Study Protocol

An Adaptive Phase 2, Open-Label, Multicentre Study Investigating the Pharmacokinetics, Pharmacodynamics, Efficacy and Safety of Teverelix Trifluoroacetate, a Gonadotropin-releasing Hormone (GnRH) Antagonist, in Participants with Advanced Prostate Cancer

TEACh (**T**everelix **E**valuated in **A**dvanced prostate **C**ancer)

EudraCT No.: 2020-000543-31

Trial No.: ANT-1111-02

Original Protocol (Version 1.0), dated 22 April 2020
Final Version 2.0, dated 21 September 2020
Final Version 3.0, dated 27 November 2020
Final Version 4.0, dated 21 July 2021

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Protocol Synopsis

Title	An Adaptive Phase 2, Open-Label, Multicentre Study Investigating the Pharmacokinetics, Pharmacodynamics, Efficacy and Safety of Teverelix Trifluoroacetate, a Gonadotropin-releasing Hormone (GnRH) Antagonist, in Participants with Advanced Prostate Cancer
Study No.	ANT-1111-02
EudraCT No.	2020-000543-31
Clinical Phase	Phase 2
Investigational Product	Teverelix trifluoroacetate (TFA)
Number of Participants	Group 1: Twenty participants will be needed to complete the first period of 28 days (Stage 1) Group 2: Sixty participants will be needed to complete the first period of 28 days (Stage 1) Group 2 subjects who are enrolled onto protocol version V4.0 dated 21 July 2021, and, are ongoing on the trial when protocol version V5.0 dated 16 May 2022 is implemented, will have the option to transfer to protocol version V5.0. They may also choose to continue on protocol version V4.0 dated 21 July 2021.
Number of Centres	Up to 7
Countries	Lithuania (Groups 1 and 2) and (potentially) Netherlands and/or Belgium (Group 2 only)
Study Duration	**Screening Period:** Up to 6 days **Treatment Period:** Core Study: Stage 1 (loading-dose period): 28 days Stage 2 (maintenance-dose period): Up to 168 days Stage 3 (follow up period): Up to 84 days (or until local lab T levels are ≥ 1 ng/mL, whichever occurs first). Final assessment is done 7 days later.
Study Objective(s)	**Primary Objective** To assess the efficacy of teverelix TFA in terms of ability to suppress serum testosterone (T) levels to below castration level (<0.5 ng/mL or

1.73 nmol/L) at Day 28

Secondary Objective(s)

- To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.2 ng/mL or 0.6934 nmol/L) at Day 28
- To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.5 ng/mL or 1.73 nmol/L) at Day 42
- To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.2 ng/mL or 0.6934 nmol/L) at Day 42
- To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.5 ng/mL or 1.73 nmol/L) at Day 168
- To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.2 ng/mL or 0.6934 nmol/L) at Day 168
- To assess the efficacy of teverelix TFA in terms of ability to maintain suppression of serum T levels below castration level (<0.5 ng/mL or 1.73 nmol/L) over time during Stage 2 (maintenance-dose period)
- To assess the efficacy of teverelix TFA in terms of ability to maintain suppression of serum T levels below castration level (<0.2 ng/mL or 0.6934 nmol/L) over time during Stage 2 (maintenance-dose period)
- To assess the time taken to achieve serum T levels below castration level (<0.5 ng/mL or 1.73 nmol/L)
- To assess the time taken to achieve serum T levels below castration level (<0.2 ng/mL or 0.6934 nmol/L)
- To assess the time taken for serum T levels to increase to >0.5 ng/mL following the final, Day 168 injection
- To delineate the pharmacokinetics (PK) profile of teverelix TFA
- To assess the effects of teverelix TFA on:
  - prostate-specific antigen (PSA)
  - T
  - follicle stimulating hormone (FSH)
  - luteinising hormone (LH)
- To assess the predictive effect for new cardiovascular (CV) events of cardiac biomarkers
  - N-terminal pro-B-type natriuretic peptide (NTproBNP)
  - D-dimer
  - C-reactive protein (CRP)
  - high-sensitivity troponin (hsTn)
- To assess the safety of teverelix TFA in terms of:
  - local tolerability (injection site reactions [ISR])
  - systemic tolerability (adverse events, vital signs, electrocardiograms (ECG), Holter monitoring (subset of 30

subjects in Group 2 only) and laboratory parameters)

Design and Methodology

This adaptive Phase 2 study will be performed as a prospective, open-label, multicentre, non-controlled study based on within-group comparison in participants with advanced prostate cancer.
The study consists of the following periods/visits:
Screening Period: Days -6 to -1
Treatment Period:

Core Study:

1. **Stage 1:** Loading dose administered at baseline (Day 0) with follow-up visits until Day 28
2. **Stage 2:** Maintenance treatment administered every 6 weeks (Groups 1 and 2) with visits from Day 28 up to Day 168 or until treatment ceases to be effective
3. **Stage 3:** Follow up period. After final, Day 168 injection, subjects will return on Day 203 and weekly thereafter until Day 252 or until serum T levels are ≥1 ng/mL (local lab result), whichever occurs first
4. **Follow-up Visit:** Day 259 or 7 days after serum T levels ≥ 1 ng/mL (local lab result), whichever occurs first

Treatments Administered:
The study is designed to evaluate up to 2 dosing regimens:

Group	Loading Dose	Maintenance Dose	Dosing Interval
1	120 mg IM+120 mg SC	120 mg SC	6 weekly
2	180 mg IM+180 mg SC	180 mg SC	6 weekly

IM=intramuscular; SC=subcutaneous
Participants will receive different doses depending on whether they join Group 1 or Group 2. The study will enrol participants into Group 1 first. On Day 0, participants in Group 1 will receive a single loading dose consisting of 2 injections, each of which will contain 120 mg of teverelix TFA. The first injection will be administered as an intramuscular (IM) injection and the other as a subcutaneous (SC) injection (Stage 1).
After Stage 1, participants in Group 1 will receive a maintenance dose, which will consist of a single 120 mg SC injection administered every 42 days.
If 3 or more participants have a total T (local laboratory) value of >2 ng/mL at Day 21 or at any subsequent study visit, the dosing regimen will have failed to meet its 90% efficacy target and, if applicable, further enrolment into Group 1 will cease.
Total T (central laboratory) samples will be frozen, and batch shipped to SGS (formerly Synlab), Münich for analysis every 3 months. Ad hoc shipments may be triggered if data review milestones require.
If the serum T value (measured by the local laboratory) at the Day 35 visit is >2 ng/mL, the participant will be withdrawn from the study without

receiving any IMP in Stage 2.
If treatment of Group 1 has been terminated early due to a low therapeutic response rate, recruitment of participants into Group 2 will start.
On Day 0, participants in Group 2 will receive a single loading dose consisting of 2 injections, each of which will contain 180 mg of teverelix TFA. The first injection will be administered as an intramuscular (IM) injection and the other as a subcutaneous (SC) injection (Stage 1).
After Stage 1, participants in Group 2 will receive a maintenance dose, which will consist of a single 180 mg SC injection administered every 42 days.
If the serum T value (measured by the local laboratory) at the Day 21 visit is >2 ng/mL, the participant will then be withdrawn from the study.
Participants will have their serum T measured by the local laboratory 1 week prior to each maintenance dose during Stage 2 of the study. If, at any point the local laboratory serum T result is >2 ng/mL the participant will be withdrawn from the study. Local laboratory serum T values ≤2 ng/mL allow the participants to continue in the study.
Total T (central laboratory) samples will be frozen and batch shipped to SGS (formerly Synlab), Münich for analysis every 3 months. Ad hoc shipments may be triggered if data review milestones require.

Study Procedures

The first IMP administration will be performed on an inpatient basis. IMP administration at consecutive visits may be performed on an outpatient basis. Study visits will be held as described below.

Screening Examination

The screening examination consists of the following assessments and procedures which will be performed within the 6 days prior to baseline assessments conducted on Day 0: determination of provision of informed consent; eligibility; medical and surgical history, especially for prostate cancer; previous medication; demographics; physical examination; body weight and height; serology (human immunodeficiency virus [HIV] and hepatitis); fasted (≥8 hours) safety laboratory tests; glycated haemoglobin (HbA1c); total T (local laboratory), triplicate 12-lead ECGs; and vital signs. As fasting is considered a study procedure informed consent must be obtained prior to asking the subjects to fast. Therefore, it may be necessary to conduct the screening visit over more than one day.

Stage 1 Visits for Group 1 and Group 2

Participants will attend study visits on Days 0, 1, 2, 3, 4, 7, 10, 12, 14, 21 and 28. At Day 0 (baseline visit), the loading dose of teverelix TFA will be administered.
Participants will attend weekly study visits from Day 14 to Day 28.

Baseline (Day 0) Visit

A check of eligibility, as well as pre-dose blood sampling for PK and pharmacodynamics (PD) analyses,and fasted (≥8 hours) safety laboratory testing will be conducted. Samples will be collected for urine analysis. A pre-dose adverse events (AE) assessment, physical examination, triplicate

12-lead ECG and assessment of vital signs (including sitting blood pressure and heart rate) will be performed.

For a subset of 30 Group 2 subjects only (first 30 enrolled subjects with no more than 8 subjects at any one site), 24 hour continuous Holter monitoring will be performed. For analysis of the continuous 12-lead ECG data, triplicate 10 second 12-lead ECGs will be extracted at time points matching PK sampling times after at least 5 minutes rest in order to facilitate concentration-QTc effect modelling. Data will be analysed for arrhythmias following completion of the entire study to investigate the potential effect of teverelix on QTc interval.

All participants will start Stage 1 with the administration of the loading dose of teverelix TFA IM followed by SC injection.
After the administration of the IMP, participants will be monitored for 24 hours for the occurrence of ISR and AEs.
If, in the opinion of the investigator, no safety concerns exist, participants will be discharged from the centre.

Day 1 to Day 14 Visits

On Days 1 to 14, blood sampling for PK and PD analysis will be performed. In addition, blood sampling for assessment of PSA will be performed on Days 7 and 14.

Day 21 Visit

On Day 21, local testing of T levels will be performed to guide decision making at the Day 28 visit. PK, total T, LH, FSH and PSA (total and high-sensitivity [hs]) samples will also be collected for central laboratory analysis.

Day 28 Visit

Before the participant is able to continue into Stage 2, laboratory results that confirm serum T levels will be checked.
For participants in Group 1, the following actions will be taken at the Day 28 visit based on the results of the locally analysed T level determined from the Day 21 visit:

[T] (ng/mL)	**Action Taken**	**Dose Administered**
≤2	Continue with Stage 2 of Group 1	No dose on Day 28. Maintenance dose of 120 mg SC teverelix TFA every 42 days
>2	Withdraw from study, safety follow-up visit on Day 28	None

SC=subcutaneous; T=testosterone; TFA=Trifluoroacetate

For participants in Group 2, the following actions will be taken at the Day 28 visit based on the results of the locally analysed T level determined from the Day 21 visit:

[T] (ng/mL)	Action Taken	Dose Administered
≤2	Continue with Stage 2 of Group 2	No dose on Day 28. Maintenance dose of 180 mg SC teverelix TFA every 42 days
>2	Withdraw from study; safety follow-up visit on Day 28	None

SC=subcutaneous; T=testosterone; TFA=Trifluoroacetate

Day 35 Visit
On Day 35, local testing of T levels will be performed to guide decision making at the Day 42 visit. PK, total T, LH, FSH and PSA (total and high-sensitivity [hs]) samples will also be collected for central laboratory analysis.

Stage 2 Visits in Groups 1 and 2

Day 28 Visit
Stage 2 will start at the Day 28 visit. However, participants will receive their first maintenance dose at the Day 42 visit and participants will visit the clinic at Day 35 to provide a blood sample for local laboratory testing of T levels.
Blood samples for PK and PD analyses (T, LH, FSH, PSA), and fasted (≥8 hours) safety laboratory testing will be collected. Samples will also be collected for urine analysis. AE assessment, physical examination, triplicate 12-lead ECG and assessment of vital signs (including sitting blood pressure and heart rate) will be performed.
If, in the opinion of the investigator, no safety concerns exist, participants will be discharged from the centre.

Visits at Day 42, Day 84, Day 126, and Day 168
On Day 42 the first maintenance dose will be administered.
Before administration of the maintenance dose, blood samples for PK and PD analyses as well as fasted (≥8 hours) safety laboratory testing will be collected. Samples will also be collected for urine analysis. Pre-dose AE assessment (including ISR), physical examination, triplicate 12-lead ECG and assessment of vital signs (including sitting blood pressure and heart rate) will be performed.
Participants will attend the clinic 1 week before each maintenance dose is given (i.e. at Days 35, 77, 119 and 161) to provide a blood sample for local laboratory assessment of T levels. At the Day 35 visit (only) PK, total T, LH, FSH and PSA (total and hs) samples will also be collected for central laboratory analysis. Based on the results of the local analysis of T level from 7 days prior to the scheduled visit, participants will receive:

[T] (ng/mL)	Action Taken	Dose Administered
≤2	Continue in Stage 2 of Group 1	Maintenance dose of 120 mg SC teverelix TFA
>2	Withdraw from study, safety follow-up visit	None

SC=subcutaneous; T=testosterone; TFA=Trifluoroacetate

After the administration of the IMP the participants will be monitored for 30 minutes for the occurrence of ISRs and AEs.

If, in the opinion of the investigator, no safety concerns exist, participants will be discharged from the centre.

At each of the maintenance dose visits, the procedures carried out at the Day 42 visit will be repeated.

Safety Follow-up Visit (28 days after last dose)(Group 1 and Group 2 subjects without Stage 3)

Blood samples will be collected for fasted (≥8 hours) safety laboratory testing. Physical examination and assessments of vital signs (including sitting blood pressure and heart rate), height/weight, and triplicate 12-lead ECG will be performed

Stage 3 Visits (Group 2 only)

After final, Day 168 injection subjects will return on Day 203 and weekly thereafter until Day 252 or until serum T levels ≥1 ng/mL (local lab result), whichever occurs first

Safety Follow-up Visit (Day 259 or 7 days after serum T levels are ≥1 ng/mL (local lab result), whichever occurs first)

Blood samples will be collected for fasted (≥8 hours) safety laboratory testing. Physical examination and assessments of vital signs (including sitting blood pressure and heart rate), height/weight, and triplicate 12-lead ECG will be performed

Pharmacokinetic and Pharmacodynamic Samplings

Stage 1:

Post-dose PK blood sampling on Day 0 is scheduled at the following timepoints: 1, 1.5, 2, 2.5, 3, 4, 8, 12, 18, and 24 hours.

Blood samples for PD analysis (total T, LH, FSH) will be initiated at 24 hours post-dose.

The participant will return to the study site for additional post-dose PK and PD blood sampling at 48 hours (Day 2) and 72 hours (Day 3), and on Days 4, 7, 10, 12, 14, and 21.

On Days 7, 14, and 21, blood sampling for PSA will be performed.

Stage 2:

Post-dose PK and PD (total T, LH, FSH, PSA) blood sampling is scheduled on the following days: Days 28, 35, 42, 84, 126 and 168, and

follow-up for Group 1 and Group 2

Treatment

Participants will receive different doses depending on whether they join Group 1 or Group 2. The study will enrol participants into Group 1 first.

On Day 0 participants will receive a single loading dose consisting of 2 injections, each of which will contain 120 mg of teverelix TFA (Group 1) or 180 mg teverelix TFA (Group 2). The first injection will be administered as an IM and the other as an SC injection (Stage 1).

After Stage 1, participants of Group 1 will receive a maintenance dose, which will consist of a single 120 mg SC injection administered every 42 days up to Day 168.

If treatment of Group 1 has been terminated early due to a low therapeutic response rate, recruitment of participants into Group 2 will start.

After Stage 1, participants in Group 2 will receive a maintenance dose, which will consist of a single 180 mg SC injection administered every 42 days up to Day 168.

The total treatment period in this study will end when the last maintenance dose is administered on Day 168.

For Group 2 subjects only a follow up period will be followed. Subjects will return on Day 203 (5 weeks after final Day 168 injection) for serum T levels to be measured. Weekly visits will continue until serum T levels are ≥ 1 ng/mL (local lab result).

A safety follow-up visit will be done 7days after serum T levels are ≥ 1 ng/mL (local lab result). Participants withdrawn early from the study will be asked to return to the study site for a safety follow-up visit ≥28 days after administration of the last dose.

Population

Inclusion Criteria

The participant must fulfil all of the following criteria:

1. Is male, aged ≤85 years (≥18 years) at the beginning of the treatment period (Day 0)
2. Has histologically proven advanced adenocarcinoma of the prostate (metastatic or non-metastatic, hormone-sensitive, non-curative), suitable for androgen deprivation therapy
3. Is treatment naïve for any of the following:
    a. GnRH analogues,
    b. Androgen receptor antagonists, or
    c. Androgen synthesis inhibitors (e.g. abiraterone)
4. Agrees to practice contraception during the entire study treatment period and for 3 months after the last dose of IMP is administered:
    a. Either by using double barrier contraception,
    b. or, is truly sexually abstinent, when this is in line with the preferred and usual lifestyle of the participant

    Note: *Periodic abstinence [e.g. calendar, ovulation, symptothermal, postovulation methods for the female partner with childbearing potential] and withdrawal are not*

acceptable methods of contraception.

5. Has provided written (personally signed and dated) informed consent before completing any study-related procedure, which means any assessment or evaluation that would not have formed a part of his normal medical care

Exclusion Criteria

If any of the following criteria apply, the participant MUST NOT be admitted to the study. The participant:

1. Has abnormal screening and/or baseline laboratory values that suggest a clinically significant underlying disease, or the following laboratory values:
    a. Liver function test (aspartate aminotransferase [ASAT/SGOT], alanine aminotransferase [ALAT/SGPT]), or total bilirubin exceeding twice the upper limit of the normal (ULN) range
    b. Creatinine twice the ULN range
    c. Uncontrolled diabetes (HbA1c >7.5%) or previously undiagnosed diabetes mellitus with HbA1c >6.5%
2. Has any contraindication to the use of teverelix TFA
3. Has a life expectancy of less than 1 year
4. Has T levels <2.0 ng/mL at screening
5. Has a medical history of bilateral orchidectomy
6. Using any of the following prohibited treatments:
    a. Within 25 weeks prior to screening: dutasteride
    b. Within 12 weeks prior to screening: finasteride
    c. Current use of any of the following:
        i. Anti-androgen therapy, including T replacement therapy and 5α-reductase inhibitor treatment etc. (Spironolactone is a permitted concomitant treatment)
        ii. Any other medication or herbal product that may affect hormone levels and might, therefore, confound interpretation of the study results (e.g. St. John's wort)
7. Has neurological disease, psychiatric disease, drug or alcohol abuse, which could interfere with the participant's proper compliance
8. Has a history of myocardial infarction, unstable symptomatic ischaemic heart disease, any ongoing cardiac arrhythmias of grade >2 (chronic stable atrial fibrillation on stable anticoagulant therapy is allowed), thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or any other significant cardiac condition (e.g. pericardial effusion, restrictive cardiomyopathy) within the 6 months prior to screening
9. Has congenital long QT syndrome or ECG abnormalities at screening of:
    a. Q-wave infarction, unless identified ≥6 months before screening
    b. Fridericia corrected QT interval (QTcF interval) >480 msec. If QTcF is prolonged in a participant with a pacemaker, the

participant may be enrolled in the study upon discussion with the project clinician

- If the QTcF interval is 450-480 msec, inclusive, in a participant with current use of medications with known effects on QT interval, the participant may be enrolled in the study following discussion with the Medical Lead

Note: Cardiac arrhythmia grading:
o Bradyarrhythmias (HR <60/min)
o Tachyarrhythmias (HR >100/min)
o Supraventricular arrhythmias – arrhythmias that originate in the sinoatrial node, atrial myocardium or atrioventricular node (regular QRS complex)
o Ventricular arrhythmias – arrhythmias that originate below the atrioventricular node (wide QRS complex)

10. Has known or suspected severe renal impairment
11. Has a medical history of diagnosis of, or treatment for, another malignancy within the 2 years prior to administration of the first dose of IMP, or previous diagnosis of another malignancy with evidence of residual disease. Participants with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection
12. Is currently using Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications
13. Has uncontrolled hypertension despite appropriate medical therapy (sitting blood pressure [BP] of >180 millimetres of mercury [mmHg] systolic and >95 mmHg diastolic at 2 separate measurements taken no more than 60 minutes apart during the screening visit). Participants with isolated systolic BP measurements >180 mmHg may be rescreened. Participants with isolated systolic BP measurements 141 to 180 mmHg or isolated diastolic BP measurements ≥95 mmHg, although eligible, should be referred for further management of hypertension if indicated
14. Has known, previously diagnosed HIV infection, active chronic hepatitis B or C, life-threatening illness unrelated to prostate cancer, or any serious medical condition that could, in the investigator's opinion, potentially interfere with participation in this study. Specific screening for chronic viral illness is at the discretion of the site and/or local Institutional Review Board (IRB)
15. Has been exposed to another investigational drug within the 3 months prior to screening
16. Has anticipated non-availability for study visits/procedures
17. Plans to undergo surgery during the study period
18. Known presence of hepatic metastases

Efficacy Endpoints

Primary Endpoint:

Proportion of participants achieving castration level with serum T <0.5 ng/mL or 1.73 nmol/L at Day 28.

Secondary Endpoints:

1. Proportion of participants achieving castration level with serum T <0.2 ng/mL at Day 28
2. Proportion of participants achieving castration level with serum T <0.5 ng/mL at Day 42
3. Proportion of participants achieving castration level with serum T <0.2 ng/mL at Day 42
4. Proportion of participants achieving a T castration rate over 168 days of treatment period

   Note: *Castration rate is defined as the observed percentage of participants who have T concentrations <0.5 ng/mL (1.73 nmol/L) at all scheduled visits.*
5. Proportion of participants achieving profound castration rate (<0.2 ng/mL) over 168 days of treatment period
6. Mean time to T levels falling below castration level (<0.5 ng/mL [1.73 nmol/L]) for the first time
7. Mean time to (first) overstep of T castration level after achieving castration
8. Mean time for serum T levels to be ≥ 0.5 ng/mL after final, Day 168 injection
9. Proportion of participants achieving castration level for LH (LH <1.1 U/L) at Day 28
10. Proportion of participants with effective LH castration rate over 168 days of treatment period
11. Mean time to LH levels falling below castration level (LH <1.1 U/L) for the first time
12. Mean time to (first) overstep of LH castration level after achieving castration
13. Changes from baseline in PD and PK parameters over time
14. Number of participants with a PSA response of ≥50% reduction at the Day 168 visit
15. Number of participants with a PSA response of ≥80% reduction at the Day 168 visit
16. Percent change from baseline in serum PSA concentration at each visit
17. Mean serum PSA concentration at each visit
18. Mean serum LH concentration at each visit
19. Mean serum T concentration at each visit
20. Mean serum FSH concentration at each visit

Safety Endpoints

Safety endpoints for the study include:

1. Number of participants with treatment-emergent AEs (defined as any AE occurring or worsening following treatment), summarised by system organ class (SOC) and preferred term (PT)

   Note: Occurrence of ISRs will be included.
2. Mean changes in vital signs, triplicate 12-lead ECG and laboratory data parameters at each visit during the 168-day treatment period, compared to baseline.
3. Continuous 12-lead, 24 hour Holter monitoring (subset of 30 Group 2 subjects only)
4. Predictive effect of cardiac biomarkers (terminal pro-B-type natriuretic peptide (NTproBNP, D-dimer, C-reactive protein (CRP), high-sensitivity troponin (hsTn)) for CV events
5. Percentage of participants with ISRs at each visit during the 168 days treatment period

   Note: *Photography of injection sites will be performed at each dosing visit, and ISRs will be scored based on a specific scoring matrix.*

Statistical Methods

Analysis Populations

Screening population: All participants who signed the informed consent form.

Safety population: All participants who received any dose of the IMP.

Intention-to-treat (ITT) analysis set: All participants included in the safety population for whom the primary endpoint is evaluable.

Per protocol (PP) analysis set: All participants included in the ITT analysis set who complete the study without major protocol violation.

The analysis will be done in 2 stages. Stage 1 will only include the analysis of the primary objective, which investigates the effect of the loading dose required to achieve castration levels by Day 28. Stage 2 will include all other analyses.

The primary objective will be assessed by determination of the proportion of participants achieving castration level T concentrations on Day 28.

The primary result will be the proportion of those participants in the PP analysis set, together with its Clopper-Pearson confidence interval (CI) and absolute frequencies. The same holds for the proportion of participants maintaining castration over 24 weeks at all scheduled visits.

In addition the calculation of the Kaplan-Meier estimate of the proportion of patients who achieve and maintain castrate T levels (T level < 50 ng/dL) from Day 28 through the end of the treatment period will be done.

All safety and efficacy endpoints will be summarised descriptively, i.e. by absolute and relative frequencies (relative to the respective analysis

population) for categorical endpoints. The distribution of continuous endpoints will be described by standard measures of location and dispersion in terms of mean, standard deviation (SD), median, Quartiles 1 and 3, minimum and maximum, and CIs for the mean.

AEs: All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology and summarised by PT and SOC. Frequencies of AEs will be presented by absolute and relative frequencies of (a) the number of AEs and (b) the number of participants experiencing an event for each SOC and PT.

AEs will be summarised separately for serious AEs, treatment-emergent AEs (defined as any new or worsening pre-existing AE with a date equal to or later than the date of IMP administration) and possibly treatment-related AEs.

PK/PD: Concentrations over time will be described by area under the concentration-time curve from time zero to last available measurement (AUC_{0-t}), maximum concentration (C_{max}), time to reach maximum concentration (T_{max}), terminal half-life ($t_{1/2}$), first-order elimination rate and graphical representation of the concentrations over time. The geometric mean will be calculated additionally for AUCs and C_{max}.

Depending on the progression of the concentrations, multiple peaks of concentrations can occur. Additional AUC, T_{max} and C_{max} will be specified accordingly (total and separated by each phase of concentration increase) for the parameters.

Missing data will not be substituted in general, but in the case of a laboratory reporting concentrations as unquantifiably low, they will be set to 0.

All study data will be reported in participant data listings.

Detailed statistical methodology, definitions and data handling will be described in a separate statistical analysis plan (SAP) prior to analysis.

Responsibilities

Sponsor's Responsible Representative:	**Carol MacLean, PhD** *VP Women's Health & Clinical Operations* Antev Limited 106 New Bond Street (3rd Floor) London W1S 1DN UK Email: cmaclean@antev.co.uk
Sponsor's Medical Expert:	**Dr Finn Larsen** *Chief Scientific Officer* Antev Limited 106 New Bond Street (3rd Floor) London W1S 1DN UK Email: flarsen@antev.co.uk
Medical Lead Insuvia UAB:	**Tomas Janusonis, MD** *Clinical Research Physician* Jonavos str. 30 Kaunas 44262 Tomas.janusonis@insuvia.com
Biometrician Quanticate International Ltd:	**Saira Ahmad** *Senior Statistician I* Bevan House, 9-11 Bancroft, Hitchin SG5 1LH Email: Saira.Ahmad@quanticate.com
Pharmacokinetic Laboratory:	**Rebecca Wright** *Senior Scientist Small Molecule Bioanalysis Drug Development Solutions* LGC Newmarket Road Fordham Cambridgeshire CB7 5WW UK Tel: +44 (0)1638 724 343 | Ext: 1343 Email: rebecca.wright@lgcgroup.com

Serious Adverse Event Reporting
All serious adverse events (SAEs) must be reported immediately (within 1 working day) to: safety@intuvigilance.com

Name and address of drug safety manager:
Nimisha Kotecha
Managing Director/EU QPPV
IntuVigilance Limited
Scotsbridge House,
Scots Hill, Rickmansworth
WD3 3BB,
Hertfordshire,
UK.

Email: nimisha.kotecha@intuvigilance.com
Phone: +44 (0)1923-545474
Fax: +44 (0) 01923 545229
Mobile: +44 (0)7834-766990

Signatures

The signatories are obliged to comply in all respects with:

- This clinical study protocol
- The standards of Good Clinical Practice as defined in the "Note for Good Clinical Practice" (CPMP/ICH 135/95) and related guidelines
- The "Declaration of Helsinki" current valid version according to applicable national regulatory and legal requirements
- All applicable regulatory requirements including national drug and data protection law

Sponsor: Antev
Responsible
Representative

Carol MacLean, PhD
VP Women's Health & Clinical Operations

Clinical Research Organisation (CRO): Quality, Regulatory and Clinical Consultancy (QRCC)
CRO Project Manager

Alex Gage
Senior PM

Sponsor's Medical
Expert

Finn Larsen, MD
Chief Scientific Officer

Biometrician

Saira Ahmad
Senior Statistician I

Declaration by the Investigator

I have read this study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol. In particular, I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the current versions of the "Declaration of Helsinki" current valid version according to applicable national regulatory and legal requirements and the guidelines on Good Clinical Practice.

I understand that all documentation supplied to me by the Sponsor and the Clinical Research Organisation (CRO) concerning this study which has not been previously published will be kept in the strictest confidence. This documentation includes the study protocol, investigator's brochure, case report forms, and other scientific data.

Responsible Investigator at the Study Centre

_____
Name/address printed

_____ _____
Place / date Signature

Abbreviations

ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse event
ALAT	Alanine aminotransferase
APC	Advanced prostate cancer
ASAT	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
$AUC_{0-\infty}$	Area under the concentration-time-curve from time zero up to infinity (∞)
AUC_{0-t}	Area under the concentration-time-curve from time zero up to the last measurable concentration at timepoint t
AUC_{0-t1}	Area under the concentration-time-curve from time zero up to concentration at timepoint t1 after which the concentrations start to rise again towards a second peak
AUC_{t1-t}	Area under the concentration-time-curve from timepoint t1 up to timepoint t (slow release component of total observed AUC)
BMI	Body mass index
BP	Blood pressure
BPH	Benign prostatic hyperplasia
CI	Confidence interval
C_{max}	Maximum plasma concentration
$C_{max,0-t1}$	Maximum plasma concentration after administration from zero up to timepoint t1
$C_{max,t1-t}$	Maximum plasma concentration after administration from timepoint t1 up to timepoint t
CRA	Clinical research associate
CRO	Clinical Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram(s)
eCRF	Electronic case report form
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-releasing hormone
HbA1c	glycated haemoglobin
HIV	Human immunodeficiency virus
hsTn	High sensitivity troponin
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular
IMP	Investigational medicinal product

I-PSS	International Prostate Symptom Score
IRB	Institutional Review Board
ISI	Injection site inspection
ISR	Injection site reaction(s)
ITT	Intention-to-treat
IV	Intravenous
L	Litre
LH	Luteinising hormone
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Millilitre
mmHg	Millimetre of mercury
msec	Millisecond
ng	Nanogram
nmol	Nanomole
NT proBNP	B-type natriuretic peptide
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per protocol
PSA	Prostate-specific antigen
PT	Preferred term
QoL	Quality of Life
QTcF	Fridericia corrected QT interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse drug reaction
T	Testosterone
$t_{½}$	Apparent terminal plasma half-life
TFA	Trifluoroacetate
T_{max}	Time to reach C_{max} after dosing
$T_{max,0\text{-}t1}$	Time to reach $C_{max,0\text{-}t1}$ after dosing
$T_{max,t1\text{-}t}$	Time to reach $C_{max,t1\text{-}t}$ after dosing
TNM	Primary Tumor, Lymph Node and Metastasis
TURP	Transurethral Resection of The Prostate
U	Unit
ULN	Upper limit of normal
λz	Apparent terminal rate constant

Table of Contents

Study Protocol 1

Protocol Synopsis 2

Responsibilities 13

Serious Adverse Event Reporting 14

Signatures 15

Declaration by the Investigator 17

Abbreviations 18

Table of Contents 20

List of In-Text Tables 23

List of In-Text Figures 23

1 Introduction 24
1.1 Background 24
1.1.1 Epidemiology of Advanced Prostate Cancer 24
1.1.2 Presentation of Advanced Prostate Cancer 24
1.1.3 Treatment Overview 25
1.2 Background Information on Investigational Medicinal Product 25
1.2.1 Preclinical Studies 26
1.2.2 Clinical Studies 27
1.2.3 Risk-benefit Assessment 28
1.3 Study Rationale 28

2 Study Objectives and Purpose 28

3 Overall Study Design and Plan Description 29
3.1 Core Study 29
3.2 Discussion of Study Design 31

4 Selection of Study Population 31
4.1 Participant Inclusion Criteria 32
4.2 Participant Exclusion Criteria 32
4.3 Participant Withdrawal Criteria 33

5 Study Treatments 34
5.1 Treatments Administered 34

5.2 Identity of Investigational Product(s) 35
5.3 Method of Assigning Participants to Treatment Groups 35
5.4 Selection of Doses in the Study 35
5.5 Selection and Timing of Dose for Each Participant 36
5.6 Supply, Packaging and Labelling 37
5.6.2 Storage 37
5.6.3 Shipment 37
5.6.4 Packaging 37
5.6.5 Labelling 38
5.7 Blinding and Randomisation 38
5.8 Prior and Concomitant Therapy 38
5.8.1 Prohibited Previous and Concomitant Treatments 38
5.8.2 Admissible Concomitant Treatments 38
5.9 Treatment Compliance and Drug Accountability 38
5.10 Safety Monitoring for Allergic Reactions 39
5.11 Management of Drug Overdose 39

6 Variables and Methods 39
6.1 Population Characteristics 39
6.1.1 Demography 39
6.1.2 Medical History 39
6.1.3 Prostate Cancer Diagnosis 40
6.1.3.1 Primary Tumor, Lymph Node and Metastasis Classification of Prostate Cancer 40
6.1.3.2 Gleason Score 41
6.2 Efficacy 42
6.2.1 Primary Efficacy Variable 42
6.2.2 Secondary Efficacy Variables 42
6.3 Safety 43
6.3.1 Vital Signs 43
6.3.2 Physical Examination 44
6.3.3 Triplicate 12-Lead Electrocardiogram 44
6.3.4 Injection Site Inspection 45
6.3.4.1 Photographic Documentation of Injection Site 45
6.3.5 Safety Laboratory Variables 46
6.3.6 Additional Safety Assessments 46
6.3.7 Adverse Events 46
6.3.7.1 Definition of Adverse Events 46
6.3.7.2 Assessment of Adverse Events 47
6.3.7.3 Follow-up of Adverse Events 50
6.3.7.4 Documentation and Reporting of Adverse Events 50
6.4 Pharmacokinetics 50

6.4.1 Pharmacokinetic Variables 50
6.4.2 Blood Sampling Time Points, Handling and Labelling of Blood Samples 51
6.5 Pharmacodynamics 52

7 Study Conduct 54
7.1 Study Schedule 54
7.2 Observations by Visit 59
7.2.2 Baseline Examination (Day 0), Stage 1 59
7.2.3 Treatment (Maintenance Dose) Period Visits (Day 28 to Day 168), Stage 2 60
7.2.4 Follow-up Visit (28 Days after Last Dose) 60
7.3 Duration of the Study 60
7.3.1 Planned Duration for the Individual Participant 60
7.3.2 Premature Termination 61

8 Statistics 62
8.1 Statistical and Analytical Plans 62
8.1.1 Analysis Populations 62
8.1.2 Adaptive Study Design 62
8.1.3 Primary Efficacy Analysis 63
8.1.4 Secondary Endpoint Analyses 63
8.1.5 Analysis of Safety Data 64
8.1.6 Missing Data 65
8.1.7 Multicentre Study 65
8.1.8 Participant Data Listings 65
8.1.9 Deviations from the Planned Statistical Analysis 65
8.1.10 Interim Analysis 65
8.1.11 Software used for Statistical Analysis 66
8.1.12 Determination of Sample Size 66
8.2 Data Management 66

9 Data Handling and Data Quality Assurance 67
9.1 Data Management 67
9.2 Documentation 67
9.2.1 Pre-screening List and Participant Identification List 67
9.2.2 Source Data and Participant Records 67
9.2.3 Electronic Case Report Form 67
9.3 Direct Access to Source Data/Documents 68
9.4 Monitoring 68
9.5 Quality Assurance 69

10 Ethical, Legal and Administrative Aspects 70
10.1 Approval Procedures 70
10.2 Protocol Amendments 70

10.3 Informed Consent 70
10.4 Confidentiality and Data Protection 71
10.5 Liability, Insurance and Finances 71
10.6 Clinical Study Report, Publication and Use of Study Findings 71
10.7 Archiving of Study Records 72

11 List of References 73

List of In-Text Tables

Table 1: Dosing Regimens under Evaluation 29
Table 2: Investigational Medicinal Product Details 33
Table 3: Decision-making in Relation to Serum Testosterone Levels 35
Table 4: Testosterone Testing in Groups 1 and 2 35
Table 6: TNM Classification of Primary Tumours [13] 38
Table 7: TNM Classification of Regional Lymph Nodes (N) [14] 39
Table 8: TNM Classification of Distant Metastasis (M)[a] [14] 39
Table 9: Gleason Scoring System 40
Table 10: Timepoints for Efficacy Variables 41
Table 11: Food and Drug Administration Local Toxicity Scale 43
Table 12: Clinical Safety Laboratory Tests 44
Table 13: Pharmacokinetic Parameters 49
Table 14: Pharmacokinetic Timepoints 50
Table 15: Pharmacodynamic Blood Sampling Schedule[a] 51
Table 16: Schedule of Assessments for Groups 1 and 2 53

List of In-Text Figures

Figure 1: Study Design 30
Figure 2: Gleason Score 41

1 Introduction

The procedures set out in this study protocol are designed to ensure that the conduct, evaluation and documentation of this study take place according to the guidelines for Good Clinical Practice for Trials on Medical Products for Human Use (GCP) of the International Conference on Harmonisation (ICH) and the current version of the Declaration of Helsinki according to applicable national regulatory and legal requirements. The study will also be carried out in keeping with national legal requirements which will be described in the national supplement to the protocol.

1.1 Background

Prostate cancer is the most commonly diagnosed cancer in men, and the second leading cause of cancer-related deaths [1]. Most prostate cancer-related deaths are due to advanced disease, which results from any combination of lymphatic, haematogenous, or contiguous local spread.

1.1.1 Epidemiology of Advanced Prostate Cancer

Approximately 11.6% of men will develop prostate cancer in their lifetime, with the likelihood increasing with age. Prostate cancer is most often diagnosed in men aged between 55 and 74 years, with a median age at diagnosis of 66 years [2]. Since the advent of prostate-specific antigen (PSA) screening, prostate cancer is being detected and treated earlier.

Overall, incidence rates of prostate cancer began declining in 2000. Acceleration in the decline began in 2008, when health organisations started to argue against routine PSA screening. From 2009 to 2013, the incidence rate decreased by approximately 8% per year [1].

A review of almost 800,000 cases of prostate cancer diagnosed from 2004 to 2013 found that although the incidence of low-risk prostate cancer decreased between 2007 to 2013 to 37% less than that of 2004, the annual incidence of metastatic prostate cancer during those years increased to 72% more than that of 2004. The increase in metastatic prostate cancer was greatest (92%) in men aged 55 to 69 years [3].

At diagnosis, 79% of prostate cancer cases are localised; in 12%, the cancer has spread to regional lymph nodes, and in 5% there are distant metastasis. The 5-year relative survival rate for localised and regional prostate cancer is 100%, compared with 29.8% for metastatic cases [2].

Since the early 1990s, prostate cancer death rates have been decreasing in men of all races and ethnicities. However, they remain more than twice as high in black men as in any other group [1]. Prostate cancer tends to not only be more aggressive and progressive in black men, leading to advanced disease, but to also be of a higher grade at diagnosis [4, 5]. Death rates are also higher in men who have advanced-stage cancer, and in men who are 75 to 84 years of age [2]. The mortality rate associated with prostate cancer continues to increase in Europe and in countries such as Australia, Japan, and Russia.

1.1.2 Presentation of Advanced Prostate Cancer

Advanced prostate cancer results from any combination of lymphatic, blood, or contiguous local spread. Manifestations of metastatic and advanced disease may include the following:

- Anaemia
- Bone marrow suppression

- Weight loss
- Pathologic fractures
- Spinal cord compression
- Pain
- Haematuria
- Ureteral and/or bladder outlet obstruction
- Urinary retention
- Chronic renal failure
- Urinary incontinence
- Symptoms related to bony or soft-tissue metastases

Treatment-related symptoms (sometimes associated with radiation therapy), such as rectal bleeding, gross haematuria, and urethrorectal fistula, need to be differentiated from the disease-specific symptoms.
Physical examination findings of adenopathy, lower-extremity oedema, and bony tenderness may indicate metastatic disease. In addition, obliteration of the lateral sulcus or seminal vesical involvement found during rectal examination often indicates locally advanced disease.
Neurologic examination, including determination of external anal sphincter tone, should be performed to help detect possible spinal cord compression.

1.1.3 **Treatment Overview**

Several treatment options exist for different stages of prostate cancer, including observation, prostatectomy, radiation therapy, chemotherapy, and hormone therapy. Hormone therapy has evolved from the use of oestrogens to gonadotropin-releasing hormone (GnRH) agonists and recently, investigational GnRH antagonists [6].
Androgen deprivation therapy (ADT) is the backbone of treatment for participants with advanced prostate cancer, and it is indicated for use in multiple clinical settings of prostate cancer. Chemical castration consists of GnRH agonists and antagonists administered intramuscularly (IM), subcutaneously (SC), or orally. One of the main concerns when using GnRH agonists is a surge in testosterone (T) caused by the medication's initial effect on the pituitary gland. This T surge could lead to a tumour flare, which is characterised by a rapid expansion of the prostate cancer, leading to pain and potential debilitation, particularly in participants with spinal metastases. This concern of tumour flare led to the development of the GnRH antagonists, which do not cause a T surge, since there is no initial stimulation of the pituitary gland by the medication. The GnRH antagonist degarelix is currently approved by the US Food and Drug Administration (FDA) for the treatment of participants with advanced prostate cancer [7].
GnRH antagonists are analogues of GnRH, and act as a competitive inhibitor of GnRH [8]. GnRH mediates stimulation of gonadotropin (i.e., follicle stimulating hormone [FSH] and luteinising hormone [LH]) secretion [9]). Unlike GnRH agonists, the GnRH antagonists do not cause an initial surge of gonadotropins. They rapidly decrease the secretion of LH and FSH from the pituitary gland, thereby leading to an immediate decrease in T secretion from the Leydig cells of the testicles [10].

1.2 **Background Information on Investigational Medicinal Product**

The investigational medicinal product (IMP) to be tested in this study is teverelix trifluoroacetate (TFA*)*, a depot formulation of a GnRH antagonist used for the treatment of advanced prostate cancer. Treatment with the IMP will start with a loading dose administered

through 2 injections, one of which will be given IM and the other of which will be given SC, followed by a maintenance SC injection every 4 or 6 weeks. Two treatment regimens will be tested in this study: 120 mg of teverelix TFA administered, after the loading dose, every 42 days and 180 mg of teverelix TFA administered, after the loading dose, every 42 days.

1.2.1 **Preclinical Studies**

In preclinical studies, teverelix has been shown to exert anti-ovulatory activity and to inhibit LH, FSH and T secretion.

No target organ toxicity was observed from subacute and chronic toxicity studies in rats and dogs following SC administration of teverelix and no adverse systemic effects have been demonstrated. In general, treatment-related effects were considered to be either physiological changes arising as a result of the pharmacological response to administration of a GnRH antagonist, or foreign body inflammatory reactions at the injection site arising as a result of the physical nature of the test material, rather than a direct toxic response to teverelix.

The most notable finding across species and studies was the clear reduction in reproductive organ and accessory gland weight, confirmed pathologically as arrested development or degeneration. Notable findings in males were spermatogenic arrest within the testes, ductal/tubular atrophy, absence of spermatozoa within the epididymides, and prostate gland atrophy. In females, atrophy of the vagina, cervix and uterus, maturation arrest within the ovaries, and atrophy of mammary gland tissue were apparent.

Injection site reactions (ISR) were noted during dose range finding studies and were cited as the limiting factor in the selection of high doses for the definitive repeat dose toxicity studies. In the rat and dog, daily SC administration of teverelix at a concentration of 10 mg/mL (doses of up to 50 mg/kg in the rat and 20 mg/kg in the dog) was unsuitable and led to unacceptable ISRs, which were considered to be a function of the physical characteristics of the test substance, the dosing regime, and the dose volume. SC doses of up to 20 mg/kg/day using a concentration of 75 mg/mL were tolerated, demonstrating that reducing the dose volume and using a higher concentration to achieve the same dose ameliorated the local response. Weekly dosing for up to 6 months in rats and 9 months in dogs using a 75 mg/mL (in 5% mannitol) formulation was associated with some evidence of clinical ISRs, but overall, dosing was tolerated. Pathologically, signs of an inflammatory response within the SC tissue, predominantly consisting of an infiltration of macrophages (foreign body-type response), was apparent.

Early screening studies indicated that teverelix acetate was devoid of anaphylactoid reactions when administered intravenously in rats (single dose 5 mg/kg) or other species including mice, rabbits, and dogs. Teverelix also had very modest histamine-releasing properties on rat mast cells. When intravenous (IV) teverelix acetate was administered to rats and cynomolgus monkeys in toxicity studies, clinical signs indicative of release of vasoactive chemical modulators were seen and some animals were found dead following administration of the highest dose. Subsequent studies with teverelix TFA administered by the SC route, which is relevant to the clinical situation, did not identify any signs of anaphylaxis or histamine release, and no effects on blood pressure [BP] were apparent. Even a single and repeat dose of 50 mg/kg administered by the SC route to rats did not induce adverse clinical signs and teverelix showed no mutagenic or clastogenic potential.

Given the pharmacological effect of teverelix on pituitary gonadotrophic hormones, a reduction in fertility is anticipated. However, studies have been conducted to determine whether restoration of fertility is seen post-dosing. A single dose of 2 mg/kg administered to male rats resulted in reduced plasma T concentrations for 5 weeks after dosing, but there was

no subsequent effect on mating performance or pregnancy outcome 11-, 14- or 17-weeks post-dosing. A single dose of 2 mg/kg administered to female rats had no effect on oestrous cyclicity 5/6 weeks post-dosing, and no effect on the capability of the females to become pregnant 12 weeks post-dosing. Lower numbers of corpora lutea, implantations, and live foetuses and a higher number of early intra-uterine deaths were consistent with the known pharmacological effect.
In embryofoetal/teratogenicity studies, an increase in post-implantation loss was noted following administration of 15 µg/kg in the rabbit but no embryotoxicity was seen up to a dose of 10 µg/kg in the rat. No evidence of teratogenicity was found in either species [11].

1.2.2 **Clinical Studies**

In Phase 1 clinical studies conducted in healthy men, teverelix produced a rapid, marked suppression of serum levels of LH, T, and to a lesser extent FSH. In the first Phase 1 studies, the teverelix-induced T suppression was fully reversible within 1 week. In higher dose Phase 1 studies, some patients had persistent T suppression for several months. A Phase 1 clinical study conducted in healthy women demonstrated that teverelix TFA reduced the serum levels of LH, FSH, oestradiol, and progesterone in a dose-dependent manner.
As early as 2 weeks after administration of two 60 mg teverelix TFA injections in participants with benign prostatic hyperplasia (BPH), a statistically significant decrease was observed in prostatic symptoms, as measured by the International Prostate Symptom Score (I-PSS). Symptomatic improvement increased over time,and was most pronounced at study completion (16 weeks). A total of 83% of participants who received teverelix TFA were classified as responders (defined as a >3 point reduction in symptom score from baseline). In addition, statistically significant improvements were observed in maximum urine flow rate, Quality of Life (QoL) and prostate size when compared to baseline. In a subsequent study, where participants were administered a single injection of 30 mg teverelix TFA, 60 mg teverelix TFA or placebo, a larger increase in maximum urinary flow rate occurred in both the 30 mg and 60 mg teverelix TFA treatment groups compared to placebo. In addition, a significant increase from baseline for mean urinary flow rate was observed in the 60 mg teverelix TFA treatment group, and the 30 mg teverelix TFA group was more than 3 times as likely to give a favourable QoL response compared to placebo. In the extension study, participants administered a second dose of either 30 mg or 60 mg teverelix TFA experienced an increase in mean and maximum urinary flow rate, compared to the placebo treated group, and were more likely to give a favourable response with respect to QoL.
In the case of advanced prostate cancer, suppression of T to castration levels (<0.5 ng/mL) was achieved within 3 days in the majority of the participants and this was maintained for 4 to 8 weeks. Some participants experienced transient castration breakthrough, where T concentrations temporarily increased to ≥0.5 ng/mL. Teverelix TFA was also shown to rapidly reduce and normalise PSA levels.
Pharmacokinetic (PK) and pharmacodynamic (PD) data from 2 studies indicate that the SC route of administration for teverelix TFA produces a more sustained suppression of T levels than the IM route. No safety concerns were identified in any of the conducted clinical studies. The most frequently reported adverse events (AEs) were mild ISRs and reversible symptoms characteristic of T and oestrogen deprivation, such as hot flushes, decrease in libido and potency, and reduction in testis size. No serious adverse events (SAEs), considered to be at least possibly related to the administration of teverelix TFA, have been reported [11].

1.2.3 Risk-benefit Assessment

No SAEs assessed as attributable to the administration of teverelix TFA have been reported. Three SAEs have been reported for teverelix TFA participants to date and none of these was thought to be related to IMP (SAE 1, jaundice cholestatic/cholelithiasis/bile duct stone/pancreatitis; SAE 2, worsening ischaemic heart disease/atrial fibrillation; SAE 3, nephrolithiasis).

The most frequently reported AEs were mild ISR and reversible symptoms characteristic of T and oestrogen deprivation, such as hot flushes, decrease in libido, erectile disorder, and reduced testes size. No signs indicative of allergic reactions have been noted in the clinical participants dosed with teverelix TFA to date.

The studies conducted so far have demonstrated no safety concerns and, in the later studies, castration levels of sex hormones in men were obtained within a few days. Teverelix TFA reduced the serum levels of LH, FSH, oestradiol, and progesterone in a dose-dependent manner in healthy women. Statistically significant improvements in symptoms were achieved in participants with BPH, and PSA levels were normalised in participants with advanced prostate cancer [11].

1.3 Study Rationale

As an GnRH antagonist, teverelix antagonises the GnRH by reversibly binding to GnRH receptors in the pituitary gland. This subsequently blocks the action of GnRH in the body and the release of both LH and FSH from the pituitary gland, which leads to a rapid suppression of T release from the testes.

Antev Ltd has conducted a Phase 1, open-label, single centre study investigating the PK, safety, and PD of a single dose of teverelix TFA administered either SC or IM to healthy male volunteers. The doses and administration schedule of teverelix TFA used in this Phase 2 study are based on the PK and PD results of the above-mentioned Phase 1 study.

The study population planned for this Phase 2 study is comparable to that of the previously conducted Phase 2 study for the development of degarelix, which has been approved by the FDA and the European Medicines Agency in 2008 based on the data from the pivotal study [2].

2 Study Objectives and Purpose

Primary Objective

To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.5 ng/mL or 1.73 nmol/L) at Day 28.

Secondary Objective(s)

- To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.2 ng/mL or 0.6934 nmol/L) at Day 28
- To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.5 ng/mL or 1.73 nmol/L) at Day 42
- To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.2 ng/mL or 0.6934 nmol/L) at Day 42
- To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.5 ng/mL or 1.73 nmol/L) at Day 168
- To assess the efficacy of teverelix TFA in terms of ability to suppress serum T levels to below castration level (<0.2 ng/mL or 0.6934 nmol/L) at Day 168

- To assess the efficacy of teverelix TFA in terms of ability to maintain suppression of serum T levels below castration level (<0.5 ng/mL or 1.73 nmol/L) over time during Stage 2 (maintenance-dose period) of the study
- To assess the efficacy of teverelix TFA in terms of ability to maintain suppression of serum T levels below castration level (<0.2 ng/mL or 0.6934 nmol/L) over time during Stage 2 (maintenance-dose period) of the study
- To assess the time taken to achieve serum T levels below castration level (<0.5 ng/mL or 1.73 nmol/L)
- To assess the time taken to achieve serum T levels below castration level (<0.2 ng/mL or 0.6934 nmol/L)
- To assess the time taken to achieve serum T levels above castration level (≥0.5 ng/mL or or 1.73 nmol/L)) following the final, Day 168 injection of teverelix TFA
- To delineate the PK profile of teverelix TFA
- To assess the effects of teverelix TFA on:
  - PSA
  - T
  - FSH
  - LH
- To assess the predictive effect for new cardiovascular (CV) events of cardiac biomarkers:
  - N-terminal pro-B-type natriuretic peptide (NTproBNP)
  - D-dimer
  - C-reactive protein (CRP)
  - high-sensitivity troponin (hsTn)
- To assess the safety of teverelix TFA in terms of:
  - local tolerability (injection site reactions [ISR])
  - systemic tolerability (adverse events, vital signs, electrocardiograms (ECG), Holter monitoring (subset of 30 subjects in Group 2 only) and laboratory parameters)

3 Overall Study Design and Plan Description

3.1 Core Study

This is an adaptive Phase 2, open-label, multicentre study to evaluate the PK, PD, efficacy and safety of teverelix TFA, a GnRH antagonist in participants with advanced prostate cancer.

For Group 1, it is planned to enrol approximately 24 participants from 3 investigational sites in Lithuania to obtain 20 evaluable participants with prostate advanced cancer. For Group 2, it is planned to enrol approximately 60 participants from up to 7 investigational sites in Lithuania and (potentially) Netherlands/Belgium in order to obtain 50 evaluable participants with advanced prostate cancer, for the assessment of treatment response on Day 28 and throughout the study up to Day 168.

Figure 1 displays the study design.

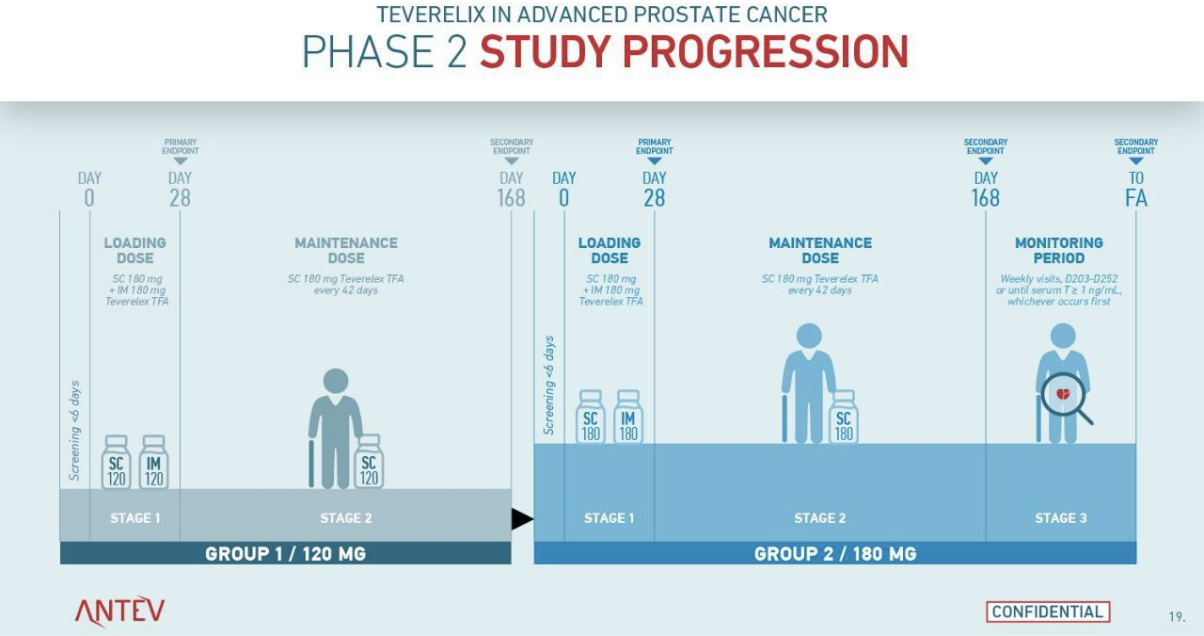
The study consists of the following periods/visits:

Screening Period: Day -6 to -1
Groups 1 & 2 Treatment Period:
Stage 1: Loading dose administered at baseline (Day 0) with follow-up visits until Day 28
Stage 2: Maintenance treatment administered every 6 weeks with visits from Day 28 up to Day 168, or until treatment ceases to become effective
Follow-up Visit: 28 days after the last dose of IMP

Group 2 (Stage 3 subjects only) Treatment Period:
Stage 1: Loading dose administered at baseline (Day 0) with follow-up visits until Day 28
Stage 2: Maintenance treatment administered every 6 weeks with visits from Day 28 up to Day 168, or until treatment ceases to become effective
Stage 3: Follow up period. Day 203 visit followed by weekly visits until D*ay 252 or until* serum T levels are ≥ 1 ng/mL (local lab result), whichever occurs first
Follow-up Visit: Day 259 or ≥7 days after serum T levels are ≥ 1 ng/mL (local lab result), whichever occurs first

An overview of the Schedule of Assessments is provided in Section 7.1. After signing the informed consent for the core study, participants will undergo a screening examination within 6 days prior to the administration of teverelix TFA to verify the participants' eligibility, and to document participant characteristics, including medical and surgical history, and disease characteristics.
Table 1 presents the 2 dosing regimens to be evaluated in this study.

Figure 1: Study Design



D0=Day 0; IM=intramuscular; SC=subcutaneous

Table 1: Dosing Regimens under Evaluation

Group	Loading Dose	Maintenance Dose	Dosing Interval
1	120 mg IM +120 mg SC	120 mg SC	6 weekly
2	180 mg IM +180 mg SC	180 mg SC	6 weekly

IM=intramuscular; SC=subcutaneous

Initially enrolment will open for Group 1 only. If, after Day 28, a participant's serum T value (as tested by the local laboratory on Day 21) is >2 ng/mL, the participant will be withdrawn from the study.

Enrolment will continue for Group 1 until 20 participants have completed the Day 28 visit with no more than 2 participants being classified as a treatment failure. Treatment failure is defined as having a T level >2 ng/mL at Day 28 (as tested by the local laboratory on Day 21) or requiring to be withdrawn at any later timepoint during the study.

If 3 or more participants fail treatment in Group 1 then further enrolment into that group will stop due to statistical confidence that a 90% responder rate cannot be achieved with that dosing regimen. All future participants will be enrolled into Group 2.

If in Group 2 at Day 28, a participant's serum T value (as tested by the local laboratory on Day 21) is >2 ng/mL, the participant will be withdrawn from the study.

If 7 or more participants fail in Group 2 then all further enrolment will be stopped and the study will be terminated.

3.2 Discussion of Study Design

Teverelix is currently being developed for chemical castration in participants with advanced prostate cancer. Five previous Phase 1 clinical studies of teverelix have been conducted in healthy male volunteers as well as 5 Phase 2 clinical studies in prostate cancer patients.

In these studies, teverelix TFA depot formulation has been tested following administration by single and multiple (2) SC injection(s) at doses of 10 mg, 30 mg, 60 mg, 120 mg or 180 mg. Teverelix produced a rapid, marked suppression of serum levels of LH, T and, to a lesser extent, FSH. The teverelix TFA-induced hormone suppression demonstrated in these studies was fully reversible within 1 week and exhibited no signs of a weight effect. Overall, teverelix TFA was safe and well tolerated.

Three Phase 2 studies in participants with BPH have been conducted as well. In participants with BPH, a statistically significant decrease was observed in prostatic symptoms as early as 2 weeks after administration of teverelix TFA. Symptomatic improvement increased over time and was most pronounced at study completion (after 16 weeks). A total of 76% of participants on teverelix TFA were classified as responders.

For participants with APC suppression of T below castration level, this was achieved within 3 days and was maintained for 4 to 8 weeks. Teverelix TFA was also shown to rapidly reduce and normalise PSA levels. In the Phase 1 and 2 studies a small number of study subjects (0.6 to1.5%) experienced transient elevated liver function enzymes. Standard monitoring of liver function enzymes is recommended for future clinical studies.

PK and PD data from 2 different studies indicate that the SC route of administration of teverelix TFA produces a more sustained suppression of T levels than the IM route. This appears to be due to the fact that the SC route is more effective at maintaining adequate systemic levels of teverelix TFA.

In this study, teverelix TFA is being tested in participants with APC with a loading dose regimen administered as 2 doses of 120 mg each, given IM and SC, followed by SC injections of 120 mg of teverelix TFA every 6 weeks thereafter, as the preferred treatment regimen. If this treatment schedule fails to induce castration levels of T (≤2 ng/mL), an

alternative treatment option will be tested: 180 mg each of teverelix TFA, given IM and SC, followed by SC injections of 180 mg of teverelix TFA every 6 weeks thereafter, for a total duration of 168 days. As this is a Phase 2 study to evaluate the dosage and effectiveness of teverelix TFA in the suppression and maintenance of serum T concentrations below castration levels, an open-label, non-controlled study design has been chosen.

4 Selection of Study Population

In this study, approximately 24 participants from Group 1, or 60 participants from Group 2 will be recruited from 7 up to study centres in Lithuania and potentially Netherlands and/or Belgium in order to provide a sample size of 20 participants from Group 1, or 50 participants from Group 2. These participants will comprise the per-protocol (PP) analysis set for evaluation of treatment response at Day 28 and throughout the study up to Day 168. As soon as this number of enrolled participants is reached, no more participants will be recruited. Enrolled participants who cannot be analysed in the PP analysis set will not be replaced. The participants for this study will be recruited from inpatient/outpatient departments of clinics/hospitals and/or general practitioners/specialists. If inpatients are included in the study, they will receive further treatment as inpatients.

4.1 Participant Inclusion Criteria

The participant is allowed to participate in the study if ALL of the following criteria are fulfilled:

1. Is male, aged ≤85 years (≥18 years) at the beginning of the treatment period (Day 0)
2. Has histologically proven advanced adenocarcinoma of the prostate (metastatic or non-metastatic hormone-sensitive non-curative), suitable for ADT
3. Is treatment naïve for any of the following:
    a. GnRH analogues
    b. Androgen receptor antagonists, or
    c. Androgen synthesis inhibitors (e.g. abiraterone)
4. Agrees to practice contraception during the entire study treatment period and for 3 months after the last dose of IMP is administered:
    a. Either by using double barrier contraception,
    b. or, is truly sexually abstinent, when this is in line with the preferred and usual lifestyle of the participant

    Note: *Periodic abstinence [e.g. calendar, ovulation, symptothermal, postovulation methods for the female partner with childbearing potential] and withdrawal are not acceptable methods of contraception.*
5. Has provided written (personally signed and dated) informed consent before completing any study-related procedure, which means any assessment or evaluation that would not have formed a part of his normal medical care

4.2 Participant Exclusion Criteria

If any of the following criteria apply, the participant MUST NOT be admitted to the study. The participant:

1. Has abnormal screening and/or baseline laboratory values that suggest a clinically significant underlying disease, or the following laboratory values:

a. Liver function test (aspartate aminotransferase [ASAT/SGOT], alanine aminotransferase [ALAT/SGPT]), or total bilirubin exceeding twice the upper limit of the normal (ULN) range
b. Creatinine twice the ULN range
c. Uncontrolled diabetes (HbA1c >7.5%) or previously undiagnosed diabetes mellitus with HbA1c >6.5%

2. Has any contraindication to the use of teverelix TFA
3. Has a life expectancy of less than 1 year
4. Has T levels <2.0 ng/mL at screening
5. Has a medical history of bilateral orchidectomy
6. Using any of the following prohibited treatments:
   a. Within 25 weeks prior to screening: dutasteride
   b. Within 12 weeks prior to screening: finasteride
   c. Current use of any of the following:
      i. Anti-androgen therapy, including T replacement therapy and 5α-reductase inhibitor treatment etc. (Spironolactone is a permitted concomitant treatment)
      ii. Any other medication or herbal product that may affect hormone levels and might, therefore, confound interpretation of the study results (e.g. St. John's wort)
7. Has neurological disease, psychiatric disease, drug or alcohol abuse, which could interfere with the participant's proper compliance
8. Has a history of myocardial infarction, unstable symptomatic ischaemic heart disease, any ongoing cardiac arrhythmias of grade >2 (chronic stable atrial fibrillation on stable anticoagulant therapy is allowed), thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or any other significant cardiac condition (e.g. pericardial effusion, restrictive cardiomyopathy) within 6 months before screening
9. Has congenital long QT syndrome or ECG abnormalities at screening of:
   a. Q-wave infarction, unless identified ≥6 months before screening
   b. Fridericia corrected QT interval (QTcF interval) >480 msec. If QTcF is prolonged in a participant with a pacemaker, the participant may be enrolled in the study upon discussion with the project clinician

- If the QTcF interval is 450-480 msec, inclusive, in a participant with current use of medications with known effects on QT interval, the participant may be enrolled in the study following discussion with the Medical Lead

Note: Cardiac arrhythmia grading:
- Bradyarrhythmias (HR <60/min)
- Tachyarrhythmias (HR >100/min)
- Supraventricular arrhythmias – arrhythmias that originate in the sinoatrial node, atrial myocardium or atrioventricular node (regular QRS complex)
- Ventricular arrhythmias – arrhythmias that originate below the atrioventricular node (wide QRS complex)

10. Has known or suspected severe renal impairment
11. Has a medical history of diagnosis of, or treatment for, another malignancy within 2 years before the first dose of IMP, or previous diagnosis of another malignancy with

evidence of residual disease. Participants with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection

12. Is currently using Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications
13. Has uncontrolled hypertension despite appropriate medical therapy (sitting BP of >180 millimetres of mercury [mmHg] systolic and >95 mmHg diastolic at 2 separate measurements taken no more than 60 minutes apart during the screening visit). Participants with isolated systolic BP measurements >180 mmHg may be rescreened. Participants with isolated systolic BP measurements 141 to 180 mmHg or isolated diastolic BP measurements ≥95 mmHg, although eligible, should be referred for further management of hypertension if indicated
14. Has known, previously diagnosed human immunodeficiency virus (HIV) infection, active chronic hepatitis B or C, life-threatening illness unrelated to prostate cancer, or any serious medical condition that could, in the investigator's opinion, potentially interfere with participation in this study. Specific screening for chronic viral illness is at the discretion of the site and/or local Institutional Review Board (IRB)
15. Has been exposed to another investigational drug within the 3 months prior to screening
16. Has anticipated non-availability for study visits/procedures
17. Plans to undergo surgery during the study period
18. Known presence of hepatic metastases

4.3 Participant Withdrawal Criteria

Premature study termination for an individual participant should be taken into consideration under the following circumstances:

- An illness/AE occurs during the study that influences the use, or the assessment of, the investigational medication
- He/she requires a forbidden concomitant medication (see Section 5.8.1)
- Adequate cooperation is not guaranteed

Decisions concerning study termination for individual participants will be made in accordance with the Medical Lead of the study and the Sponsor.

Premature study termination for an individual participant is mandatory under the following circumstances:

- Lack of efficacy and progressive disease (e.g. T levels >2 ng/mL)
- Lost to follow-up (the participant did not show up for the examination and the study personnel were unable to contact the participant)
- Death of the participant

The study must be terminated for an individual participant if the participant withdraws his/her consent or it is, in the investigator's opinion, necessary from a medical point of view (e.g. allergic reactions to the study medication).

If possible, a complete final examination, as planned for the visit that takes place on Day 168, should be carried out and documented on the corresponding pages of the electronic case report form (eCRF) for all participants who stop taking part in the study. If possible, the participant will also be asked to return to the site for a safety follow-up visit 28 days after the last administration of teverelix TFA.

Although participants may withdraw from the study at any time without giving any reasons, efforts should be made to find out the cause and document it.

For follow-up of participants' withdrawal because of an AE please see Section 6.3.7.3.

Participants who terminate the study prematurely will not be replaced.
For criteria concerning the termination of the whole study please refer to Section 7.3.2.

5 Study Treatments

The IMP to be tested in this study is teverelix TFA, which is administered on Day 0 as a loading dose, followed by a maintenance dose as per the schedule below.

5.1 Treatments Administered

Participants will receive different doses depending on whether they join Group 1 or Group 2. The study will enrol participants into Group 1 first.
On Day 0, participants will receive a single loading dose consisting of 2 injections, each of which will contain 120 mg of teverelix TFA (Group 1). The first injection will be administered as an IM injection and the second as an SC injection (Stage 1). After Stage 1, participants will receive a maintenance dose, which in Group 1 will consist of a single 120 mg SC injection administered every 42 days, and in Group 2, will consist of a single 180 mg SC injection administered every 42 days (see Table 1).
If treatment of Group 1 has been terminated early due to a low therapeutic response rate, recruitment into Group 2 will start.
The total treatment period will be up to 168 days (24 weeks) in the core study, or until treatment ceases to be effective (serum T >2 ng/mL).
Participants withdrawn early from the study will be asked to return to the study site 28 days after the last dosing for a safety follow-up visit.
Depending on the safety and efficacy of the study drug observed during the core study, participants who complete the core study and who maintain serum T levels (local laboratory) ≤2 ng/mL at the end of the core study (at the Day 168 visit) may be offered the opportunity to continue in an extension study, during which the maintenance treatment will be continued up to D336. The decision to extend the treatment period for eligible subjects will be made when 5 or more subjects have reached D28 with D21 local laboratory T levels ≤ 2 ng/mL.

5.2 Identity of Investigational Product(s)

Table 2 presents the details of the IMP.

Table 2: Investigational Medicinal Product Details

Active Ingredient	Teverelix TFA
Brand name	-
Dosage form	Powder presented in glass vials (powder weight is 250 mg net weight with 200 mg base weight)
Strength	120 mg (Group 1) and 180 mg (Group 2) injection
Frequency	Every 6 weeks (Groups 1 and 2)
Route of administration	Loading dose: IM injection followed by SC injection Maintenance dose: SC injections
Supplied by	Antev Ltd.

IM=intramuscular; IMP=investigational medicinal product; SC=subcutaneous

5.3 Method of Assigning Participants to Treatment Groups

All enrolled participants will be identifiable throughout the study. The investigator will maintain a personal list of participant numbers and participant names to enable records to be found at a later date.

Upon enrolment each participant receives a 5-digit screening number, which is sufficient for unambiguous identification:

Digits 1 and 2: Study centre (11, 12, 13, etc.)

Digits 3, 4 and 5: Individual participant number within the centre (consecutively in the order of enrolment within the centre: 001, 002, etc.)

Enrolled participants who drop out of the study before their baseline visit will retain their screening number.

On completion of the screening phase, the participant's eligibility will be confirmed. Eligible participants will receive treatment on Day 0. All participants will receive the same dose per treatment group (Group 1 or Group 2) of teverelix TFA as defined in Section 5.1. Medication will be dispensed in numerical order, starting with the smallest number available in the centre.

5.4 Selection of Doses in the Study

The goal of this study is the selection of an optimal treatment regime, which allows achievement of the highest level of efficacy with an acceptable safety profile and optimal convenience for patients and physicians. For this reason, 2 treatment regimens will be evaluated.

The treatment regimen for Group 1 comprises a dose of 120 mg administered SC and IM as a loading dose and SC as a maintenance dose every 6 weeks. For Group 2, the dose will be 180 mg administered SC and IM as a loading dose and SC as a maintenance dose every 6 weeks. The 180 mg dosage has been administered in 4 Phase 1 studies conducted in healthy male volunteers and 2 Phase 2 studies conducted in participants with APC. No severe or serious AEs were noted in these studies. The dosing regimen and treatment period will be according to the details described in Section 5.1.

5.5 Selection and Timing of Dose for Each Participant

Participants will receive different doses depending on whether they join Group 1 or Group 2. The study will enrol participants into Group 1 first.

On Day 0 participants will receive a single loading dose consisting of 2 injections, each of which will contain 120 mg of teverelix TFA (Group 1) or 180 mg (Group 2). The first injection will be administered as an IM injection and the other as an SC injection (Stage 1).

After Stage 1, participants in Group 1 will receive a maintenance dose, which will consist of a single 120 mg SC injection administered every 42 days.

If the serum T value (measured by the local laboratory) at the Day 35 visit is >2 ng/mL, the participant will be withdrawn from the study.

If 3 or more participants have a total T (local laboratory) value of >2 ng/mL at Day 21 or at any subsequent study visit, the dosing regimen will have failed to meet its 90% efficacy target and, if applicable, further enrolment into Group 1 will cease.

If treatment of Group 1 has been terminated early due to a low therapeutic response rate, recruitment of participants into Group 2 will start.

After Stage 1, participants in Group 2 will receive a maintenance dose, which will consist of a single 180 mg SC injection administered every 42 days.

If the serum T value (measured by the local laboratory) at the Day 21 visit is >2 ng/mL, the participant will be withdrawn from the study.

Participants will have their serum T measured by the local laboratory 1 week prior to each maintenance dose during Stage 2 of the study. If, at any point the local laboratory serum T result is >2 ng/mL the participant will be withdrawn from the study. Local laboratory serum T values ≤2 ng/mL allow the subjects to continue in the study.

Table 3 describes the decision-making process for doses participants will receive based on the results of the locally analysed T level from 7 days prior to the scheduled dosing visit.

Table 3: Decision-making in Relation to Serum Testosterone Levels

[T] (ng/mL)	Action Taken	Dose Administered
≤2	Continue in Stage 2	**Group 1:** Maintenance dose 120 mg SC teverelix TFA **Group 2:** Maintenance dose 180 mg SC teverelix TFA
>2	Withdrawal from study, safety follow-up visit	None

SC=subcutaneous; T=testosterone; TFA=Trifluoroacetate

Depending on the level of T prior to dosing, a decision will be made regarding whether to continue the participant in the study, request a re-test 7 days prior to the next scheduled dosing visit, or initiate early study withdrawal. If T levels are ≥2 ng/mL, the participant will be withdrawn from the study.

In the event that a participant of Group 1 will be continued during Stage 2, each dose will be administered according to Table 4: Testosterone Testing in Groups 1 and 2 every 6 weeks.

Table 4: Testosterone Testing in Groups 1 and 2

Local [T] Testing	Teverelix TFA Dose
DAY 21 [T]	DAY 28: No teverelix TFA dose
DAY 35 [T]	DAY 42: Maintenance dose 120 or 180 mg SC
DAY 77 [T]	DAY 84: Maintenance dose 120 or 180 mg SC
DAY 119 [T]	DAY 126: Maintenance dose 120 or 180 mg SC
DAY 161 [T]	DAY 168: Maintenance dose 120 or 180 mg SC
***DAY 203 [T]**	**No dose**
***DAY 210 [T]**	**No dose**
***DAY 217 [T]**	**No dose**
***DAY 224 [T]**	**No dose**
***DAY 231 [T]**	**No dose**
***DAY 238 [T]**	**No dose**
***DAY 245 [T]**	**No dose**
***DAY 252 [T]**	**No dose**

SC=subcutaneous; T=testosterone

*Group 2 subjects with Stage 3 only

5.6 Supply, Packaging and Labelling

5.6.1 Supply

The study medication teverelix TFA will be provided by the Sponsor. The IMP will be manufactured, packed, labelled, and released by a qualified person and distributed under the responsibility of the Sponsor in accordance with the principle of Good Manufacturing Practice (GMP) and the applicable local regulations.
Teverelix TFA is supplied as a white powder to be reconstituted with 5% mannitol (w/v) in water for injection.

5.6.2 Storage

The study medication teverelix TFA has to be stored at -20°C±5°C. The diluent, mannitol, shall be stored at +20°C±5°C.

5.6.3 Shipment

The IMP will be shipped according to local regulations. The responsible investigator/responsible study personnel at the study site will confirm correct receipt of the IMP in writing and ensure it is stored safely and correctly. The investigator will document the distribution date and the amount used on the forms provided for this purpose.

5.6.4 Packaging

The packaging will be performed by the Sponsor according to GMP and all local legal requirements.

5.6.5 Labelling

The labelling will be performed by the Sponsor according to GMP and all local legal requirements. The labels will be written in the local language.

5.7 Blinding and Randomisation

Not applicable as this is an open-label study with regards to the administration of IMP.

5.8 Prior and Concomitant Therapy

Any concomitant therapies and medications administered during the study have to be documented. This also includes any non-medicinal treatment and hormonal contraception. The following details must be given: nature of the disease (indication), date of diagnosis, name of medicine (including active ingredient[s]) or specification of measures, dosage, route of administration and the dates of the start and end of the treatment.

5.8.1 Prohibited Previous and Concomitant Treatments

In line with the inclusion and exclusion criteria, during the study the use of the following drugs is prohibited:

- Antiarrhythmic medications
  - Class IA (e.g. quinidine, procainamide)
  - Class III (e.g. amiodarone, sotalol)

- Anti-androgen therapy (e.g. T replacement therapy, and 5α-reductase inhibitor treatment etc.) (Spironolactone is a permitted concomitant treatment)
- GnRH analogue or antagonists
- Androgen receptor antagonist
- Androgen synthesis inhibitors (e.g. abiraterone)
- Any other medication (e.g. 5-alpha reductase inhibitors) or herbal product (e.g. St. John's wort) that may affect hormone levels and might, therefore, confound interpretation of study results
- Finasteride and dutasteride within 12 weeks and 25 weeks, respectively, prior to screening

5.8.2 Admissible Concomitant Treatments

All other medicines, as well as over-the-counter medicines, apart from those mentioned in the prohibited treatments are allowed provided they do not affect the primary endpoint or integrity of this study.
This applies also specifically to following treatment options for prostate cancer:

- Prostate surgery
- Radiation therapy (discuss with Antev medical monitor prior to inclusion)
- Chemotherapy
- Cryotherapy
- Immunotherapy

5.9 Treatment Compliance and Drug Accountability

The reconstitution of the IMP will be prepared by the investigator or by study personnel assigned by the investigator. The IMP will be administered by the investigator to the participants according to the study protocol.
The investigator will ensure that the provided IMP will only be used within the framework of this study and as directed by the study protocol.
IMP accountability must be documented at each site and will be checked by a study monitor. All used and unused IMP will be collected by the study monitor and returned to the Sponsor upon completion of the study. Receipt, distribution, and return of the IMP must be documented according to study-specific instructions provided separately.

5.10 Safety Monitoring for Allergic Reactions

To ensure subject safety, investigators must be able to diagnose and treat immediate hypersensitivity reactions, including anaphylaxis. Medication and equipment necessary to treat immediate hypersensitivity reactions, including anaphylaxis must be available at the study centre. Subjects will be observed during drug administration and for at least 30 minutes following the injection for fever, chills, or other administration-related reactions. Should an immediate hypersensitivity reaction associated with hypotension and/or syncope occur, appropriate supportive measures (e.g., leg elevation; oxygen administration; intravenous fluids; and, medications such as epinephrine, antihistamines and corticosteroids, alone or in combination) will be employed, in accordance with standard emergency procedures of the study centre.

5.11 Management of Drug Overdose

No consequences are to be expected in case of drug overdose.

6 Variables and Methods

6.1 Population Characteristics

6.1.1 Demography

The following demographic characteristics will be documented in the eCRF:

- Year of birth
- Age
- Weight and height
- Body mass index (BMI)

6.1.2 Medical History

General medical history findings in the past 5 years, considered relevant to the study by the investigator, will be documented in the eCRF together with the respective dates and periods (it should be indicated whether the condition is a past or an ongoing disease/illness at study entry). Relevant findings include, but may not be limited to, major surgeries, heart diseases, respiratory diseases, central nervous system and neurological diseases, psychiatric disorders, blood disorders, hepatorenal disorders, genitourinary disorders, and known allergies.

6.1.3 Prostate Cancer Diagnosis

Details of the underlying condition will be documented in the eCRF, including:

- Type of adenocarcinoma of the prostate
    - Metastatic
    - Non-metastatic
    - Hormone-sensitive
    - Non-curative
- Date of first diagnosis
- Presence of metastases (body region)
- Clinical signs and symptoms

6.1.3.1 Primary Tumor, Lymph Node and Metastasis Classification of Prostate Cancer

Table 5 presents the Primary Tumor, Lymph Node and Metastasis (TNM) classification of primary tumours.

Table 5: TNM Classification of Primary Tumours [13]

Clinical (cT)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histologic finding in ≤5% of tissue resected (at time of transurethral resection of the prostate [TURP])
T1b	Tumour incidental histologic finding in >5% of tissue resected (at time of TURP)
T1c	Tumour identified by needle biopsy (because of elevated PSA level)
T2	Tumour confined within prostate ***Note:*** *Tumours found in 1 or both lobes by needle biopsy but not palpable on digital rectal examination or reliably visible by imaging are classified as T1c)*
T2a	Tumour involves one-half of 1 lobe or less
T2b	Tumour involves more than one-half of 1 lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule ***Note:*** *invasion into the prostatic apex, or into—but not beyond—the prostatic capsule is classified as T2*
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invading seminal vesicle(s)
T4	Tumour fixed or invades adjacent structures other than seminal vesicles (e.g. bladder, levator muscles, and/or pelvic wall)

TNM= Primary Tumor, Lymph Node and Metastasis

Table 6 presents TNM classification of regional lymph nodes.

Table 6: TNM Classification of Regional Lymph Nodes (N) [13]

Clinical (cN)	
NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

TNM= Primary Tumor, Lymph Node and Metastasis

Table 7 presents TNM classification of distant metastasis.

Table 7: TNM Classification of Distant Metastasis (M)[a] [13]

Clinical (cM)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph nodes(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

TNM= Primary Tumor, Lymph Node and Metastasis
[a] If more than 1 site of metastasis is present, use the most advanced category

6.1.3.2 **Gleason Score**

The Gleason score is the grading system used to determine the aggressiveness of prostate cancer. Gleason grades range from 1 to 5 and describe how much of the cancer from a biopsy looks like healthy tissue (lower score) or abnormal tissue (higher score). Most cancers score a Grade 3 or higher [14].

Since prostate tumours are often made up of cancerous cells that have different grades, 2 grades are assigned for each participant. A primary grade is given to describe the cells that make up the largest area of the tumour and a secondary grade is given to describe the cells of the next largest area. These numerical values are added to calculate the Gleason score (see Table 8 and Figure 2).
For instance, if the Gleason score is written as 3 + 4 = 7, it means most of the tumour is Grade 3 and the next largest section of the tumour is Grade 4, together they make up the total Gleason score. If the cancer is almost entirely made up of cells with the same score, the grade for that area is counted twice to calculate the total Gleason score.

Typical Gleason scores range from 6–10 (Table 8) The higher the Gleason score, the more likely that the cancer will grow and spread quickly. Each specimen is assigned 2 grades based on the most common and second most common pattern.

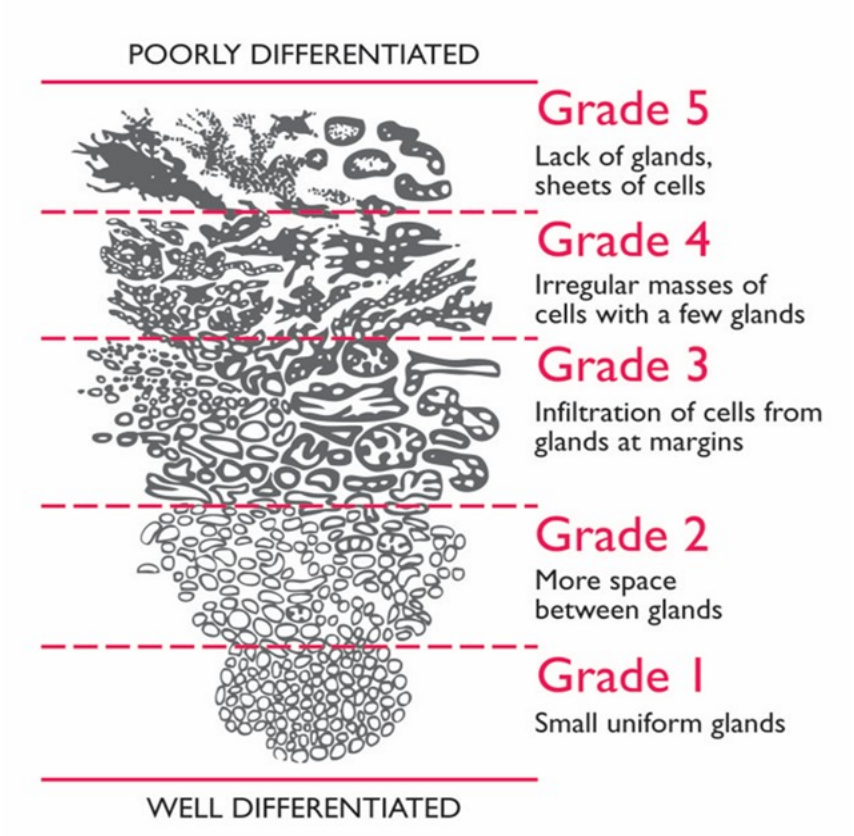


Figure 2: Gleason Score

Table 8: Gleason Scoring System

Grade Group	Gleason Score	Gleason Pattern(s)
1	≤6	≤3 + 3
2	7	3 + 4
3	7	4 + 3
4	8	4 + 4 (3 + 5/5 + 3)
5	9 or 10	4 + 5, 5 + 4, 5 + 5

6.2 Efficacy

6.2.1 Primary Efficacy Variable

The primary efficacy analysis is the evaluation of serum T concentration at Day 28.

6.2.2 Secondary Efficacy Variables

Secondary efficacy analyses include the evaluation of the following variables:

- T (Total)
- LH
- FSH
- PSA

All these variables will be assessed at the timepoints shown in Table 9.

Table 9: Timepoints for Efficacy Variables

Stage	Group	Timepoint	Variables				
			Local T	Central T	LH	FSH	PSA
Stage 1	1 and 2	Baseline (pre-dose)		•	•	•	•
		24 hours post-dose		•	•	•	
		48 hours post-dose		•	•	•	
		72 hours post-dose		•	•	•	
		Day 4		•	•	•	
		Day 7		•	•	•	•
		Day 14		•	•	•	•
		Day 21[a]	•	•	•	•	•
Stage 2	1 and 2	Day 28		•	•	•	•
		Day 35	•	•	•	•	•
		Day 42		•	•	•	•
		Day 77	•				
		Day 84		•	•	•	•
		Day 119	•				
		Day 126		•	•	•	•
		Day 161	•				
		Day 168		•	•	•	•
Stage 3	2 only	Day 203	•	•	•	•	•
		Day 210	•	•	•	•	•
		Day 217	•	•	•	•	•
		Day 224[b]	•	•	•	•	•
		Day 231[b]	•	•	•	•	•
		Day 238[b]	•	•	•	•	•
		Day 245[b]	•	•	•	•	•
		Day 252	•	•	•	•	•
		Follow up visit	•	•	•	•	•

FSH=follicle stimulating hormone; LH=luteinising hormone; PSA=prostate-specific antigen; T=testosterone

[a] If PSA is <0.06 ng/mL, hs PSA will be measured and reported. If PSA is ≥0.06 ng/mL then hs PSA will not be measured and reported.

[b]Weekly assessments from Day 203 until Day 252 or until serum T levels are ≥1 ng/mL (local lab result), whichever occurs first

6.3 Safety

6.3.1 Vital Signs

Vital signs parameters will be measured at screening, baseline (Day 0), and Day 28 for both Groups 1 and 2. During Stage 2 these assessments will be performed on the day of the maintenance dose. In both groups this will occur at Days 42, 84, 126, and168 and follow-up. These vital signs will be measured with the participant in sitting position for at least 5 minutes.

In the clinic, measurements of the vital signs described below will be made by a trained and authorised person:

- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- Heart rate (bpm)
- Respiratory rate (breaths per minute)
- Body temperature (°C)

The investigator will evaluate any worsening in vital signs for its clinical relevance as to whether it meets the definition of an AE (see Section 6.3.7). All changes in vital signs that meet the definition of an AE must be documented as an AE in the eCRF.

A manual or automated sphygmomanometer will be used to measure systolic and diastolic BP. BP results will be recorded in mmHg. Pulse rate will be measured in the radial artery for 60 seconds and will be recorded as beats per minute. If possible, BP and pulse rate should preferably be measured in the same arm at each visit.

Weight will be measured while the participant is clothed with shoes off and recorded in kilograms (kg).

Height will be measured in centimetres at the screening visit (Visit 1) only.

6.3.2 Physical Examination

A physical examination will be performed at the timepoints specified in Table 15, Error: Reference source not found, and Error: Reference source not found. Any abnormalities must be specified in the eCRF and, if observed after administration of teverelix TFA, the abnormality must also be documented as an AE (see Section 6.3.7).

The complete physical examination will consist of evaluation of general appearance, the skin, head, eyes (including size and reactivity of the pupils), ears, nose, throat, neck, thyroid, lungs, heart, lymph nodes, abdomen, and extremities (to include deep tendon reflexes, clonus, and muscle rigidity). Any abnormalities noted should be described.

6.3.3 Triplicate 12-Lead Electrocardiogram

At screening (Visit 1), 12-lead ECG recordings will be obtained in triplicate (within an approximate 2- to 5-minute window) with the participant in a supine position, suitably rested (for at least 5 minutes). At baseline (Visit 2), 12-lead ECGs will be performed in triplicate before administration of the first dose of the IMP; the results should be reviewed by **the cardiologist at the site delegated to review all study ECGs (ie the rater)** to confirm that the participant may be dosed (see Exclusion Criterion Number 8).

Subsequently, triplicate 12-lead ECGs (within an approximate 5-minute window) will be obtained at each dosing visit and at the follow-up visit.
All 12-lead ECGs, including those performed at screening, will be of at least 10-second duration.
The confirmation of the decision regarding the participant's eligibility for the study and all ECGs are to be based on local readings. For evaluation of participants with left bundle branch block, a cardiology consultation is strongly recommended.
At a minimum, interval data (QTcF), ventricular rate, and overall interpretation will be reported for each ECG.
The investigator will record on the eCRF whether the results are normal or abnormal (not clinically significant or clinically significant). If recorded as abnormal and clinically significant, the machine-read results and any clinical interpretations must be incorporated into the eCRF, and, if observed after administration of teverelix TFA, the abnormality must also be documented as an AE (see Section 6.3.7).

6.3.4 Continuous 12-lead Holter Electrocardiogram (Subset of 30 Group 2 subjects)

Continuous 12-lead Holter ECGs will be performed in a subset of 30 Group 2 subjects only (first 30 enrolled subjects with no more than 8 subjects at any one site). Continuous 12-lead Holter data will be obtained from subjects in accordance with time points detailed in the Schedule of Assessments (Table 16).

For analysis of the continuous 12-lead ECG data, triplicate 10 second 12-lead ECGs will be extracted at time points matching certain PK sampling times after at least 5 minutes rest in order to facilitate concentration-QTc effect modelling.

6.3.4 Injection Site Inspection

Each injection site will be visually inspected at each visit for local reactions such as pain, tenderness, erythema/redness and swelling. If the only reaction is induration, this should be indicated on the eCRF and reported as an AE. Any other local reactions will be graded according to the grades mentioned as specified in Table 10 [15] and reported as an AE. Upon complete resolution of an injection site reaction, injection site inspections of that injection site can cease.
During the first administration of the injection, an injection site inspection (ISI) will be performed to ensure that the injection site is free from blemishes, tattoos, or other marks that may make subsequent ISIs difficult. ISIs will also be performed at 30 minutes, 4, 12, and 24 hours post-dose. The ISI will be performed at 30 minutes post-dose for all other IMP administration. ISRs will be reported as AEs.

At maintenance dose visits ALL injection sites must be inspected unless an injection site reaction has fully resolved (including induration). For example, at Day 42 the following injection sites should be inspected: D0 SC; D0 IM; D42 SC. And at Day 84 the injection sites for D0 SC; D0 IM; D42 SC; D84 SC should be inspected. Only when an injection site reaction (including induration) has fully resolved can inspection of that injection site stop.

Table 10: Food and Drug Administration Local Toxicity Scale

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	ER visit or hospitalisation
Tenderness	Mild pain to touch	Pain with movement	Significant pain at rest	ER visit or hospitalisation
Erythema/Redness[a]	2.5–5 cm	5.1–10 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling[b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

ER=emergency room
[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[b] Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

6.3.4.1 Photographic Documentation of Injection Site

The investigator should photograph the injection site (abdomen or buttock, as applicable) at the time the injection is given. This is to provide a pre-reaction/baseline photograph in the event that a reaction does occur.

If a visible ISR (i.e. one that could be observed in a photograph) subsequently develops, a digital photograph of the injection site will be taken by the investigator. The picture must be uploaded into the eCRF. Prior to the photograph being taken, a label will be placed close to the injection site. This label will display a centimetre ruler and contain space for the entry of participant number, visit number, date of visit and time of photograph. The photograph must be taken with the camera at an angle 90 degrees perpendicular to the injection site wherever possible. The details regarding the instructions for taking the photograph will be documented in the photography manual.
ISRs at the abdominal site should be monitored and photographed at each study visit until complete absence/resolution. ISRs at the buttock site should be monitored and photographed at each study visit until Day 42 or until complete absence/resolution, whichever is later.

6.3.5 Safety Laboratory Variables

Fasted (≥8 hours) blood samples for haematology and biochemistry tests, as well as a urine sample for urinalysis, will be collected for safety monitoring at screening, baseline, Day 28, all dosing visits of Stage 2 and the follow-up visit. For safety analysis, a blood volume of approximately 8 mL will be drawn per timepoint. Full details of blood volumes drawn during

the study are documented in the Laboratory Manual. An overview of measured parameters is given in Table 11.

Table 11: Clinical Safety Laboratory Tests

Haematology:	Haemoglobin Erythrocytes Leucocytes Thrombocytes Neutrophils Eosinophils Basophils Lymphocytes Monocytes	**Biochemistry:**	Alkaline phosphatase ASAT ALAT ■-GT Creatinine Fasting glucose Fasting insulin Urea Total Bilirubin Total protein Sodium Potassium Total cholesterol LDL HDL VLDL Triglycerides HbA1c (screening visit only)
Urinalysis:	Leucocytes Erythrocytes Epithelial cells pH Protein Glucose Urobilinogen Ketones Bilirubin Nitrite Specific density		

ALAT=alanine aminotransferase; ASAT=aspartate aminotransferase; HDL=high-density lipoprotein; LDL=low-density lipoprotein; VLDL=very low-density lipoprotein; ■-GT=gamma-glutamyl transpeptidase

6.3.6 Additional Safety Assessments

It will be left to the investigators' discretion to perform safety assessments in addition to those outlined above. Unless useful for specific purposes (e.g. individual SAEs), the data from these additional safety assessments will not form part of the database of the present study.

6.3.7 Adverse Events

All AEs, including intercurrent illnesses or pathological changes in laboratory values, must be reported and documented in detail including the time of start and end of onset and the outcome. The measures taken will be documented in the eCRF as well as intensity, relationship to study medication and seriousness of the AE.

6.3.7.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a participant or clinical investigation participant who is administered a pharmaceutical product. This untoward medical occurrence does not necessarily have a causal relationship with the administered treatment. An AE can, therefore, be defined as any unfavourable and unintended sign (including abnormal laboratory findings), symptom, or disease that is temporally associated with the use of a medicinal (investigational) product, whether or not related to that medicinal (investigational) product. If, during treatment with an investigational product, pathological laboratory values occur which were not present before the treatment started, further clinical or laboratory tests must be

carried out until the values return to the normal range or until a plausible explanation is found (e.g. concomitant disease) for the change in the laboratory values.
Symptoms or clinically significant laboratory or instrumental (e.g. electrocardiographic) abnormalities of a pre-existing condition, such as cancer or other diseases, should not be considered an AE. However, occurrence of new symptoms, laboratory, or instrumental abnormalities, as well as worsening of pre-existing ones, are considered AEs.

Laboratory values outside the normal laboratory-specific reference range, which make an intervention necessary and/or are considered clinically significant by the investigator must be reported as AEs. If the abnormal laboratory value is a sign of a disease, only this diagnosis should be reported as an AE.

An AE is considered to be an adverse drug reaction (ADR) if a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

6.3.7.2 Assessment of Adverse Events

The investigator will identify the occurrence of pre-dose events and/or AEs through non-leading questioning and examination of the participant.

For each AE, the investigator will document the following:

- **Signs and symptoms** of the event (if a specific disease can be diagnosed, this disease should be the reported AE; if only signs and symptoms can be evaluated, each sign or symptom should be reported as a separate AE)
- **Onset date and time** (if a change from pre-dose in a laboratory test is reported as an AE, the start date is the date of collection of the first laboratory sample that shows the change)
- **End date and time** (if a change from pre-dose in a laboratory test is reported as an AE, the end date is the date of collection of the first laboratory sample that shows a return to pre-dose level)
- **Measure taken** (none, drug treatment required, hospitalisation or prolonged hospitalisation, study discontinuation, other measures [specification])
- **Outcome** (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown)

In addition, each AE will be rated by the investigator according to the following categories (the Sponsor has to carry out a separate assessment for causal relationship, seriousness, and expectedness):

Relationship to Study Medication

If the AE is a deterioration in the study disease and, therefore, indicates a lack of efficacy of the study medication, the causality assessment "no relationship" will be made, as the impairment of health is not caused by a intolerability of the study medication. "Deterioration of study disease" is to be given as the cause of the AE.
Assessments of relationship to study medication will be made by the investigator first.
For the evaluation of the relationship between AEs and IMP the following definitions will be used:

Related This category applies to those AEs which the investigator feels are incontrovertibly related to the IMP. The relationship between the IMP and an AE is considered definite if the AE:

- follows a reasonable temporal sequence after administration of the IMP or after achieving effective levels in body fluids and tissues, respectively
- is already known as side effect in relation to the IMP
- disappears or decreases on cessation of the IMP
- recurs with re-exposure to the IMP

Probable This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty by the investigator to be related to the IMP. The relationship between the IMP and an AE is considered probable if the AE:

- follows a reasonable temporal sequence after administration of the IMP
- has already been described as a side effect of the IMP
- disappears or decreases on cessation of the IMP
- cannot be reasonably explained by the participant's clinical state

Possible This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the IMP appears improbable but cannot be ruled out with certainty. The relationship between the IMP and an AE is considered possible if the AE:

- follows a reasonable temporal sequence after administration of the IMP
- has already been described as an AE in connection with the IMP
- could also be reasonably explained by a number of other causes

Unlikely In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged with a high degree of certainty to be unrelated to the IMP. The relationship between the IMP and an AE is considered unlikely if the AE:

- does not follow a reasonable temporal sequence after administration of the IMP
- could also be reasonably explained by a number of other causes
- does not follow a known pattern of response to the IMP

Not related This category applies to those AEs which, after careful consideration, are clearly and incontrovertibly due to causes other than the IMP (intercurrent disease, worsening of study indication/lack of efficacy, concomitant disease, concomitant therapy, other).

Intensity

Regardless of the classification of an AE as serious or non-serious (see below), its intensity must be assessed according to medical criteria alone using the Common Terminology Criteria for Adverse Events (CTCAE) classification (v5.0):

Grade 1 (mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 (moderate): minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g. preparing meals, shopping, using the telephone, managing money, etc.)

Grade 3 (severe):	severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living (e.g. bathing, dressing, undressing feeding self, using toilet, taking medications, and not bedridden, etc.)
Grade 4 (life-threatening):	life-threatening consequences; urgent intervention indicated
Grade 5 (death):	death related to AE (death is reported as an outcome of an AE)

It should be noted that a severe AE does not necessarily have to be serious in nature and that a serious AE need not be severe.

Seriousness
An SAE is an untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires in-participant hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly or birth defect

or

- is an important medical event that does not have to be immediately life-threatening or result in death or hospitalisation, but which may jeopardise the participant or may require medical intervention to prevent 1 of the outcomes listed above.

All SAEs must be reported immediately (within 1 working day) to the drug safety department at IntuVigilance Limited, by the investigator.

All AEs that do not fall into any of the above categories are defined as non-serious.

Expectedness
At the drug safety department at IntuVigilance Limited an additional rating for expectedness of AEs will be given:

Expected:	The event is judged expected if its description agrees in nature, severity, frequency, and specificity with the description of events in the Investigator's Brochure.
Unexpected:	SAEs which do not fall into the expected category are assessed to be unexpected.

A suspected unexpected serious adverse drug reaction (SUSAR) is defined as an untoward and unintended response to an IMP, which is not listed in the applicable product information, and meets 1 of the above-mentioned serious criteria. The drug safety department at IntuVigilance Limited, acting on behalf of the Sponsor, will ensure that all SUSARs associated with the IMP will be reported to the applicable regulatory authority/competent authorities and the relevant independent ethics committees(IECs)/IRBs in accordance with the applicable national/local regulations (usually within 7 calendar days for life-threatening and fatal SUSARs or within 15 calendar days for all other SUSARs). The drug safety department at IntuVigilance Limited will also promptly notify all investigators about any SUSAR.

6.3.7.3 Follow-up of Adverse Events

Regardless of the duration of the study, each AE must be followed-up until it subsides or until the cause is known or an adequate final assessment can be given. The maximum follow-up period will be 6 weeks after the participant's study termination. If after 6 weeks no final outcome can be acquired, the outcome of the AE is 'unresolved'.

6.3.7.4 Documentation and Reporting of Adverse Events

Any AE has to be documented in the eCRF with the specifications made in Section 6.3.7.2.
All SAEs must be reported immediately (within 1 working day) to the drug safety manager or the responsible person and/or the clinical research associate (CRA) by the investigator (see Responsibilities).
All SAEs must be reported by the investigator immediately (within 24 hours) to the drug safety department at IntuVigilance Limited via the eCRF (see below).
A specific SAE form for immediate reporting will be provided to the investigators as part of the eCRF. In case of a SAE, this form should be completed and checked immediately within the eCRF. These data entries will be used to automatically create the corresponding SAE reporting form. Furthermore, any other requested data (like concomitant medications) already present in the eCRF will be used to populate the respective fields of the SAE reporting form.
A trigger mechanism implemented in the eCRF will ensure that the form will be sent automatically via email to the drug safety department at IntuVigilance Limited within 24 hours.

Note: *Any changes in fields being part of these reports will create a new (follow-up) report, which will also be sent automatically.*

If due to any reason the electronic completion and forwarding of the SAE reporting form via the eCRF is not possible, the investigator may fill out the pre-printed Sponsor SAE reporting form manually and send the required information via scanned email to both parties mentioned above (see Responsibilities for contact details).
Follow-up reports will be provided by the investigator each time new information on the SAE becomes available (until the case is solved or the participant has recovered). For reporting of follow-up information, a similar procedure as for reporting of initial SAEs will apply.
Notification to the regulatory authorities, the IECs, and the investigator sites about all SUSARs will be performed by and to the investigator sites and/or by the investigator (as applicable) according to all applicable national/local regulations.

6.4 Pharmacokinetics

6.4.1 Pharmacokinetic Variables

Pharmacokinetic parameters will be generated using Phoenix WinNonlin Version 6.4 or higher for evaluation.
The concentrations of all participants who successfully complete the study will be analysed and samples of withdrawn or dropout participants will not be analysed. This analysis may include the parameters shown in Table 12. Full details will be presented in the statistical analysis plan (SAP).

Table 12: Pharmacokinetic Parameters

PK Parameter	Description	Unit
AUC_{0-t}	Area under the concentration-time-curve from time zero up to the last measurable concentration at timepoint t	ng•h/ mL
AUC_{0-t1}	Area under the concentration-time-curve from time zero up to concentration at timepoint t1 after which the concentrations start to rise again towards a second peak, t1 will be determined after review of the concentration-time profiles (immediate release component of total observed AUC)	ng•h/ mL

PK Parameter	Description	Unit
AUC_{t1-t}	Area under the concentration-time-curve from timepoint t1 up to timepoint t (slow release component of total observed AUC)	ng•h/ mL
$AUC_{0-\infty}$	Area under the concentration-time-curve from time zero up to infinity (∞)	ng•h/ mL
C_{max}	Maximum plasma concentration	ng/mL
$C_{max,0-t1}$	Maximum plasma concentration after administration from zero up to timepoint t1	ng/mL
$C_{max,t1-t}$	Maximum plasma concentration after administration from timepoint t1 up to timepoint t	ng/mL
T_{max}	Time to reach C_{max} after dosing	h
$T_{max,0-t1}$	Time to reach $C_{max,0-t1}$ after dosing	h
$T_{max,t1-t}$	Time to reach $C_{max,t1-t}$ after dosing	h
λz	Apparent terminal rate constant	1/h
$t_{½}$	Apparent terminal plasma half-life	h

h=hours; PK=pharmacokinetic

6.4.2 **Blood Sampling Time Points, Handling and Labelling of Blood Samples**

Blood samples for PK evaluation will be collected by venepuncture (or by using an indwelling catheter). A blood volume of 5 mL will be drawn per timepoint.
Blood is drawn for PK analysis according to the schedule below, where timepoints are relative to IM injection of teverelix TFA at time zero, and the pre-dose PK sample is collected within 30 minutes prior to IM injection (Table 13).
Handling and labelling of blood samples for PK analysis will be performed according to the instructions provided by the central analytical laboratory. Special tubes, labels, packaging, and instructions for storage and shipment will also be provided by the analytical laboratory.
Blood samples should be shipped for analysis on the day of collection.
Blood teverelix TFA concentrations will be determined from all collected samples using a validated sensitive analytical procedure (e.g. inductively coupled plasma mass spectrometry) at a specialised central analytical laboratory.
After completion of all analyses, any leftover blood or blood samples will be destroyed immediately after termination of the study.

Stability data supports the storage of teverelix PK samples:

- In a freezer set at nominally -20°C for up to 376 days
- In a freezer set at nominally -80°C for up to 60 days

Table 13: Pharmacokinetic Timepoints

Timepoint	Pre-dose	1 h	1.5 h	2 h	2.5 h	3 h	4 h	8 h	12 h	18 h	24 h[a]	48 h	72 h
Window	±0 day	±15 min	±15 min	±15 min	±15 min	±15 min	±15 min	±15 min	±15 min	±15 min	±15 min	±1 hour	±1 hour
	•	•	•	•	•	•	•	•	•	•	•	•	•

Timepoint	Day 4[b]	Day 7[b]	Day 10[b]	Day 12[b]	Day 14[b]	Day 21[b]	Day 28[c]	Day 35	Thereafter at each dosing visit and follow up visits[d]
Window	±0 day	±0 day	±1 day	±1 day	±1 day	±1 day	±3 days	±3 days	±3 days
	•	•	•	•	•	•	•	•	•

PK=pharmacokinetic
[a] Participants will remain in the clinic as in-participants until after the 24-hour PK blood sample has been drawn after which time they will be discharged.
[b] From Day 4 onwards, when a PK sample is to be drawn on a non-dosing day, the PK sample should be drawn at the same time of day as the Day 0 pre-dose PK sample was drawn (+ 1 hour).
[c] Before dosing (up to 30 minutes pre-dose). Dosing should be done at the same time of day throughout the study (or at least + 1 hour of this timepoint).
[d]Including Day 203 to Final Assessment visits for Group 2 subjects

6.5 Pharmacodynamics

The following parameters will be investigated:

- T
- LH
- FSH
- PSA

Table 14 presents the PD blood sampling schedule for the study.

Table 14: Pharmacodynamic Blood Sampling Schedule[a]

	Day 0 (pre-dose)	24h	48h	72h	Day 4	Day 7	Day 10	Day 12	Day 14	Day 21[b]	Day 28	Day 35[c]	Thereafter 7 days prior to each dosing visit	Thereafter at each dosing visit and follow up visits[d]
T (local)										•		•	•	
T (central)	•	•	•	•	•	•	•	•	•	•	•	•		•
LH	•	•	•	•	•	•	•	•	•	•	•	•		•
FSH	•	•	•	•	•	•	•	•	•	•	•	•		•
PSA	•					•			•	•	•	•		•

FSH=follicle stimulating hormone; hs=high-sensitivity; LH=luteinising hormone; PD=pharmacodynamic; PK=pharmacokinetic; PSA=prostate-specific antigen; T=testosterone

[a] PD blood draws should be done at the same time of day as PK blood draws (pre-dose on Day 0)

[b] If PSA is <0.06 ng/mL hs PSA will be measured and reported. If PSA is ≥0.06 ng/mL then hs PSA will not be measured and reported.

[c] Group 1 only

[d] Including Day 203 to Final Assessment Visit for Group 2 subjects

7 Study Conduct

7.1 Study Schedule

Table 15 presents the study schedule for Groups 1 and 2.

Table 15: Schedule of Assessments for Groups 1 and 2

Visit/ Procedure	Screening	Treatment Period Groups 1 & 2																			Follow-up	Unsched. Visit
		Stage 1										Stage 2										
Days/ Weeks		Day 0	Day 1	Day 2	Day 3	Day 4	Day 7	Day 10	Day 12	Day 14	Day 21	Day 28	Day 35	Day 42	Day 77	Day 84	Day 119	Day 126	Day 161	Day 168	28 days after last dose	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	
Window	D-6 To -1	±0 D	±0 D	±0 D	±0 D	±0 D	±0 D	±1 D	±1 D	±1 D	±1 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	
Informed Consent	•																					
Inclusion and Exclusion Criteria	•	•																				
Medical History	•																					
Physical Exam.	•	•										•		•		•		•		•	•	•
12-Lead ECG[1]	•	•										•		•		•		•		•	•	•
Holter ECG (Group 2 only)		•	•																			
Safety Labs[1]	•	•										•		•		•		•		•	•	•
Vital Signs	•	•										•		•		•		•		•	•	•
Demography[2]	•	•										•		•		•		•		•	•	•

[1] Safety laboratory tests are detailed in Section 6.3.5.

[2] Demographic details include height, weight, year of birth and age; During baseline and other visits including follow up (28 days after last dose) height, weight and BMI only will be measured.

Visit/ Procedure	Screening	Treatment Period Groups 1 & 2																			Follow-up	Unsched. Visit
		Stage 1										Stage 2										
Days/ Weeks		Day 0	Day 1	Day 2	Day 3	Day 4	Day 7	Day 10	Day 12	Day 14	Day 21	Day 28	Day 35	Day 42	Day 77	Day 84	Day 119	Day 126	Day 161	Day 168	28 days after last dose	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	
Window	D-6 To -1	±0 D	±0 D	±0 D	±0 D	±0 D	±0 D	±1 D	±1 D	±1 D	±1 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	
Injection of teverelix TFA IM[3]		•																				
Injection of teverelix TFA SC		•												•		•		•		•		
Blood draw for pre-dosing local lab T testing	•										•		•		•		•		•			

[3] IM injection and SC injection of teverelix TFA will be given immediately sequentially (within 10 minutes of each other); IM first; all PK time points detailed relative to the IM injection time. Participants to be monitored for hypersensitivity reaction for 30 minutes following SC injection.

Visit/ Procedure	Screening	Treatment Period Groups 1 & 2																		Follow-up	Unsched. Visit
		Stage 1										Stage 2									
Days/ Weeks		Day 0	Day 1	Day 2	Day 3	Day 4	Day 7	Day 10	Day 12	Day 14	Day 21	Day 28	Day 35	Day 42	Day 77	Day 84	Day 119	Day 126	Day 161	Day 168	28 days after last dose
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21
Window	D-6 To -1	±0 D	±0 D	±0 D	±0 D	±0 D	±0 D	±1 D	±1 D	±1 D	±1 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D
PK/PD Blood Draw[4]		•[5]	•[6]	•[7]	•[8]	•[9]															•

[4] On Day of dosing visit, blood samples for PK/PD analysis will be collected before the administration of the Maintenance Dose.

Visit/ Procedure	Screening	Treatment Period Groups 1 & 2																			Follow-up	Unsched. Visit
		Stage 1										Stage 2										
Days/ Weeks		Day 0	Day 1	Day 2	Day 3	Day 4	Day 7	Day 10	Day 12	Day 14	Day 21	Day 28	Day 35	Day 42	Day 77	Day 84	Day 119	Day 126	Day 161	Day 168	28 days after last dose	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	
Window	D-6 To -1	±0 D	±0 D	±0 D	±0 D	±0 D	±0 D	±1 D	±1 D	±1 D	±1 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	
PSA/hs PSA[10]		•					•			•	•	•	•	•		•		•		•	•	
Cardiac biomarkers		•										•		•		•		•		•	•	
Injection Site Inspection		•	•	•	•	•	•	•	•	•	•	•		•		•		•		•	•	
Injection Site Photograph[k]		•	•	•	•	•	•	•	•	•	•	•		•		•		•		•	•	
Prior and current Concomitant Medications	•	•	•	•	•	•	•	•	•	•	•	•		•		•		•		•	•	•

[5] Post-dose PK blood sampling on Day 0 is scheduled at the following time points: at 1, 1.5, 2, 2.5, 3, 4, 8, 12, 18 hours.

[6] Post-dose PK blood sampling at 24 hours. At the time point of 24 hours post-dose sampling for PD analysis (T, LH, FSH) will be initiated.

[7] Post-dose PK blood sampling at 48 hours.

[8] 72 hour PK profile: PD testing blood draw to be done at same time of day as the Day 0 pre-dose PK blood draw.

[9] PK and PD testing blood draw to be done at same time of day as pre-dose PK blood draw.

[10] If PSA is <0.06 ng/mL hs PSA will be measured and reported. If PSA is ≥0.06 ng/mL then hs PSA will not be measured and reported.

[k] If a visible injection site reaction is present, two photographs should be taken and the better photograph uploaded to the eCRF

[l] ECGs to be done in triplicate at each visit

Visit/ Procedure	Screening	Treatment Period Groups 1 & 2																			Follow-up	Unsched. Visit
		Stage 1										Stage 2										
Days/ Weeks		Day 0	Day 1	Day 2	Day 3	Day 4	Day 7	Day 10	Day 12	Day 14	Day 21	Day 28	Day 35	Day 42	Day 77	Day 84	Day 119	Day 126	Day 161	Day 168	28 days after last dose	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	
Window	D-6 To -1	±0 D	±0 D	±0 D	±0 D	±0 D	±0 D	±1 D	±1 D	±1 D	±1 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•		•		•		•		•	•	•

BMI=body mass index; D=days; ECG=electrocardiogram; hs=high-sensitivity; IM=intramuscular; PD=pharmacodynamic; PK=pharmacokinetic; PSA=prostate-specific antigen; SC=subcutaneous; T=testosterone

Table 17: Schedule of Assessments for Group 2 (subjects with Stage 3 included)

Visit/ Procedure	Screening	Treatment Period Group 2 (with Stage 3 only)																					Unsched. Visit
		Stage 1										Stage 2									Stage 3		
Days/ Weeks		Day 0	Day 1	Day 2	Day 3	Day 4	Day 7	Day 10	Day 12	Day 14	Day 21	Day 28	Day 35	Day 42	Day 77	Day 84	Day 119	Day 126	Day 161	Day 168	Day 203	Follow up Visit	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21 *	FA	
Window	D-6 To -1	±0 D	±0 D	±0 D	±0 D	±0 D	±0 D	±1 D	±1 D	±1 D	±1 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	
Informed Consent	•																						
Inclusion and Exclusion Criteria	•	•																					
Medical History	•																						
Physical Exam.	•	•										•		•		•		•		•		•	•
12-Lead ECG[l]	•	•										•		•		•		•		•		•	•
Holter ECG (Group 2 only)		•	•																				
Safety Labs[11]	•	•										•		•		•		•		•		•	•
Vital Signs	•	•										•		•		•		•		•		•	•

[11] Safety laboratory tests are detailed in Section 6.3.5.

[?] Demographic details include height, weight, year of birth and age; During baseline and other visits including follow up (28 days after last dose) height, weight and BMI only will be measured.
*Subjects should attend on Day 203 and every 7 days until serum T levels are >1 ng/mL (local lab result). A final assessment visit should be conducted 7 days after serum T levels are >1 ng/mL (local lab result).

Visit/ Procedure	Screening	Treatment Period Group 2 (with Stage 3 only)																				Unsched. Visit
		Stage 1										Stage 2									Stage 3		
Days/ Weeks		Day 0	Day 1	Day 2	Day 3	Day 4	Day 7	Day 10	Day 12	Day 14	Day 21	Day 28	Day 35	Day 42	Day 77	Day 84	Day 119	Day 126	Day 161	Day 168	Day 203	Follow up Visit	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21 *	FA	
Window	D-6 To -1	±0 D	±0 D	±0 D	±0 D	±0 D	±0 D	±1 D	±1 D	±1 D	±1 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	
Demography[12]	•	•										•		•		•		•		•		•	•
Injection of teverelix TFA IM[13]		•																					
Injection of teverelix TFA SC		•												•		•		•		•			
Blood draw for pre-dosing local lab T testing	•										•		•		•		•		•		•		

[12] Demographic details include height, weight, year of birth and age; During baseline and other visits including follow up (28 days after last dose) height, weight and BMI only will be measured.
*Subjects should attend on Day 203 and every 7 days until Day 252 or until serum T levels are >1 ng/mL (local lab result). A final assessment visit should be conducted on Day 259 or 7 days after serum T levels are >1 ng/mL (local lab result), Whichever occurs first.
[13] IM injection and SC injection of teverelix TFA will be given immediately sequentially (within 10 minutes of each other); IM first; all PK time points detailed relative to the IM injection time. Participants to be monitored for hypersensitivity reaction for 30 minutes following SC injection.

Visit/ Procedure	Screening	Treatment Period Group 2 (with Stage 3 only)																				Unsched. Visit
		Stage 1										Stage 2									Stage 3		
Days/ Weeks		Day 0	Day 1	Day 2	Day 3	Day 4	Day 7	Day 10	Day 12	Day 14	Day 21	Day 28	Day 35	Day 42	Day 77	Day 84	Day 119	Day 126	Day 161	Day 168	Day 203	Follow up Visit	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21 *	FA	
Window	D-6 To -1	±0 D	±0 D	±0 D	±0 D	±0 D	±0 D	±1 D	±1 D	±1 D	±1 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	
PK/PD Blood Draw[14]		•[15]	•[16]	•[17]	•[18]	•[19]	•	•	•	•	•	•	•	•		•		•		•	•	•	

[14] On Day of dosing visit, blood samples for PK/PD analysis will be collected before the administration of the Maintenance Dose.

[15] Post-dose PK blood sampling on Day 0 is scheduled at the following time points: at 1, 1.5, 2, 2.5, 3, 4, 8, 12, 18 hours.

[16] Post-dose PK blood sampling at 24 hours. At the time point of 24 hours post-dose sampling for PD analysis (T, LH, FSH) will be initiated.

Visit/ Procedure	Screening	Treatment Period Group 2 (with Stage 3 only)																					Unsched. Visit
		Stage 1										Stage 2									Stage 3		
Days/ Weeks		Day 0	Day 1	Day 2	Day 3	Day 4	Day 7	Day 10	Day 12	Day 14	Day 21	Day 28	Day 35	Day 42	Day 77	Day 84	Day 119	Day 126	Day 161	Day 168	Day 203	Follow up Visit	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21 *	FA	
Window	D-6 To -1	±0 D	±0 D	±0 D	±0 D	±0 D	±0 D	±1 D	±1 D	±1 D	±1 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	
PSA/hs PSA[20]		•					•			•	•	•	•	•		•		•		•	•	•	
Cardiac biomarkers		•										•		•		•		•		•		•	
Injection Site Inspection		•	•	•	•	•	•	•	•	•	•	•		•		•		•		•		•	
Injection Site Photograph[k]		•	•	•	•	•	•	•	•	•	•	•		•		•		•		•		•	
Prior and current Concomitant Medications	•	•	•	•	•	•	•	•	•	•	•	•		•		•		•		•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•		•		•		•		•	•	•	•

[17] Post-dose PK blood sampling at 48 hours.

[18] 72 hour PK profile: PD testing blood draw to be done at same time of day as the Day 0 pre-dose PK blood draw.

[19] PK and PD testing blood draw to be done at same time of day as pre-dose PK blood draw.

[20] If PSA is <0.06 ng/mL hs PSA will be measured and reported. If PSA is ≥0.06 ng/mL then hs PSA will not be measured and reported.

[11] If a visible injection site reaction is present, two photographs should be taken and the better photograph uploaded to the eCRF

[12] ECGs to be done in triplicate at each visit

7.2 Observations by Visit

7.2.1 Screening Examination (Day -6 to Day -1)

At the screening examination the following will be carried out and/or documented:

- Participant signs ICF as a part of the written participant information including the agreement concerning protection of personal data and direct access to source documents
- Date of visit
- Demographic data (height, weight, year of birth, age)
- Diagnosis of study indication (specify duration, severity as requested)
- Relevant medical history for the past 5 years
- Pre-treatment during the past 6 months
- Concomitant disease(s) (including date of diagnoses), concomitant therapy(ies)
- Physical examination (see Section 6.3.2)
- 12-Lead ECG (see Section 6.3.3)
- Safety laboratory tests (fasted ≥ 8 hours)
- Total T (local laboratory)
- HbA1c
- Vital signs
- Check of inclusion and exclusion criteria

Concomitant diseases are to be documented, taking into consideration the medical history of the participant for the past 5 years. Findings that are not medically relevant for the study are: operation scars, accident scars, and bad sight etc.

7.2.2 Baseline Examination (Day 0), Stage 1

At baseline examination the following will be carried out and/or documented:

- Date of visit
- Weight, and BMI
- Documentation of changes in concomitant diseases and/or concomitant therapies (also medication taken only once and any non-prescription medicine)
- AEs (for definition see Section 6.2.4)
- Check of inclusion and exclusion criteria
- Physical examination
- 12-Lead ECG
- Continuous 24 h, 12-lead Holter ECG (Subset of 30 Group 2 subjects only)
- Safety laboratory tests (fasted (≥8 hours))
- Vital signs
- Pre-dose blood sampling for PK, PSA and PD analysis
- Pre-dose blood sampling for cardiac biomarkers (Group 2 only)
- Administration of the loading dose of teverelix TFA, which consists of IM followed by SC injection
- ISI
- Post-dose PK blood sampling

Additional Visits for Pharmacokinetic and Pharmacodynamic Samplings during Stage 1:

- During Stage 1, the participant will return to the study site for additional PK and PD blood sampling at 24, 48 and 72 hours post-dose, and on Days 4, 7, 10, 12, 14, and 21
- On Day 21 local testing of T levels will be performed
- On Days , 7, 14, and 21, blood sampling for PSA will be performed

7.2.3 Treatment (Maintenance Dose) Period Visits (Day 28 to Day 168), Stage 2

At the treatment period visits, the following examinations will be carried out and/or documented:

- Date of visit
- Date and time of day when the medication was administered
- Documentation of changes in concomitant diseases and/or concomitant therapies (also medication taken only once and any non-prescription medicine)
- AEs (for definition see Section 6.3.7)
- Physical examination
- 12-Lead ECG
- Safety laboratory tests (fasted (≥8 hours))
- Vital signs
- Blood sampling for PK, PSA, and PD analysis (before administration of teverelix TFA) (see Table 15 and Error: Reference source not found)
- Pre-dose blood sampling for cardiac biomarkers (Group 2 only)
- ISI
- Administration of the maintenance dose of teverelix TFA, which consists of an SC injection

7.2.4 Follow-up Visit (28 Days after Last Dose)(Group 1 and Group 2 subjects without Stage 3)

At the final visit, the following examinations will be carried out and/or documented:

- Date of visit
- Documentation of changes in concomitant diseases and/or concomitant therapies (also medication taken only once and any medicine taken without a prescription)
- AEs
- Physical examination
- 12-Lead ECG
- Safety laboratory tests (fasted (≥8 hours))
- Blood sampling for PK, PSA, and PD
- Blood sampling for cardiac biomarkers (Group 2 only)
- ISI
- Vital signs
- Demography (only weight)
- Final assessment by investigator and participant

7.2.5 Follow-up Visits (starting 35 days after Last Dose)(Group 2 with Stage 3 subjects only)

Five weeks after the Day 168 maintenance dose injections (Day 203), subjects will attend the clinic and the following procedures will be done:

- Date of visit
- Documentation of changes in concomitant diseases and/or concomitant therapies (also medication taken only once and any medicine taken without a prescription)
- AEs
- Blood sampling for PK, PSA, and PD (local AND central lab serum T levels)

Subjects will continue to attend the clinic every 7 days where the above procedures will be done. Weekly visits will continue until Day 252 or until serum T levels (local lab result) are ≥ 1 ng/mL (local lab result) when the subject will attend the clinic 7 days later and the following procedures will be done:

- Date of visit
- Documentation of changes in concomitant diseases and/or concomitant therapies (also medication taken only once and any medicine taken without a prescription)
- AEs
- Physical examination
- 12-Lead ECG
- Safety laboratory tests (fasted (≥8 hours))
- Blood sampling for PK, PSA, and PD
- Blood sampling for cardiac biomarkers (Group 2 only)
- ISI
- Vital signs
- Demography (only weight)
- Final assessment by investigator and participant

7.3 Duration of the Study

The study will be terminated when all participants have completed the planned investigation period.

7.3.1 Planned Duration for the Individual Participant

For the individual participants, the core study lasts for a maximum of 184 days. The study duration might be shorter for individual participants in the event that the treatment ceases to be effective.

7.3.2 Premature Termination

Study

At any time, the study as a whole will be terminated prematurely by the Sponsor if:

- New toxicological or pharmacological findings or SAEs invalidate the earlier positive benefit–risk assessment
- The development of the study IMP is discontinued, a market authorisation is no longer intended, or the study proves not to meet the expected goal

- Other important reasons, not named above, call for the premature termination of the study

Centre
At any time, an individual centre participating in the study can be excluded from participation by a joint decision between Insuvia UAB, QRCC and the Sponsor if the centre fails to:

- Comply with the requirements of the protocol
- Comply with GCP standards
- Recruit the first participant within a reasonable period

Participant
Individual participants are to be withdrawn from the study according to the criteria specified in Section 4.3.

8 Statistics

8.1 Statistical and Analytical Plans

All statistical analyses will be outlined in detail in a SAP which will be prepared and signed prior to any study-specific analyses. In general, all continuous measures will be summarised descriptively, including number of available values, minimum, Quartiles 1 and 3, median, mean, standard deviation (SD), maximum, and 95% confidence interval (CI) for the mean if appropriate. Categorical data will be presented by frequency and percentage. Ordinal ratings may be handled as continuous data if appropriate. The analysis will be done in 2 stages. Stage 1 will include the analysis of the primary objective: the effect of the loading dose on achievement of castration levels by Day 28 (primary endpoint analysis). Stage 2 will include all other analyses (full analysis).

8.1.1 Analysis Populations

All participants who have received least 1 dose of study medication will be included in the safety analysis (safety population). The efficacy analysis will be performed on an "intention-to-treat (ITT)" basis and a "PP" basis (see definitions below). Participants with major protocol violations will be excluded from the latter. For this purpose, protocol violations that could interfere with the objectives of the study, incorrect concomitant medications or violation of the inclusion/exclusion criteria etc. will be assessed as 'minor' or 'major' in collaboration with the Sponsor. The criteria for this assessment will be defined before analysis. Listings will be prepared to show the eligibility of all participants. These listings will be presented in a Data Review Meeting.

Definition of Analysis Populations:

Population	Description
Screening population	All participants who signed the ICF
Safety population	All participants who received any dose of the IMP
Intention-to-treat (ITT) analysis set	All participants included in the safety population for whom the primary endpoint is evaluable
Per protocol (PP) analysis set	All participants included in the ITT analysis set who complete the study without major protocol violation

The primary analysis will be performed on the PP analysis set. In addition, a sensitivity analysis will be performed using the ITT analysis set. All efficacy assessments on the PP analysis set will be repeated for the ITT analysis set.

8.1.2 Adaptive Study Design

In this study the decision of whether or not the treatment regimen for Group 2 will be tested is based on the treatment effect observed in Group 1 on Day 28. If serum T levels at Day 28 are <0.5 ng/mL, the participant is classified as a treatment responder. Participants with serum

T levels at Day 28 of >2 ng/mL will be classified as non-responders. The target group treatment response is 90%.
Enrolment will continue for Group 1 until 20 participants have completed the Day 28 visit with no more than 2 participants being classified as a treatment failure. Treatment failure is defined by a serum T concentration >2 ng/mL at Day 28 or requiring to be withdrawn at any later timepoint during the study.
If 3 or more participants in Group 1 fail treatment then further enrolment into that group will stop due to statistical confidence that a 90% responder rate cannot be achieved with that dosing regimen. All future participants will be enrolled into Group 2.
If in Group 2 at Day 28, a participant's serum T value (as tested by the local laboratory) is >2 ng/mL, the participant will be withdrawn from the study.
If 7 or more participants fail in Group 2 then all further enrolment will be stopped and the study will be terminated.
The planned Group 1 treatment continuation analysis will be described in greater detail in the SAP.

8.1.3 Primary Efficacy Analysis

Primary Endpoint

The primary endpoint of the study is the proportion of participants achieving castration level with serum T <0.5 ng/mL or 1.73 nmol/L at Day 28.
The primary parameter analysis will be performed on the PP analysis set. In addition, a sensitivity analysis will be performed on the ITT analysis set.

8.1.4 Secondary Endpoint Analyses

Secondary Endpoints

1. Proportion of participants achieving castration level with serum T <0.2 ng/mL at Day 28
2. Proportion of participants achieving castration level with serum T <0.5 ng/mL at Day 42
3. Proportion of participants achieving castration level with serum T <0.2 ng/mL at Day 42
4. Proportion of participants achieving a T castration rate over 168 days of treatment period
   Note: *Castration rate is defined as the observed percentage of participants who have T concentrations <0.5 ng/mL (1.73 nmol/L) at all scheduled visits.*
5. Proportion of participants achieving profound castration rate (<0.2 ng/mL) over 168 days of treatment period
6. Mean time to T levels falling below castration level (<0.5 ng/mL [1.73 nmol/L]) for the first time
7. Mean time to (first) overstep of T castration level after achieving castration
8. Mean time for serum T levels to be ≥ 0.5 ng/mL after final, Day 168 injection
9. Proportion of participants achieving castration level for LH (LH <1.1 U/L) at Day 28
10. Proportion of participants with effective LH castration rate over 168 days of treatment period
11. Mean time to LH levels falling below castration level (LH <1.1 U/L) for the first time
12. Mean time to (first) overstep of LH castration level after achieving castration
13. Changes from baseline in PD and PK parameters over time

14. Number of participants with a PSA response of ≥50% reduction at the Day 168 visit
15. Number of participants with PSA response of ≥80% reduction at the Day 168 visit
16. Percent change from baseline in serum PSA concentration at each visit
17. Mean serum PSA concentration at each visit
18. Mean serum LH concentration at each visit
19. Mean serum T concentration at each visit
20. Mean serum FSH concentration at each visit

The secondary efficacy parameters will be analysed in an exploratory manner using descriptive statistics.
Secondary efficacy variables will be summarised by number of available values, minimum, Quartiles 1 and 3e, median, mean, SD, maximum, and 95% CI for the mean if appropriate. Categorical data will be presented by frequency and percentage.
These parameters are according to the secondary endpoints:

- Percentage of participants who have T concentrations <0.2 ng/mL at the end of Stage 1 (Day 28)
- Percentage of participants who have T concentrations <0.5 ng/mL and < 0.2 ng/mL at all scheduled visits
- Percentage of participants who have LH concentrations <1.1 U/L at all scheduled visits
- Time to T levels falling below castration level (<0.5 ng/mL) for the first time
- Time to first T concentration ≥0.5 ng/mL after castration has been achieved
- Time to LH levels falling below castration level (<1.1 U/L) for the first time
- Time to first LH concentration ≥1.1 U/L after castration has been achieved
- PD (LH, FSH, PSA, T) and PK (teverelix TFA concentrations) parameters over time (see Sections 6.4 and 6.5) and their changes from baseline
- Serum PSA concentration at each visit including absolute and relative change from baseline
- Number of participants with a PSA response of ≥50% reduction at the Day 168 visit compared to baseline
- Number of participants with a PSA response of ≥90% reduction at the Day 168 visit compared to baseline
- Serum LH concentration at each visit
- Serum FSH concentration at each visit

PK/PD parameters will be analysed by measuring actual times for each concentration. Descriptive statistics will be based on the scheduled times. The participants' concentration-time curves will be presented graphically per parameter.
Further details regarding PK/PD analyses, including scale transformations, parameter formulas and determination of terminal rate will be detailed in the SAP.

8.1.5 Analysis of Safety Data

Safety Endpoints

1. Number of participants with treatment-emergent AEs (defined as any AE occurring or worsening following treatment), summarised by system organ class (SOC) and preferred term (PT)

Note: *Occurrence of ISRs will be included.*

2. Mean changes in vital signs, triplicate 12-lead ECGs and laboratory data parameters at each visit during the 168-day treatment period, compared to baseline
3. Continuous 24 hour 12-lead Holter ECG (subset of 30 Group 2 subjects only)
4. Percentage of participants with ISRs at each visit during the 168-day treatment period

   Note: *Photography of injections sites with visible injection site reactions will be performed at each visit, and ISRs will be scored based on a specific scoring matrix*

The treatment-emergent AEs (defined as any AE occurring or worsening with the same date or later than that of the first application of study treatment) will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) available at the study start date. This version will be used throughout the entire study. Updates to MedDRA will not be applied afterwards. Frequency tables for the preferred terms will be compiled based on participants experiencing an AE and on the number of AEs. These frequency tables will take the SOC into consideration.
All reported AEs will be listed and ISRs will be summarised.
The vital sign, triplicate 12-lead ECG, and laboratory data parameters will be presented using descriptive statistics and shift-tables with respect to normal ranges for each visit including changes from baseline.
Concomitant diseases and medical history will also be coded using MedDRA. These data will be presented using frequency tables by SOC and PT.
Previous medication and concomitant medication will be coded using the Anatomical Therapeutic Chemical Classification (ATC) dictionary. Frequency tables will be compiled based on the coding for the medication.

8.1.6 **Missing Data**

Missing efficacy data will not be replaced in general.
If a laboratory reports concentrations as unquantifiable (too low), the value will be set to 0.
Values for samples that are not technically evaluable will be set to missing.
In case a start date for an AE is missing or incomplete, so that it is not possible to evaluate if it has occurred pre- or post-treatment, this AE will be classified conservatively as treatment-emergent. More information on missing data imputation will be described in the SAP.

8.1.7 **Multicentre Study**

This study will be performed as a multicentre study. Count and proportion of participants achieving castration level within the first 28 days, and participants maintaining castration over the 168-day treatment period will be stratified by site. No other risks are expected.

8.1.8 **Participant Data Listings**

All recorded data will be presented in-participant data listings.

8.1.9 **Deviations from the Planned Statistical Analysis**

Any deviations from the planned statistical analysis have to be discussed in the final study report and should be defined in the SAP.
Any deviations from the original SAP should be described and justified in the final study report.

8.1.10 **Interim Analysis**

After completion of Stage 1, i.e. after all participants have completed the visit at Day 28 and their T concentration levels are available, an analysis of the primary efficacy parameter will be performed analysing the number and proportion of participants reaching castration level by Day 28 with the loading dose of teverelix TFA.
The study will proceed during the analysis and all other efficacy, safety and demographic parameters will be evaluated at the end of the study (full analysis, Stage 2).

8.1.11 **Software used for Statistical Analysis**

The SAS® software version 9.2 (SAS® Institute) or higher will be used for the statistical analysis and for the reporting of this study. PK/PD analyses will be performed with Phoenix® WinNonlin® Version 6.3 or higher (Certara L.P).

8.1.12 **Determination of Sample Size**

Initially, since no confirmatory analyses were planned, no sample size calculations were performed. A total of 24 participants was deemed sufficient for 1 treatment group to obtain at least 20 evaluable participants (Day 168 visit completed).

Subsequently the Sponsor undertook a formal sample size calculation so that the Group 2 data could be used to support the dose selection for future Phase 3 clinical trials.

A sample size of 60 has been chosen on clinical grounds. This number gives good power to detect a minimum proportion of 90% subjects achieving castration with central lab serum T <0.5 ng/mL or 1.73 nmol/L at Day 28 from the per protocol population. It is based on the null hypothesis that the true response rate is 74.5%, the average response rate in previous Teverelix trials not achieving 90% response rate. This is tested using a two-sided test with a 5% alpha level against the alternative hypothesis that the response rate is 90%, the minimally clinically relevant response rate. Based on this, fifty participants give power of 80%. Assuming a dropout rate of 16%, sixty patients are recommended.
Sixty patients will ensure acceptable precision for justification for further analysis of this regimen in Phase 3. A true 90% response rate in this instance would give a confidence interval of (79,96) and if 10 subjects drop out, and interval of (78,97). A true 95% response rate with 60 participants would give a confidence interval of (86,99) and if 10 subjects drop out, an interval of (85,99).

8.2 **Data Management**

Data management will be performed using Oracle Clinical Version 3.3 or later running on 2 Microsoft Windows NT servers. Details will be defined in the data management manual, which will be signed by the Sponsor and the Clinical Research Organisation (CRO) prior to start of the data entry.

9 Data Handling and Data Quality Assurance

9.1 Data Management

Data will be captured using the eCRF provided by the designated CRO. The eCRF is specifically designed to meet the data recording requirements of the clinical study protocol. Only the investigator and his/her authorised staff who are trained appropriately on the eCRF system are allowed to fill in the eCRFs or to make corrections, and will have access to the data or may change data (however this access will be granted without the possibility to delete the original entries). After completion, each eCRF will be electronically signed and dated by the investigator. Central laboratory test results will be imported automatically into the eCRF. The overall procedures for quality assurance of clinical study data are described in the respective standard operating procedures (SOPs) of the CRO. A document describing the functional specification will be prepared by the CRO in cooperation with the eCRF provider and will be approved by the Sponsor prior to the start of the study. This functional specification will describe in detail the structure and functionality of the eCRF. In addition, the CRO will prepare a data management plan to describe the procedures and processes of data collection and data coding.
Electronic validation of the data entered in the eCRFs will take place (e.g. check of ranges, consistency, and plausibility). All plausibility checks will be defined in the data validation plan to be approved by the Sponsor. Additionally, the eCRFs will be reviewed by qualified data management and medically qualified personnel for completeness, consistency, and plausibility. Any data anomalies will be communicated to the site(s) for clarification/resolution (data query). Procedures of data entry and correction will be tracked and appropriately documented in the audit trail of the eCRF.

9.2 Documentation

9.2.1 Pre-screening List and Participant Identification List

A screening log will be kept by the investigator, listing all participants screened for this study. Participants will be identified by initials and year of birth. The status of the participant, i.e. whether enrolled in this study or not, will be entered on the log.
All participants who have given informed consent to participate in the study – regardless of whether the participant has received any investigational product(s) or not – have to be entered on the participant identification list by the investigator, giving full name, initials, year of birth, and participant identification code. The participant identification list will be kept in the investigator's file.

9.2.2 Source Data and Participant Records

In this study, all collected data in the participant file are considered source data. All data reported in the eCRF must be supported by appropriately signed identified source documents.

9.2.3 Electronic Case Report Form

An appropriate eCRF in English will be developed by the CRO. An eCRF completion manual for the use of the electronic data capture system will be provided prior to the study start, and

investigators will be trained on how to enter all study-specific data into the eCRF.
Investigators must enter the information required by the protocol into the eCRF and should complete the eCRF as soon as possible, but on the 3rd working day after a participant visit at the latest (or in case of on-site assessment results: within 3 working days after the on-site assessment). No questions must be left unanswered.

Note: *All SAEs must be reported by the investigator immediately (within 24 hours) via the SAE form in the eCRF (see Section 6.3.7.4).*

Monitors will review the eCRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The eCRFs are saved immediately after entering the data by the investigator. All eCRF data are stored in a central database at the eCRF provider while the study is ongoing and at the responsible CRO for final analysis after study completion.
After study completion, the study site will receive a CD/DVD with a compilation of the eCRF study data per site (electronic PDF files) for filing with its study documents. The Sponsor will receive electronic, bookmarked PDF files of individual eCRFs (including audit trail). The Sponsor will also receive a list of queries and SAE forms after database closure.

9.3 Direct Access to Source Data/Documents

Checking of eCRFs for completeness and clarity, and cross-checking with source documents will be required to monitor the progress of the study. The CRAs are entitled to compare eCRF entries with source data and to inform the investigator about errors and omissions. The investigator will provide direct access to source data/documents for the Sponsors designated representatives (CRAs and auditors) as well as IRB/IEC members and regulatory inspections. Regulatory authorities and/or the Sponsor's Clinical Quality Assurance Group may also carry out such source data checks and/or on-site audit inspections. They will be carried out giving due consideration to data protection and medical confidentiality. The investigator is to give the CRO and the Sponsor whatever support is necessary.

9.4 Monitoring

Monitoring will be done in accordance with the stipulations of Chapter 5.18 of the ICH GCP Guideline by Insuvia UAB CRAs.
During the course of the study, a CRA will make site visits to review protocol compliance, compare eCRFs and individual participants' medical records, assess drug accounting, and ensure that the study is being conducted according to pertinent regulatory requirements and the protocol. eCRF entries will be verified against source documentation in accordance with the applicable SOPs of the Sponsor/CRO. CRAs of the CRO will maintain confidentiality of the personal data of participants.
The investigator will allow the study monitor to make regular visits during the course of the study to:

- Verify that written informed consent was obtained prior to each participant’s participation in the study
- Discuss any emergent problem
- Check the eCRFs for completeness and plausibility
- Review accountability, correct storage, and handling of the IMP
- Ensure that the study is being conducted according to pertinent regulatory requirements, ICH GCP E6(R2), and the protocol

A close-out visit will be performed upon the conclusion of the study site's participation in the study.
The Sponsor reserves the right to order special examinations of laboratory samples if there is any doubt concerning the validity of individual participant data or the accuracy of data generation at an investigational site.

9.5 Quality Assurance

Risk-based quality management will be implemented in this study based on the requirements of the Integrated Addendum of the Good Clinical Practice guideline ICH E6(R2). Aspects of risk-based quality management will be detailed in a risk management plan.
A member of the Sponsor's (or designated CRO's) quality assurance unit may conduct an audit at the study site to ensure compliance with the protocol, GCP, and the applicable regulatory requirements.
In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator or his/her designee should notify the Sponsor immediately of any such inspection.
The investigator is expected to cooperate with such inspections and to discuss any findings with the auditor. The observations and findings of the auditor will be documented and the investigator will be informed of the audit outcome.

10 Ethical, Legal and Administrative Aspects

The study will be carried out in conformity with the ethical principles enunciated in the Declaration of Helsinki. The current valid version according to applicable national regulatory and legal requirements will be considered.
The study will also be carried out in accordance with the Integrated Addendum of the ICH Guideline on Good Clinical Practice E6(R2), the Regulation EU No. 536/2014, which will replace the EU Clinical Trial Directive 2001/20/EC, the Commission Directive 2005/28/EC (April 8, 2005), and all local laws, regulatory requirements, and guidelines applicable in the participating countries.
By signing the Investigator's Declaration, the investigator agrees to conduct the study as set out in this protocol and in accordance with the moral, ethical and scientific principles governing clinical research.
Signatures of Sponsor and CRO representatives can be found on the Signature Page.

10.1 Approval Procedures

Before the start of the study, the study protocol and/or other relevant documents will be approved by the appropriate Ethics Committee.
The relevant authorities, in accordance with local legal requirements will be notified/asked for approval of the intended study.

10.2 Protocol Amendments

After initiation of the study, any change in this protocol will require a formal amendment. The amendment must be signed by all of the signatories to the original protocol. Once the study has started, amendments will be made only in exceptional cases.
If ethically relevant aspects are concerned, the Ethics Committee(s) will be informed of amendments and approval will be sought.
All protocol amendments will be submitted to the regulatory authorities as regulated by national law.
Changes to the protocol may only be implemented after all appropriate requirements listed above (ethics, regulatory approval of all responsible personnel) have been fulfilled.

10.3 Informed Consent

Before participants can be admitted to the study, their informed consent will be obtained according to the regulatory and legal requirements. To this end, the investigator or an authorised designate will explain the nature, purpose, significance, and scope of the study, including its potential risks, to the participant. In addition to this oral information, the participant will receive for his/her own records the written participant information sheet summarising the relevant information. Sufficient time will be allowed to discuss any questions raised. Consent for participation can only be given after this information has been provided. The consent form must be personally signed and dated by the participant giving consent, and it must be retained by the investigator as part of the study records. A copy of the signed ICF will be handed out to the participant.
The investigator will not undertake any investigation required for the clinical study until informed consent has been obtained. The terms of the consent and the date when it was obtained should also be entered into the eCRF.

After releasing an amendment to the protocol, the contents of which might influence the participant's decision for participation, the participant information sheet and the ICF must be amended accordingly. They must be submitted to the relevant Ethics Committee and the relevant authority as requested by local law. In addition, any relevant new information on the study medication that becomes available during the study will be passed on to the investigators and the participants. Depending on the nature of the amendment it might be necessary that participants already enrolled must confirm their informed consent on the basis of the new information.

10.4 Confidentiality and Data Protection

All relevant provisions of the European General Data Protection Regulation (GDPR [EU] 2016/679, 27 April 2016) and all local legal requirements regarding protection of personal data will be adhered to.

The anonymity of study participants will be maintained. Participants' names will not be supplied to the Sponsor or designated CRO. Participants will be identified on all eCRFs, image media (CDs or DVDs) and other documents by a specific participant identification (screening) number.

Documents which identify the participant (e.g. the signed informed consent) must be maintained in confidence by the investigator. The Sponsor, CRO, central laboratory, and off-site readers will only be given pseudonymised data, samples, or images.

The participants will be informed about all media used in this study for documentation, storing, and transferring the participants' study findings and will be assured that all data will be handled in the strictest confidence.

This study protocol, any other unpublished documentation (e.g. eCRF), any information provided to the investigator regarding the IMP (e.g. investigator's brochure), and any results derived from the study will be regarded as confidential. The investigators and members of their research teams will not be allowed to disclose such information without prior written approval from the Sponsor.

10.5 Liability, Insurance and Finances

The Sponsor has taken out appropriate 3rd-party liability insurance cover in accordance with all local legal requirements in the respective country in which the study is performed. It covers the eventuality that personal injury may be caused by using the IMP or by any study-specific procedure carried out according to this protocol.

The general insurance conditions will be kept in the investigator's file and will be made available for participants at any time.

The financial agreements for each site (e.g. clinical study agreement) are addressed in 1 or more documents. The parties must sign the agreement before each site is initiated. All the investigators, and other relevant site staff participating in this study must complete a financial disclosure form.

10.6 Clinical Study Report, Publication and Use of Study Findings

An integrated study report according to the standards of the ICH E3 guideline, covering clinical and biometrical aspects, will be prepared by the Sponsor or its designee within 1 year of the end of the study (last protocol-defined contact with any enrolled participant). The report will be reviewed and approved by the coordinating investigator.

A publication policy will be prospectively defined before the start of the study. Any results derived from this study may be published in a scientific journal or presented at a scientific meeting with the Sponsor's consent. The Sponsor will be provided with a copy of the manuscript for review and approval prior to any such submission.
The Sponsor will make the results of this study publicly available on the internet at www.clinicaltrials.gov and in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database. Upon completion of the study and when the study results are available, the participant has the right to be informed by the investigator about the overall study results.

10.7 Archiving of Study Records

Essential documents as listed in ICH GCP E6(R2), Chapter 8, shall be archived safely and securely in such a way that they are readily available upon authorities' request.
Copies of the protocol, participant information sheet/ICF, participant identification list, printout of eCRF (or a CD with the eCRF), the participant record with all original data and all other documents pertaining to this study will be retained for a minimum of 25 years after the completion and approval of the integrated study report or for a period that is in accordance with national regulatory requirements, whichever is longest.
The Sponsor will inform the investigator when the prescribed period for archiving study documents has elapsed and the investigator no longer needs to retain the records relating to the study. The investigator site file is not to be destroyed without the Sponsor's approval.
The final integrated study report must be retained by the Sponsor for 5 years beyond the lifetime of the IMP.

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