performed.

3.3 Final Analysis

Planned analyses will be done when all participants complete study and after database lock.

4 ANALYSIS SETS

Screened Set

The screened set will contain all participants who signed an informed consent for this study.

In case of re-screening, the participant will be counted once only in the screened set. The previous site and assigned subject numbers will be collected to link the first and second screening data.

Enrolled Set

The enrolled set will contain all participants who were enrolled to study treatment. A participant will be considered as enrolled if he has signed the informed consent form and is assigned to treatment.

Intent-to-Treat Set

The intent-to-treat (ITT) Set will contain all participants who signed an informed consent form and received at least one administration of study intervention and have a serum testosterone level <1.735 nmol/L (50 ng/dL) on Day 1 (pre-dose measurement).

Full Analysis Set

The full analysis set (FAS) will contain all participants who signed an informed consent form and received two administrations of study intervention and completed all visits for testosterone measurement (Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337). Note, a participant will be included in the FAS if his testosterone measurement is ≥50 ng/dl before the end of treatment, end of study or withdrawn from study, whichever is earlier.

Per Protocol Set

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

Safety Set

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

5 STATISTICAL METHODS/ANALYSES

The statistical analyses will be performed in accordance with ICH E9 guideline and guidelines presented in section 9.

5.1 General Considerations

All tables, listings and figures will be produced, and statistical analysis performed using the Statistical Analysis System® software version 9.4 or a later version.

5.1.1 Outputs Presentation

5.1.1.1 Presentation of Visits / Timepoints

For by-visit summaries, the nominal visit as collected in the Electronic Case Report Form (eCRF) will be used in general for analysis purpose unless stated otherwise. Analysis visit window described in Section 6.1 will be used for slotting actual testosterone and prostate-specific antigen (PSA) assessment dates into planned schedule. Unscheduled visits will not be displayed in summaries but will be listed.

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

Period	Long Visit Name	Short Name	Protocol Time Interval
Screening	Day -28 to Day – 1 (Screening)	Scr	
Intervention Period	Day 1 (Baseline)	Bsl	
	Week 1 – Day 3	D3	Day 3 after first injection
	Week 1 – Day 7	D7	Day 7 after first injection
	Week 4 – Day 29	D29	±3 day
	Week 12 – Day 85	D85	±3 day
	Week 20 – Day 141	D141	±3 day
	Week 24 – Day 169	D169	±3 day
	Week 25 – Day 171	D171	Day 3 after last injection
	Week 25 – Day 175	D175	Day 7 after last injection
	Week 36 – Day 253	D253	±3 day
	Week 44 – Day 309	D309	±3 day
EoS/ED	Week 48 – Day 337	D337	±3 day

5.1.2 Descriptive Statistics

Due to the single-arm nature of the study, all statistical analyses will be descriptive. 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 applicable. Unless 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.

For the efficacy analyses, the descriptive statistics of treatment effects and corresponding 95% CIs for the primary endpoint and secondary endpoints will be presented if applicable.

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).

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 2.

5.2 Enrolment, Disposition and Analysis Sets

A Listing presenting study treatment dispensation details will be provided (Listing 16.1.7).

Following disposition summaries will be provided:

- Summary table with the number and percentage of participants screened, screen failed, reason for screen failures, enrolled, treated, having completed the study, withdrawn and reason for withdrawal,
- Summary table with the number and percentage of participants enrolled per visit,
- Summary table with the number and percentages of participants screened and enrolled per country and site,
- Summary table on duration of subject participation in the study,
- Summary of the number and percentage of participants in each analysis set based on all screened participants with reasons for exclusion from each analysis set (see section 5.3 about the Protocol deviations leading to the subject exclusion from the PP set).

Following listings will be provided:

- Listing of participant disposition including screen failure participants, and withdrawal participants,
- Listing of dates of visit including duration of subject participation for the enrolled participants,
- 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 Specifications. The protocol deviations related to Coronavirus Disease 2019 (COVID-19) will also be considered. The list of protocol deviations impacting the PP set will be reviewed prior to database lock. The list may be updated, up to the point of database lock, to include any additional major protocol deviations impacting inclusion in the PP set.

Following protocol deviation summary and listing will be provided on the enrolled 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).
- A listing of all major protocol deviations.

5.4 Demography and Other Baseline Characteristics

Baseline and demographic information (age, ethnicity, race, height, weight at baseline, body mass index [BMI] at baseline, Eastern Cooperative Oncology Group [ECOG] at screening) will be listed and summarised. For continuous variables, the summary will consist of descriptive statistics (number of participants, mean, SD, minimum, median, and maximum). For categorical variables, the summary will consist of number and percentage of participants in each category.

All demographic and baseline characteristics summaries and listings will be provided for the SAF set. No statistical comparison will be performed.

Following summaries will be provided on:

- Demographic variables (refer to Appendix 5 for European Union Drug Regulating Authorities Clinical Trials Database [EudraCT] age categories),
- Prostate cancer history and disease characteristics (time from histological diagnosis to screening, TNM Classification of Malignant Tumors [TNM] Stage, PSA and Testosterone from central lab at Baseline).

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 and surgical procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using World Health Organization-Drug dictionary.

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

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

Rules for classification of prior and concomitant medication/non-drug therapies, surgical procedures in case of partial/missing date are detailed in Appendix 2.

Medical history and concurrent medical conditions will be summarised by system organ class (SOC) and preferred term (PT). Medication history and concomitant medications will be summarised by Anatomical Therapeutic Class (ATC) code and preferred name (PN). The therapeutic class will correspond to the second level of ATC code, that is, corresponding to the first three figures.

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

- Medical and surgical history by SOC and PT,
- Prior medications for the studied disease by ATC class and PN (ATC level 2),
- Prior radiotherapies for cancer by primary SOC and PT,
- Prior surgical procedures for the studied disease by primary SOC and PT,
- Concomitant surgical procedures by primary SOC and PT,
- Prior medications by ATC class and PN (ATC level 2),
- Concomitant medications by ATC class and PN (ATC level 2),
- Prior non-drug therapies by primary SOC and PT,
- Concomitant non-drug therapies by primary SOC and PT.

Listings will be provided for prior and concomitant medication/non-drug therapies, and surgical procedures. These listings should include a flag indicating the category (P, PC, C) as described in the table above.

5.6 Compliance

The compliance will be calculated as defined in section 7.

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

- Descriptive statistics of compliance including number of percentage of participants by compliance category (<50%, 50 - <70%, 70 -<90%, 90-100%),
- A listing of treatment compliance.

5.7 Efficacy

5.7.1 General Considerations

The FAS set will be used for efficacy analyses unless explicitly stated differently.

A listing of all efficacy data (raw and derived) will be provided (see listing detail conventions in Appendix 4).

5.7.1.1 Significance Testing and Estimations

The statistical analysis of efficacy is only descriptive therefore no formal statistical significance testing will be performed.

5.7.1.2 Handling of Dropouts and Missing Data

Completely missing data are generally not imputed. Partial missing start and end dates will be imputed for medication category and treatment-emergent adverse event (TEAE) determinations. Details are provided in the Appendix 2.

5.7.1.3 Statistical/Analytical Issues

Adjustments for Covariates

Covariates adjustment is not applicable to this study.

Interim Analyses and Data Monitoring

See section 3.

Multicentre Studies

This is a multicentre study conducted in seven countries (Belgium, Czech Republic, France, Germany, Lithuania, Netherlands, Spain). Due to the limited sample size, this is an open-label study, no adjustment for centre effects is planned for this study.

Multiple Comparisons/Multiplicity

No formal testing will be performed in this study and multiplicity adjustment is not applicable.

5.7.2 Analysis of Primary Efficacy Endpoint

5.7.2.1 Primary Efficacy Endpoint, Treatment Effect and Estimand Definition

To assess the primary objective, the primary estimand will be defined by the following attributes:

- Population: participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue as defined by the listed Inclusion/Exclusion criteria in sections 5.1 and 5.2 of the protocol, respectively.
- Variable/Endpoint: castration maintenance rate during the study defined as percentage of participants castrated (testosterone <1.735 nmol/L (50 ng/dL)) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337, with two complete study intervention administrations.
- Key Intercurrent event (ICE):
  - (a) ICE 1 - Subjects discontinued from study prior to Day 337 without evidence of inadequate testosterone suppression (testosterone measurement >= 50 ng/dL)

    The testosterone values of these participants will not be considered for the main analysis (principal stratum strategy).
  - (b) ICE 2 - Subjects with at least one planned testosterone measurement missing on or prior to Day 337 without evidence of inadequate testosterone suppression (testosterone measurement >= 50 ng/dL)

    The testosterone values of these participants will not be considered for the main analysis (principal stratum strategy).

(c) ICE 3 - Subjects discontinued treatment prior to receiving the second study intervention administration without evidence of inadequate testosterone suppression (testosterone measurement >= 50 ng/dL)

The testosterone values of these participants will not be considered for the main analysis (principal stratum strategy).

(d) ICE 4 - Subjects received a prohibited medication during the study

Prohibited medication with impacts on the testosterone value will be identified through blinded data review. Subjects receiving identified prohibited medication (for example, finasteride, dustasteride, or abiraterone) will be included in the primary analysis as non-responder. In contrast, all testosterone measurements from subjects receiving prohibited medications other than identified ones during the study will be included in the primary analysis (composite strategy).

- Treatment regimen: triptorelin 6-month formulation administered subcutaneously and potential intake of permitted concomitant medications (for a list, see protocol section 6.3)
- Population-level summary of the treatment effect of interest: percentage of participants with a castration maintenance.

5.7.2.2 Primary Analysis

Primary analysis of castration maintenance rate will be based on the primary estimand in the FAS. Percentage of participants maintaining castrate levels of serum testosterone during the study along with the corresponding 95% exact CI will be provided in the FAS.

By-subject listing will be produced for all enrolled subjects.

5.7.2.3 Sensitivity Analysis

Sensitivity analysis for the primary estimand is intended to assess treatment effects when using different strategies. Details are listed in the following.

Estimand ID	Primary-S1	Primary-S2	Primary-S3
Estimand	Primary	Primary	Primary
Analysis Type	Sensitivity	Sensitivity	Sensitivity
Analysis Set	ITT	ITT	ITT
Variable/Endpoint	Castration maintenance rate	Castration maintenance rate	Castration maintenance rate
Intercurrent Event	Strategy		
ICE1	Subjects will be included in the analysis regardless early withdraw status (Treatment policy)	Subjects will be included in the analysis regardless early withdraw status (Treatment policy)	Subjects will be included in the analysis regardless early withdraw status (Treatment policy)

Estimand ID	Primary-S1	Primary-S2	Primary-S3
ICE2	With analysis window being applied, subjects without 2 consecutive missing testosterone value will be included in the analysis and subjects with at least 2 consecutive missing testosterone values will be considered as non-responders (Composite policy)	Without analysis window being applied, subjects without 2 consecutive missing testosterone value will be included in the analysis and subjects with at least 2 consecutive missing testosterone values will be considered as non-responders (Composite policy)	Analysis window is not applicable. Subjects with only one missing testosterone will be included in the analysis and available testosterone values will be analyzed as observed. For subjects with at least 2 missing testosterone values and without evidence of inadequate testosterone suppression (testosterone measurement ≥ 50 ng/dL), only testosterone values prior to the first missing will be included in the analysis. For subjects with at least 2 missing testosterone values and with evidence of inadequate testosterone suppression (testosterone measurement ≥ 50 ng/dL), available testosterone values will be analyzed as observed (Composite policy)
ICE3	Subjects will be included in the analysis regardless early treatment discontinuation status (Treatment policy)	Subjects will be included in the analysis regardless early treatment discontinuation status (Treatment policy)	Subjects will be included in the analysis regardless early treatment discontinuation status (Treatment policy)
ICE4	Same as primary estimand		
Population-level summary			
	Same as primary estimand	Same as primary estimand	Probability of Castration maintenance at Day 337 based on Kaplan-Meier estimate

5.7.2.4 Supplementary Analysis

Primary estimand analysis will be conducted in the PP set if more than 10% of FAS subjects are excluded in the PP set.

5.7.2.5 Subgroup Analysis

The primary analysis of castration maintenance rate will be summarized within subgroups listed along with 95% exact CI in a forest plot. In the case a subgroup includes less than 20 subjects, the analysis for the given subgroup will not be carried out or combining subgroups may be considered.

- Age (<65, ≥65 years [65 to <75, 75 and above])
- Race (White, Black, Other)
- Baseline ECOG performance score (0, 1)

- Baseline weight (<65 kg, 65 to <85 kg, ≥85 kg)
- Time since histological diagnose (<median, ≥ median).

5.7.3 Analysis of Key Secondary Efficacy Endpoints

5.7.3.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are listed below:

- Percentage of participants castrated at each timepoint on Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337 (castration defined as testosterone <1.735 nmol/L (50 ng/dL))
- Percentage of participants with a serum testosterone level <0.694 nmol/L (20 ng/dL) during the study
- Percentage of participants with a serum testosterone level <0.69 nmol/L (20 ng/dL) at each timepoint on Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337
- Percentage of participants castrated on Day 3 and Day 7 after each injection administered on Day 1 and Day 169 (castration defined as testosterone <1.735 nmol/L (50 ng/dL))
- Percent change in PSA from baseline (prior to injection) at Day 169 and Day 337 (Percent change in PSA defined as the absolute value of difference between the PSA values at Day 169 and Day 337 and the baseline value divided by the baseline value).

5.7.3.2 Main Secondary Analysis

The same strategies as those for the primary estimand will be used for the main secondary analysis in the FAS, with castration maintenance criteria being replaced with 0.694 nmol/L (20 ng/dL) whenever applicable.

For binary secondary endpoints, including castration maintenance (<50 ng/dL) rate at specific timepoints, castration maintenance (<20 ng/dL) rate during the study, castration maintenance (<20 ng/dL) rate at each timepoint, castration maintenance rate along with the associated 95% exact CI will be provided. For percent change in PSA from baseline at Day 169 and Day 337, descriptive statistics will be provided.

5.7.3.3 Subgroup Analysis

No subgroup analyses are planned for the secondary endpoints.

5.7.3.4 Sensitivity Analysis

For castration maintenance (<20 ng/dL) rate during the study, the Kaplan-Meier estimate at Day 337 using the same strategies as Primary-S3 with castration maintenance criteria replacing with as <20 ng/dL will be provided.

5.7.4 Analysis of Other Secondary Efficacy Endpoints

No other secondary efficacy endpoint analyses are planned for this study.

5.7.5 Analysis of Exploratory Endpoints

No exploratory analyses are planned for this study.

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 subject data listings (see listing detail conventions in Appendix 4).

Baseline value definition is given in section 5.1.3.

5.8.2 Extent of Exposure

Administration of triptorelin embonate 22.5 mg 6-month formulation will be summarized by descriptive statistics for the following: duration of exposure, number of injections administered, number of subjects with at least one dose reduction or injection delayed. Duration of exposure will be defined in months as:

([last dose date – first dose date] + 1) / (365.25/12).

- Exposure listing will also be generated.

5.8.3 Adverse Event

All adverse events (AEs) recorded in the eCRF will be coded using MedDRA dictionary. All AEs will be classified by MedDRA PT and SOC. Severity will be graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 or higher. Adverse events will be classified as TEAEs if meeting one of the rules below:

- Events with start date/time on or after the date/time of first IMP administration and within 168 days after the last dose of study treatment, or up to Day 337, whichever is later.
- Events whose severity worsens on or after the date/time of first IMP administration,

For AE with partial or missing start date, refer to Appendix 2 for TEAE determination algorithm.

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:

- Overview of TEAE,
- TEAE by SOC and PT,
- TEAE by PT,
- Most common (≥ 10%) TEAEs by SOC and PT,
- TEAE by SOC, PT, and worst toxicity grade,
- Grade 3 or 4 TEAE by SOC and PT,
- TEAE by SOC, PT, and treatment relationship,
- Treatment-related TEAE by SOC, PT, and worst toxicity grade,
- Grade 3 or 4 treatment-related TEAE by SOC and PT,
- Non-serious TEAE by SOC and PT.

TEAE summaries will be presented in decreasing frequency of SOC, decreasing frequency of PT within SOC, and then in alphabetical order. TEAE summaries by PT will be presented in decreasing frequency of PT, and then alphabetically.

Multiple occurrence of TEAEs will be presented as follows:

- Participants will be counted at most once at the PT, and at most once at the SOC;

- Participants reporting multiple TEAEs coded within the same SOC/ PT will be presented in the worst-case grade category (grade order: 5>4>3>2>1>missing) ever reported in that SOC/PT;
- Participants reporting multiple TEAEs coded within the same SOC/ PT will be presented in the TEAE with the worst-case relationship to study treatment (order: related > not related > missing) ever reported;
- For TEAE summary by worst toxicity grade, participants reported single occurrence TEAE while the associated toxicity grade is missing, the participant will be presented in the toxicity grade missing category;
- TEAEs with missing relationship to study treatment will be considered treatment-related in the summary.

The number of events will also be displayed in the summary tables, when applicable.

Deaths, SAEs, and Other Significant Adverse Events

The following summaries will be presented:

- Serious TEAE by SOC and PT,
- Most common (≥ 5%) serious TEAEs by SOC and PT,
- Treatment-related serious TEAE by SOC and PT,
- TEAEs leading to treatment discontinuation by SOC and PT,
- TEAE leading to treatment interruption by SOC and PT,
- TEAEs leading to a dose reduction by SOC and PT,
- Death summary.

By-subject listing will be produced for all AEs, all serious adverse events (SAEs), all AEs leading to dose reduction, treatment interruption, treatment discontinuation, and fatal AE. Treatment emergence status will be flagged in the listing whenever applicable.

5.8.4 Laboratory Data

Clinical safety laboratory tests will be assessed by local laboratories. All laboratory data will be presented in the units of International System of Units (SI).

Haematological and biochemical toxicities will be graded according to the NCI-CTCAE criteria, where available. The toxicity grades will be assigned programmatically by applying the NCI-CTCAE guideline as described in Section 7 (11). All scheduled and unscheduled laboratory test results will be included in the worst toxicity grade summary. For white blood cells, neutrophils, platelets and haemoglobin, with associated grade 3 or 4 toxicities, nadir and day to nadir from most recent injection will be presented in the listing.

The neutrophils values will be imputed as defined in Section 7 (12).

The following summaries will be provided:

- A summary of the actual and change from baseline in each laboratory haematology parameter (platelet count, haemoglobin, white blood cell counts, neutrophils, lymphocytes, monocytes, eosinophils, basophils) and in each laboratory biochemistry parameter (creatinine, non-fasting glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin and conjugated bilirubin) at Day 337,
- Shift from baseline to end of study based on abnormalities,
- Shift from baseline to end of study based on CTCAE toxicity grading.

The following listings are to be provided:

- A listing of all laboratory data (with flag indicating abnormal values),
- A listing of laboratory data for subjects with at least one post-baseline abnormal value (with flag indicating abnormal values),
- A listing of relevant laboratory data for subjects with at least one CTCAE grade 3 or higher post-baseline laboratory result.

5.8.5 Vital Signs

The following summaries will be presented:

- Summary of the actual and change from baseline in each vital sign parameter (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature) by timepoint,
- Summary of subjects experiencing Potentially Clinically Significant Abnormalities (PCSA). Note: PCSA criteria are defined in Appendix 1 for systolic blood pressure, diastolic blood pressure and heart rate.
- Shift from baseline to each post-baseline visit based on clinical abnormality evaluation.

The following listings are to be provided:

- All vital sign data, with abnormal value flagged.
- Listing of PCSA. All relevant vital sign data for subjects with at least one post-baseline PCSA record.

5.8.6 Electrocardiogram

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

- RR interval (msec),
- PR interval (msec),
- QRS duration (msec),
- QT interval (msec),
- Fridericia corrected QT (QTcF) 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:

- Summary of the actual and change from baseline in each ECG parameter by timepoint (Baseline and Day 337),
- Summary of subjects experiencing PCSA. Note: PCSA criteria are defined in Appendix 1 for QTc and delta QTc.
- Shift from baseline based on clinical abnormality evaluation.

A listing of ECG data is to be provided with abnormal value and PCSA records flagged.

5.8.7 Physical Examination

The following summaries will be provided:

- Summary of subjects reporting abnormal finding in physical examination by body system (cardiovascular system, respiratory system, gastrointestinal system, neurological system, and other) for a shift from baseline (normal versus abnormal) to each post-baseline visit,
- Summary of the actual and change from baseline in weight and BMI by timepoint,
- Summary of subjects meeting PCSA criteria in weight (defined in Appendix 1).

By-subject physical examination listing will be provided with records meeting PCSA criteria or being considered as clinical abnormal flagged.

6 DATA HANDLING

6.1 Visit window

The time window for visit/timepoints will be applied as below for the blood samples for testosterone. In case of multiple unscheduled and planned visits enclosing within the defined analysis time interval, the non-missing value in a visit closest to the target visit day will be used in the summary tables.

Study phase	Scheduled visit	Protocol Time Interval	Analysis Time Interval* (days)
Screening	Day -28 to Day -1		-28 to -1
Intervention Period	Day 1 (first injection)	<1	<=1
	Week 1 – Day 3	3	2 to 5
	Week 1 – Day 7	7	6 to 18
	Week 4 – Day 29	29	19 to 57
	Week 12 – Day 85	85	58 to 113
	Week 20 – Day 141	141	114 to 155
	Week 24 – Day 169 (second injection)	169 (D2)	156 to D2
	Week 25 – Day 171	171 (D2+2)	D2+1 to D2+4
	Week 25 – Day 175	175 (D2+6)	D2+5 to D2+45
	Week 36 – Day 253	253 (D2+84)	D2+46 to D2+112
	Week 44 – Day 309	309 (D2+140)	D2+113 to D2+154
End of Study/Early Discontinuation	Week 48 – Day 337	337 (D2+168)	≥D2+155

*Analysis visit window after screening are defined using the mid-point between each scheduled visit and reset with the second injection.

6.2 Unscheduled Visits, Retest, Withdrawal Visit,

All listings will include retest measurement and assessments from unscheduled visits. For by-visit summary, only planned visits in the protocol will be presented.

Assessments from unscheduled visit and retest measurements will be included for baseline value determination whenever applicable. These measurements will also be used to determine worst toxicity grade for laboratory data, or meeting PCSA criteria in vital signs or ECG.

If an assessment requires a retest (for example, safety laboratory, vital signs and ECG), the closest non-missing 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 at the end of study / early discontinuation visit in the eCRF.

7 DERIVED DATA

The following derived data will be calculated and included in the listings:

(1) Baseline value

Baseline value is defined as the last non-missing measurement taken prior to first IMP administration (including unscheduled assessments) (see section 5.1.3).

(2) Duration of subject participation (study exposure)

Study exposure will be calculated as:

Study exposure (days) = last assessment or visit performed – informed consent date +1. It will be then divided by 30.4375 to be presented in months.

(3) Age

Subject age (years) will be as collected in eCRF.

(4) BMI

BMI (kg/m^2) will be derived as Weight (kg)/[Height(cm)/100]2 and rounded to the nearest decimal.

(5) Time from diagnosis to screening

Time from diagnosis to screening will be calculated as (date of screening – date of diagnosis). It will be then divided by 30.4375 to be presented in months.

In case of missing screening day, the day will be imputed to 15. In case of missing screening month, the month will not be imputed.

In the same way, in case of missing diagnosis day, the day will be imputed to 15. In case of missing diagnosis month, the month will not be imputed.

No imputation will be performed for missing year.

(6) Compliance

Compliance will be calculated as:

Dose administered divided by dose planned to be administered multiplied by 100. The percentage of residual will be considered to determine the percentage of dose non-administered, and so the dose administered.

A total of two injections will be considered as planned dose administration in this study.

(7) Percent change from baseline

Percent change from baseline will be calculated as:

((assessment at the visit – assessment at baseline)/ assessment at baseline)*100.

Zero will be used if both assessment at baseline and change from baseline are zero.

(8) Changes from baseline

Changes from baseline will be calculated as a difference from baseline (e.g. assessment at the visit – assessment at baseline).

(9) Study drug exposure

Study drug exposure will be calculated as:

Study drug exposure (days) = last study drug administration date – first study drug administration date +1. It will be then divided by 30.4375 to be presented in months.

(10) Time from first study dose for adverse event

If the start date of the AE is identical to the date of first administration, then "<1" day will be presented.

The time will be calculated as (AE start date – first administration date)+1 and presented in days.

If the AE start date is partial due to missing day, the time from first dose will be presented as a superior inequality (e.g.: for an AE started in FEB2004 after the first administration performed on 31JAN2004, the time from first dose will be as "≥2" days).

If the first administration date is partial due to missing day, the time from first dose will be presented as a superior inequality (e.g. for an AE started on 01FEB2004 after the first administration performed in JAN2004, the time from first dose will be as "≥2" days).

If both the AE start day and the first administration day are missing, the time from first dose will not be presented.

If the AE start month is missing or the first administration month is missing, the time from first dose will not be presented.

If the AE start date is missing or the first administration date is missing, the time from first dose will not be presented.

(11) NCI-CTC AE grades for laboratory parameters

For NCI-CTC gradable laboratory parameters, appropriate grades should be attributed according to the coding rules specified in the NCI-CTCAE version 5.0 if this grade is not present in the database. The grading will be performed based on the laboratory values. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

(12) Neutrophils values

In some cases, laboratory data may not be reported as they may be difficult to detect. When the White Blood Cells (WBC) counts are non-missing and recorded as WBC < 0.5*10^9/L, the neutrophils value will be imputed as zero in the analysis and CTCAE grade 4 will be assigned.

8 CHANGES FROM PROTOCOL

In SAP section 2.1, the hypotheses have been rephrased from Protocol section 9.1: “after 12 months” was updated to “from date of first dose to Day 337” to stick to the protocol endpoints. Twelve months would consider the screening period up to 28 days.

In SAP section 4, the ITT Set was added. The ITT population was mentioned in Protocol section 3 for second estimand while the definition was missed in the protocol. .

The multiple imputation was removed in Protocol Section 3, but it is still present in Protocol Section 1.1 and Section 9.4.2. The multiple imputation will not be used for the statistical analysis considering the new FAS definition and the new estimands definition.

9 REFERENCES

Reference to ICH regulatory guidelines:

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

Reference to European Medicines Agency (EMA) or point to consider guidelines:

- Investigation of subgroups in confirmatory clinical trials
- Missing data in confirmatory clinical trials.

Reference to Food and Drug Administration (FDA) guidelines:

- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Standard Ipsen Study Data Tabulation Model (SDTM) user guide

Ipsen Global Style guide

- Agresti A, Coull BA. Approximate is better than “exact” for interval estimation of binomial proportions. The American Statistician, 1998;52:119-26.
- Michael Laposata, MD PhD, SI unit conversion guide. The New England Journal of Medicine,1992
- Bodner, T. E. (2008). “What Improves with Increased Missing Data Imputations?” Structural Equation Modeling 15:651–675.

References for guidance on analysing ECG data:

- ICH E14 (2005) Note for guidance on the clinical evaluation of QT/QTC interval prolongation and proarrhythmic potential for non-anti-arrhythmic drugs (CHMP/ICH/2/04)
- Shah R.R, Drugs, QTc interval prolongation and final ICH E14 guideline. Drug Safety 2005: 28(11):1009-1028

10 APPENDICES

Appendix 1 List of PCSA Criteria

A1. List of PCSA Criteria

PCSA for Vital Signs parameters:

Parameter	PCSA
Systolic Blood Pressure	≤ 90 mmHg and change from baseline ≤ -20 mmHg ≥ 180 mmHg and change from baseline ≥ 20 mmHg
Diastolic Blood Pressure	≤ 50 mmHg and change from baseline ≤ -15 mmHg ≥ 105 mmHg and change from baseline ≥ 15 mmHg
Heart Rate	≤ 50 bpm and change from baseline ≤ -15 bpm ≥ 120 bpm and change from baseline ≥ 15 bpm

PCSA for ECG parameters (source ICH E14):

Parameter	PCSA
QTc	]450; 480] msec]480; 500] msec >500 msec
Delta QTc	]30;60] msec increase from baseline >60 msec increase from baseline

PCSA for Weight from Physical Examination parameters:

Parameter	PCSA
Weight	≤ -5% change from baseline ≥ 5 % change from baseline

Appendix 2 Partial/Missing Date Convention

A2. Partial/Missing Date Convention

In all listings, missing or incomplete dates should be left as they have been recorded.

Algorithm for Prior/ Concomitant

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

In case of partial start and/or stop dates, temporary date imputation will be done to determine the classification and derive the duration of occurrence:

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

The duration of the occurrence will be calculated using the start and end date of the occurrence as end date – start date + 1. In case of partial start or end dates, the duration will be reported as "≤ xx" since at least one date is imputed and maximised.

In case of ongoing occurrence (e.g. at the end of the study or at the time of interim analysis):

- If the start date is complete, the duration will be reported as "≥ xx" and the date of end of study date or last attended visit will be considered as end date.
- If start date is incomplete, the duration is not calculated.

Algorithm for Medical Histories

In case of partial start and/or stop dates, temporary date imputations will be done to determine the duration of occurrence:

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

The duration of the occurrence will be calculated using the start and end date of the occurrence as end date – start date + 1. In case of partial start or end dates, the duration will be reported as "≤ xx" since at least one date is imputed and maximised.

In case of ongoing medical history:

- If the start date is complete, the duration will be "≥ xx" using the screening visit date and the start date of the medical history.
- If start date is incomplete, the duration is not calculated.

Algorithm for TEAE

For deriving the TEAE flag the following process of temporary date imputation is done (for AE start date only assuming no AE end date are missing). The date imputation algorithm for incomplete adverse event start dates is described in Table 2. Classification of adverse event according to its treatment-emergent status is then done using the imputed date. The date imputation algorithm for incomplete adverse event end dates is described in Table 3 assuming the latest possible date.

Table 2 Data Imputation Algorithm for Adverse Event Start Date (ASTDT) with first IMP administration on 2002-08-11

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)

Dates are presented using an YYYY-MM-DD format.
YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

Table 3: Data imputation algorithm for AE end date (AENDT) with last visit/contact date on 2022-02-22 (for AE not ongoing at EoS)

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day is missing			
YYYY-MM < YYYY-MM of [Last visit/contact]	YYYY-MM-31	2021-07-XX	2021-07-31
YYYY-MM = YYYY-MM of [Last visit/contact]	YYYY-MM-22	2022-02-XX	2022-02-22
Day and month are missing			
YYYY < YYYY of [Last visit/contact]	YYYY-12-31	2021-XX-XX	2021-12-31
YYYY = YYYY of [Last visit/contact]	YYYY-02-22	2022-XX-XX	2022-02-22
Day, month, and year are missing (AE not ongoing at EoS)			
XXXX-XX-XX	No imputation	XXXX-XX-XX	

Dates are presented using an YYYY-MM-DD format.
YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

AEs duration will be calculated using the start and end date of the AE as end date – start date

+ 1. In case of partial start/end date the temporary imputed date will be used.
The duration of the AE will be calculated using the start and end date of the AE as end date – start date + 1. In case of partial start or end dates, the duration will be reported as "≤ xx" since at least one date is imputed and maximised.

In case of ongoing AE (e.g. at the end of the study or at the time of interim analysis):

- If the start date is complete, the duration will be reported as "≥ xx" and the date of end of study date or last attended visit will be considered as end date.
- If start date is incomplete, the duration is not calculated.

Appendix 3 Programming Convention for Outputs

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 95% CI 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. Unless otherwise specified, percentage will be calculated using N as denominator. The denominator 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.

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].

Appendix 4 Listings Conventions

A4 Listings Conventions

Any listings will contain at least the following data: subject identifier and age. When dates are presented, the associated study days should be included. They should be sorted by subject identifier. Listings should be broken down by centre.

Appendix 5 EudraCT Categories for Age

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). Only adults are planned for this study.

Adolescents (12-17 years old)
Adults (18-64 years old)
From 65 to 84 years old
85 years old and over