Compound: Teverelix Trifluoroacetate (Teverelix TFA)
Protocol Number: ANT-1111-02
Study Phase: Phase 2

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.: 2020-00543-31

Statistical Analysis Plan

Version: 1.0

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Abbreviations

ADR	Adverse Drug Reaction
ALAT	Alanine aminotransferase
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
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
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
ECG	Electrocardiogram(s)
eCRF	Electronic case report form
EudraCT	European Union Drug Regulatory Authorities Clinical Trials
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase (γ-GT)
GMP	Good Manufacturing Practise
GnRH	Gonadotropin-releasing hormone
h	Hours
HbA1c	glycated haemoglobin
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HLGT	High level group term
HLT	High level term
hs PSA	High sensitivity prostate-specific antigen
hsTn	High sensitivity troponin
ICF	Informed consent form
IM	Intramuscular(ly)
IMP	Investigational medicinal product
IRB	Institutional Review Board
ISI	Injection site inspection
ISR	Injection site reaction(s)
ITT	Intention-to-treat

L	Litre
LDL	Low-density lipoprotein
LH	Luteinising hormone
LLT	Lowest level term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mg	Milligram
mL	Millilitre
mmHg	Millimetre of mercury
msec	Millisecond
NCI	National Cancer Institute
ng	Nanogram
nmol	Nanomole
NT proBNP	B-Type natriuretic peptide
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per protocol
PSA	Prostate-specific antigen
PT	Preferred term
QTcF	Fridericia corrected QT interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous(ly)
SD	Standard deviation
SI	Système International
SOC	System organ class
T	Testosterone
$t_{½}$	Apparent terminal plasma half-life
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
TFA	Trifluoroacetate
t_{last}	Time of the last quantifiable concentration
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 Tumour, Lymph Node and Metastasis
TURP	Transurethral Resection of The Prostate
U	Unit
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein
lambdaz	Apparent terminal rate constant (λ_z)

Table of Contents

1. Introduction

This statistical analysis plan (SAP) is based on protocol ANT-1111-02 Version 5.0 dated 31 May 2022. The SAP contains a complete and detailed specification of the statistical analyses.

1.1 Rationale

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

Since the advent of prostate-specific antigen (PSA) screening, prostate cancer is being detected and treated earlier.

Hormone therapy has evolved from the use of oestrogens to gonadotropin-releasing hormone (GnRH) agonists and recently, investigational GnRH antagonists. 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 characterized 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 testosterone surge, since there is no initial stimulation of the pituitary gland by the medication.

GnRH antagonists are analogues of GnRH, and act as a competitive inhibitor of GnRH. GnRH mediates stimulation of gonadotropin (i.e., follicle-stimulating hormone [FSH] and luteinising hormone [LH]) secretion). 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.

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.

In previous studies, 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. Following attainment of castration with a relatively high dose of teverelix TFA, maintenance of castration can be achieved with a much lower dose of teverelix TFA. This is a class effect and is also observed with cetrorelix, degarelix, relugolix and other GnRH antagonists.

No safety concerns were identified in any of the conducted clinical studies. The most frequently reported adverse events (AE) were mild Injection Site Reactions (ISR) 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.

2. Summary of the Protocol

2.1 Study Objectives

2.1.1 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.

2.1.2 Secondary Objectives

The secondary efficacy objectives of the study comprise the following:

- 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) across treatment period from Day 28 until 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) across treatment period from Day 28 until 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 1.73 nmol/L) following the final, Day 168 injection of teverelix TFA.
- To delineate the pharmacokinetics (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)

The safety objectives of the study comprise the following:

- To assess the safety of teverelix TFA in terms of
  - Local tolerability (injection site reaction [ISRs])
  - Systemic tolerability (AEs, vital signs, electrocardiograms (ECG), Holter monitoring (subset of 30 subjects in group 2 only) and laboratory parameters)

All PK parameters will be described with details in a separate SAP.

2.2 Study Design

2.2.1 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 advanced prostate 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

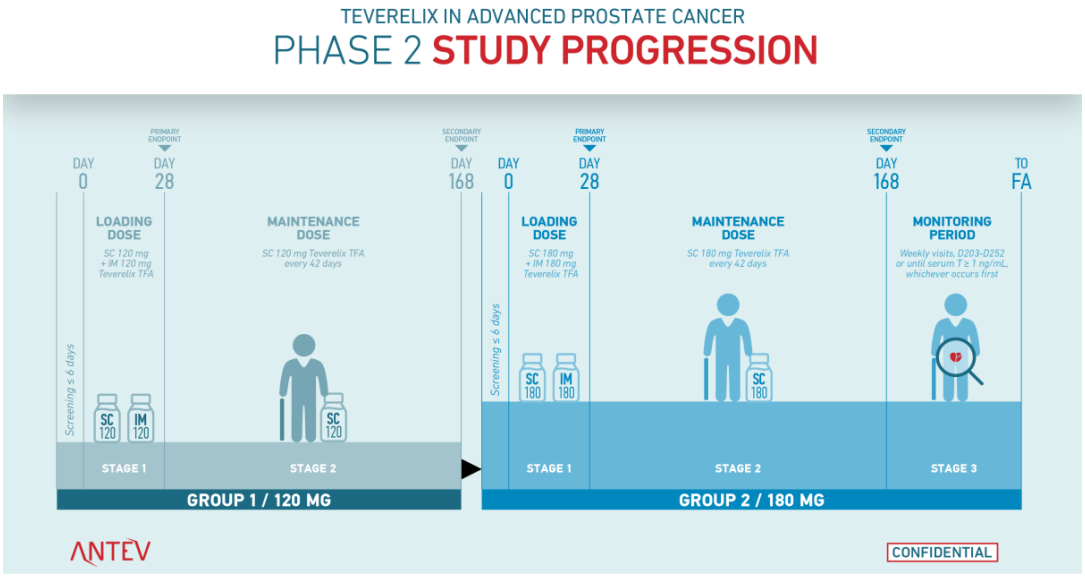
Stage 3: Follow up period. Day 203 visit followed by weekly visit until Day 252 or until serum T levels are ≥ 1 ng/mL (local lab result), whichever occurs first

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 **Error! Reference source not found.**. 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 two 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.

Table 2 presents the testosterone testing schedule in Groups 1 and 2.

Table 2 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.

2.2.2 Treatment and Visit Labels

Error! Reference source not found. presents the treatment group labels that will be used in all outputs.

Table 3 Study Treatments

Actual Treatment	Treatment Label
120 mg SC	120 mg SC
120 mg IM	120 mg IM
180 mg SC	180 mg SC
180 mg IM	180 mg IM

IM=intramuscular; SC=subcutaneous

Table 4 presents the visit labels that will be used in all outputs.

Table 4 Study Visits

Stage	Group	Visit	Visit Label
Screening	1 and 2	V1 – Screening (D -6 to -1)	Screening
1	1 and 2	V2 – Day 0 (± 0)	Baseline
1	1 and 2	V3 – Day 1 (± 0)	Day 1
1	1 and 2	V4 – Day 2 (± 0)	Day 2

Stage	Group	Visit	Visit Label
1	1 and 2	V5 – Day 3 (± 0)	Day 3
1	1 and 2	V6 – Day 4 (± 0)	Day 4
1	1 and 2	V7 – Day 7 (± 0)	Day 7
1	1 and 2	V8 – Day 10 (± 1)	Day 10
1	1 and 2	V9 – Day 12 (± 1)	Day 12
1	1 and 2	V10 – Day 14 (± 1)	Day 14
1	1 and 2	V11 – Day 21 (± 1)	Day 21
2	1 and 2	V12 – Day 28 (± 3)	Day 28
2	1 and 2	V13 – Day 35 (± 3)	Day 35
2	1 and 2	V14 – Day 42 (± 3)	Day 42
2	1 and 2	V15 – Day 77 (± 3)	Day 77
2	1 and 2	V16 – Day 84 (± 3)	Day 84
2	1 and 2	V17 – Day 119 (± 3)	Day 119
2	1 and 2	V18 – Day 126 (± 3)	Day 126
2	1 and 2	V19 – Day 161 (± 3)	Day 161
2	1 and 2	V20 – Day 168 (± 3)	Day 168
3	2 only	V21 – Day 203 (± 3)	Day 203
3	2 only	V22 – Day 210 (± 3)	Day 210
3	2 only	V23 – Day 217 (± 3)	Day 217
3	2 only	V24 – Day 224[b] (± 3)	Day 224
3	2 only	V25 – Day 231[b] (± 3)	Day 231
3	2 only	V26 – Day 238 [b] (± 3)	Day 238
3	2 only	V27 – Day 245 [b] (± 3)	Day 245
3	2 only	V28 – Day 252 (± 3)	Day 252
Follow-up	1 and 2 (not entered in Stage 3 [a])	FU – 28 days after last dose (± 3)	Follow-up
Final Assessment	2 only (entered in Stage 3)	1 Week after last Stage 3 visit or >28 days after last injection for EW)	Final Assessment
Unscheduled Visit			

[a] Subjects not entered in Stage 3 will have follow- up, Subjects who entered stage 3 will have final assessments.

[b] 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).

2.3 Schedule of Assessments

Table 5 presents the schedule of assessments for Group 1 and 2 respectively.

Table 5 Schedule of Assessments for Groups 1 & 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[l]	○	○										○		○		○		○		○	○	○

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	
Holter ECG (Group 2 only)		○	○																			
Safety Labs[a]	○	○										○		○		○		○		○	○	○
Vital Signs	○	○										○		○		○		○		○	○	○
Demography[b]	○	○										○		○		○		○		○	○	○
Injection of teverelix TFA IM[c]		○																				

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 SC		○												○		○		○		○		
Blood draw for pre-dosing local lab T testing	○										○		○		○		○		○			
PK/PD Blood Draw[d]		○[e]	○[f]	○[g]	○[h]	○[i]	○[i]	○[i]	○[i]	○[i]	○[i]	○[i]	○[i]	○[i]		○[i]		○[i]		○[i]	○	
PSA/hs PSA[j]		○					○			○	○	○	○	○		○		○		○	○	

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	
Cardiac biomarkers		○										○		○		○		○		○	○	
Injection Site Inspection		○	○	○	○	○	○	○	○	○	○	○		○		○		○		○	○	
Injection Site Photograph[k]		○	○	○	○	○	○	○	○	○	○	○		○		○		○		○	○	

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	
Prior and current Concomitant Medications	○	○	○	○	○	○	○	○	○	○	○	○		○		○		○		○	○	○
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.

[a] Safety laboratory tests are detailed in Section 4.2.6.

[b] 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.

[c] 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.

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

[e] 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.

[f] 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.

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

[h] 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.

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

[j] 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

Table 6 Schedule of Assessments for Groups 2 (Subjects entered in Stage 3)

Visit/ Procedure	Screening	Treatment Period Groups 1 & 2 (with Stage 3 subjects only)																				Final Assessment (1 week after last Stage 3 visit or ≥ 28 days after last injection for EW)
		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-Day 252	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21 - V28	
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.	○	○										○		○		○		○		○		○

Visit/ Procedure	Screening	Treatment Period Groups 1 & 2 (with Stage 3 subjects only)																				Final Assessment (1 week after last Stage 3 visit or ≥ 28 days after last injection for EW)
		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-Day 252	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21 - V28	
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	
12-Lead ECG[l]	○	○										○		○		○		○		○		○
Holter ECG (Group 2 only)		○	○																			
Safety Labs[a]	○	○										○		○		○		○		○		○
Vital Signs	○	○										○		○		○		○		○		○
Demography[b]	○	○										○		○		○		○		○		○

Visit/ Procedure	Screening	Treatment Period Groups 1 & 2 (with Stage 3 subjects only)																				Final Assessment (1 week after last Stage 3 visit or ≥ 28 days after last injection for EW)
		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-Day 252	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21 - V28	
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[c]		○																				
Injection of teverelix TFA SC		○												○		○		○		○		
Blood draw for pre-dosing local lab T testing	○										○		○		○		○		○			

Visit/ Procedure	Screening	Treatment Period Groups 1 & 2 (with Stage 3 subjects only)																			Final Assessment (1 week after last Stage 3 visit or ≥ 28 days after last injection for EW)
		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-Day 252	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21 - V28	
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[d]		O[e]	O[f]	O[g]	O[h]	O[i]	O[i]	O[i]	O[i]	O[i]	O[i]	O[i]	O[i]	O[i]		O[i]		O[i]		O[i]	O	O
PSA/hs PSA[j]		O					O			O	O	O	O	O		O		O		O	O	O
Cardiac biomarkers		O										O		O		O		O		O		O
Injection Site Inspection		O	O	O	O	O	O	O	O	O	O	O		O		O		O		O		O

Visit/ Procedure	Screening	Treatment Period Groups 1 & 2 (with Stage 3 subjects only)																				Final Assessment (1 week after last Stage 3 visit or ≥ 28 days after last injection for EW)
		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-Day 252	
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21 - V28	
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 Site Photograph[k]		○	○	○	○	○	○	○	○	○	○	○		○		○		○		○		○
Prior and current Concomitant Medications	○	○	○	○	○	○	○	○	○	○	○	○		○		○		○		○	○	○
Adverse Events	○	○	○	○	○	○	○	○	○	○	○	○		○		○		○		○	○	○

[a] Safety laboratory tests are detailed in Section 4.2.6.

* Subjects should attend on Day 203 and weekly Day 252 (or until total T (local lab) is > 1 ng/mL – whichever occurs first)

[b] 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.

[c] 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.

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

[e] 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.

[f] 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.

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

[h] 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.

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

[j] 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

3. Patient Analysis Sets

3.1 Analysis Populations

The analysis sets of interest are:

- Screening Population
- Safety Population
- Intention-to-Treat (ITT) Analysis Set
- Non-missing Central Lab Serum T Record at Day 28 (Lab Serum T Day 28) Analysis Set
- Per Protocol (PP) analysis Set
- Pharmacokinetic (PK) Analysis Set

The primary analysis will be performed on the per protocol (PP) population. In addition, a sensitivity analysis will be prepared in the intention to treat (ITT) population. All efficacy assessments on the PP population will be repeated for the ITT population. See Section 6.8 for further details.

It is planned that a separate PK SAP will be developed to provide a detailed description of the PK analysis based on the Pharmacokinetic (PK) Analysis set. The current SAP will only present general information as per the study protocol. It should be noted that the Pharmacokinetic Analysis set presented in the current SAP is solely for general information purposes and will not be utilized for any analysis described in this document.

3.2 Screening Population

All participants who signed the ICF will be included in the screening population.

3.3 Safety Population

All participants who have received any dose of IMP will be included in the safety population.

3.4 Intention-to-Treat (ITT) Analysis Set

All participants included in the safety population and for whom the primary endpoint is evaluable will be included in the ITT analysis set. Participants for whom the primary efficacy measure is evaluable are those who have a non-missing central lab serum T record at Day 28.

3.5 Non-missing Central Lab Serum T Record at Day 28 (Lab Serum T Day 28) Analysis Set

All participants included ITT analysis set, except for patients who received concomitant medications and herbal supplements that could possibly affect T levels, will be included in the Lab Serum T Day 28 analysis set.

If at the time of analysis this population is the same as the ITT population the analysis is conducted on, then results will not be repeated where the same question has been asked for the ITT population.

3.6 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set is defined as the subset of the Per protocol (PP) analysis set providing analysable samples to assess the pharmacokinetics of the active substance.

A PK profile for a subject may be excluded from the PK Analysis Set in the relevant period/on that sampling occasion if the subject:

- did not receive active treatment (e.g. excluding samples taken pre-dose and following administration with Placebo) or the correct dose.
- did not provide analysable samples at more than 50% of planned time points in the PK profile (e.g. due to drop out or laboratory errors).

All PK analyses will be performed on the PK Analysis Set.

In addition, PK data may be flagged to be excluded from specific summaries if, for example, the derived parameters are considered unreliable.

3.7 Per Protocol (PP) Analysis Set

All participants included in the ITT analysis set who complete the study without major protocol violation will be included in the PP analysis set. Participants with major protocol violations will be excluded.

Protocol Violations will be classified as either 'major' or 'minor' in collaboration with the Sponsor. The criteria for this assessment will be defined before database lock. Patient inclusion or exclusion from this population will be confirmed following data review and prior to database lock. Listings will be prepared to show the eligibility of all participants prior to database lock. These listings will be presented in a Data Review Meeting.

3.8 Analysis of Subgroups

No subgroup analyses are planned.

4. Study Measures

This section describes the measures that were collected and/or derived duraing the study at the time points specified in the Schedule of Assessments (**Error! Reference source not found.**). This includes efficacy, safety, tolerability and subject characteristics data.

The Baseline value for all variables is defined as the last non-missing measurement collected/derived prior to the first study medication administration at Visit 2/Day 0. This includes unscheduled visits.

The change from Baseline value at each post-baseline visit for all variables will be calculated as the difference between the measurement obtained/derived at the specific post-baseline visit, and the Baseline value.

The two dose groups will be analysed separately – the combined results will not be of interest for the analyses. The combined results would not be of interest as Group 2 would only open to recruitment if Group 1 was deemed ineffectual.

4.1 Efficacy Measures

The efficacy endpoints described in this section will form part of the efficacy analyses and will be analysed according to the analysis methods described in Section 6.8.

4.1.1 Primary Efficacy Measure

The primary efficacy measure is the proportion of subjects achieving castration with central lab serum T <0.5 ng/mL or 1.73 nmol/L at Day 28. The denominator is the number of subjects who have a non-missing central lab T record at Day 28 in the relevant population.

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.

4.1.2 Secondary Efficacy Measures

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 7 below.

Table 7 Timepoints of Efficacy Variables

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

Stage	Group	Timepoint	Variables				
			Local T	Central T	LH	FSH	PSA
		Day 238[b]	O	O	O	O	O
		Day 245[b]	O	O	O	O	O
		Day 252	O	O	O	O	O
		Follow up visit	O	O	O	O	O

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] These visits will only be done if local lab T result at previous visit was <1 ng/mL. If it is >1 ng/mL then their next study visit would be the Final Assessment/Follow up visit

List of Secondary Analysis Endpoints to be Included in the Study Results:

1. Proportion of participants achieving castration level with serum T <0.2 ng/mL at Day 28. Percentage of participants who have T concentrations <0.2 ng/mL at the end of Stage 1 (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 castration level with serum T <0.5 ng/mL across treatment period from Day 28 until Day 168
   Note: 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 level(<0.2 ng/mL) across treatment period from Day 28 until Day 168.
6. Time to T levels falling below castration level (<0.5 ng/mL [1.73 nmol/L]) for the first time.
7. Time to (first) overstep of T castration level after achieving castration.
   Note: Overstep of T castration level is defined as the first instance of T levels being above castration level after a patient has achieved castration.
8. 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 level across treatment period from Day 28 until Day 168
11. Time to LH levels falling below castration level (LH <1.1 U/L) for the first time
12. Time to (first) overstep of LH castration level after achieving castration.
13. Changes from baseline in PD and PK parameters over time
14. Confirmed PSA Response Rate
15. PSA response rate at day 28
16. Number of participants with a PSA response of ≥50% reduction at the Day 168 visit
17. Number of participants with PSA response of ≥80% reduction at the Day 168 visit
18. Percent change from baseline in serum PSA concentration at each visit
19. Serum PSA concentration at each visit
20. PSA levels at each visit
21. Mean nadir PSA up to Day 168
22. Time to nadir PSA level
23. Percent change from baseline in Serum LH concentration at each visit
24. Serum LH concentration at each visit

25. LH levels at each visit
26. Serum T concentration at each visit
27. Percent change from baseline in Serum FSH concentration at each visit
28. Serum FSH concentration at each visit
29. FSH levels at each visit

All PK parameters analysis will be described with details in a separate SAP.

4.1.2.1 Local Lab T Level

Local lab serum T level (ng/mL) and number of subjects with local lab serum T <2 ng/mL will be measured at Screening, Visit 11/Day 21 and 7 days prior to each dosing visit. For comparison, the number of subjects with local lab serum T ≥2 ng/mL will also be recorded. See Table 8 below.

Local laboratory data will not be reported.

Table 8 PD 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 who enter Stage 3.

4.1.3 Supplementary FDA Recommended Efficacy Measure

Supplementary analysis will be conducted utilizing the Kaplan-Meier technique to estimate the proportion of patients who achieve and maintain castrate T levels (<0.5 ng/mL or 1.73 nmol/L) from Day 28 through the end of the treatment period.

4.2 Safety Measures

The safety endpoints described in this section will be analysed according to the analysis methods described in Section 6.9.

4.2.1 Exposure to Study Medication

Duration of exposure, number of injections received, whether subjects received all planned injections and total dose received will be presented.

4.2.2 Adverse Events

An adverse event (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 related to that medicinal (investigational) product.

AE data will be collected from the time that informed consent was given, for the duration of the trial.

Missing AE data will be handled according to the rules specified in Section 6.9.2.

4.2.3 Adverse Event Definitions

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:

- **Relationship to study medication**: Related, Probable, Possible, Unlikely, Not related. Investigator record from the eCRF will be reported.
- **Intensity**: Grade 1(mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (death). This is based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), and investigator record from the electronic Case Report Form (eCRF) will be reported.
- **Seriousness**: Serious AEs reported from the time of informed consent until 31 days after the dose of study medication will be recorded on the eCRF.

- **Expectedness**: Expected, Unexpected.

A treatment-emergent AE (TEAE) is defined as any new or worsening pre-existing AE with a date equal to or later than the date of IMP administration.

A treatment-emergent serious AE (TESAE) is defined as any new or worsening pre-existing SAE with a date equal to or later than the date of IMP administration.

An AE is an adverse drug reaction (ADR) if a causal relationship between a medicinal product and an AE is at least a reasonable possibility. An AE will be classified as related to study medication if the relationship to study medication was recorded (on the 'Study Adverse Events' CRF page,) as 'Unlikely', 'Possible', 'Probable', 'Related'. An AE will be classified as unrelated to study medication if the relationship to study medication was recorded as 'Unrelated'.

Any AE that leads to discontinuation of treatment will have 'Action Taken with Study Treatment' reported as 'Drug Withdrawn' on the 'Adverse Event' page.

4.2.3.1 Coding of Adverse Event Terms

The AE term (Investigator term) will be assigned to the lowest level term (LLT), and a preferred term (PT) will be classified by a high-level term (HLT), a high-level group term (HLGT) and a system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, Version 25.0.

Although there can be multiple SOCs for a PT, each PT will be linked with one SOC, namely the primary SOC which is automatically assigned by MedDRA via one HLT, HLGT route.

The following coding data will be presented:

- LLT (Investigator term)
- PT
- Coding data per primary SOC:
  - HLT
  - HLGT

If no coding information is available for a specific AE, the AE will be presented as an 'Uncodable Event' in all summary tables.

AEs will be reported on a per-subject basis and per-event. On a per-subject basis this means that even if a subject reported the same event repeatedly (i.e., events mapped to the same PT) during the study period, the event will be counted only once. In the latter case the event will be assigned the worst intensity and the strongest relationship to the study medication. The earliest date will be regarded as start date of the event and the latest date/time will be regarded as stop date of the event within the assigned study period.

4.2.4 Prostate Cancer Diagnosis

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

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

4.2.4.1 TNM classification of prostate cancer

Table 9 presents the Primary Tumour, Lymph Node and Metastasis (TNM) classification of primary tumours.

Table 9 TNM Classification of Primary Tumours

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 prostate specific antigen [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 Tumour, Lymph Node and Metastasis

Error! Reference source not found.10 presents TNM classification of regional lymph nodes.

Table 10 TNM Classification of Regional Lymph Nodes (N)

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

TNM= Primary Tumour, Lymph Node and Metastasis

Table 11 presents TNM classification of distant metastasis.

Table 11 TNM classification of distant metastasis (M)[a]

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

4.2.4.2 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 the cancer from a biopsy looks like healthy tissue (lower score) or abnormal tissue (higher score). Most cancers score a grade 3 or higher.

Since prostate tumours are often made up of cancerous cells that have different grades, two 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 12 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 (**Error! Reference source not found.**). The higher the Gleason score, the more likely 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

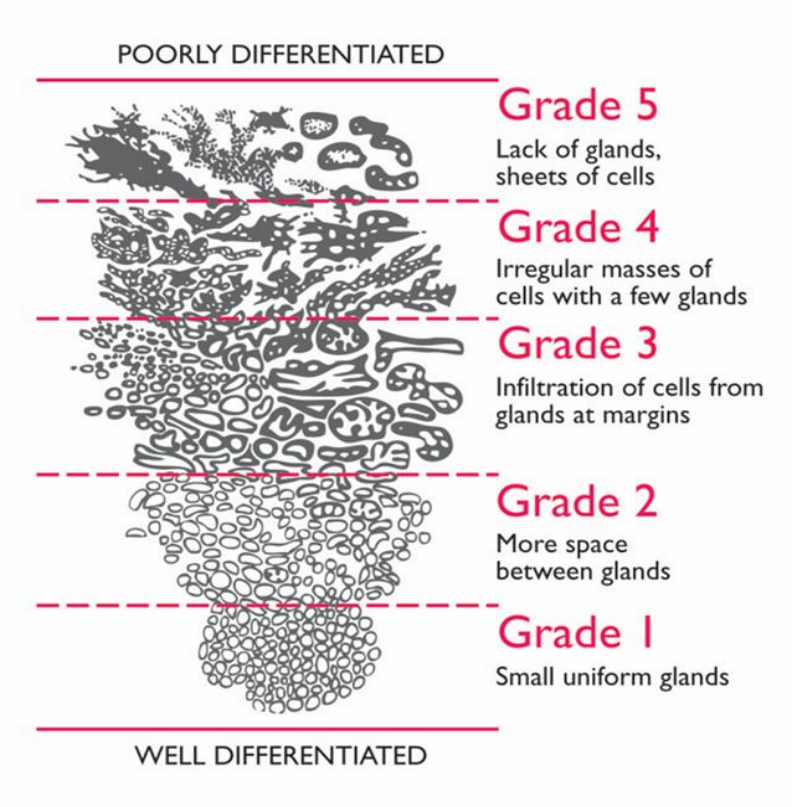


Table 12 Gleason Scoring System

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

4.2.5 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 13 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 13 FDA 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.

4.2.6 Clinical Laboratory Evaluations

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.

All laboratory results are standardized to Système International (S.I) units.

An overview of measured parameters is given in Table 14.

Table 14 Clinical Safety Laboratory Tests

Haematology:	**Biochemistry:**
Haemoglobin (mmol/l) Erythrocytes (10E12/l) Leucocytes (10E9/l) Thrombocytes (10E9/l) Neutrophils (%) Eosinophils (%) Basophils (%) Lymphocytes (%) Monocytes (%)	Alkaline phosphatase (U/l) ASAT (U/l) ALAT (U/l) GGT (U/l) Creatinine (mcmol/l) Fasting glucose (mmol/L) Fasting insulin (mIU/l) Urea (mmol/l) Total Bilirubin (mcmol/l) Total protein (g/L) Sodium (mmol/l) Potassium (mmol/l) Total cholesterol (mmol) LDL (mmol/l) HDL (mmol/l) VLDL (mmol/l) Triglycerides (mmol/l) HbA1c (screening visit only)
Urinalysis:	
Leucocytes (HPF) Erythrocytes (HPF) Epithelial cells (LPF) pH Protein (g/L) Glucose (mmol/L) Urobilinogen (mmol/L) Ketones (mg/dL) Bilirubin (mmol/L) Nitrite: positive or negative (presence or absence) Specific density (g/L)	

ALAT=alanine aminotransferase; ASAT=aspartate aminotransferase; HDL=high-density lipoprotein; LDL=low-density lipoprotein; VLDL=very low-density lipoprotein; GGT=gamma-glutamyl transpeptidase; HbA1c= glycated haemoglobin

In case a re-test is conducted for any of the quantitative and qualitative laboratory parameters during any visit, the results of the re-test will be utilized.Quantitative test results at each visit will be categorised by the laboratory as ‘Normal’ (within the reference range) or ‘Abnormal’ (outside the reference range) according to the subjects’ individual reference ranges provided by the analysing laboratory. Abnormal results will be further classified as being ‘Low’ or ‘High’ depending on whether the result is below or above the reference range limits. For all abnormal values, clinical significance (as determined by the Investigator) should be indicated.

Based on the normal ranges supplied by the lab and noted in Attachment 2, markedly 'Abnormal Low' or 'High' laboratory test results will be identified at each visit.

For the qualitative laboratory parameters (urinalysis, etc.), the presence or absence ('Present' or 'Absent') of each parameter will be recorded.

4.2.7 Electrocardiogram (ECG) Evaluations

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 2- to 5-minute window) will be obtained at each dosing visit and 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 as described in Section 6.9.2.

Error! Reference source not found. presents the quantitative and qualitative ECG parameters that were collected.

Table 15 ECG Parameters

ECG Parameters (Unit)
Conduction Times
Ventricular Rate (msec)
QT Interval (msec)
QTcF Interval (msec)

Note: QTcF = QT/CubeRootRR(seconds)

Thresholds for a significant QTcF prolongation are defined as follows:

- QTcF >450 ms
- QTcF >480 ms
- QTcF >500 ms
- An increase from baseline of >30 ms
- An increase from baseline of >60 ms
- QTcF >500 ms or an increase from baseline of >60 ms.

For the qualitative ECG parameters (morphology), it will be recorded whether the parameter at the specific visit was 'Normal' or 'Abnormal'. Each collected quantitative (conduction times) ECG parameter will be classified as 'Normal' or 'Abnormal' at each visit. For all abnormal values, clinical significance (as determined by the Investigator) and any ECG findings should be indicated.

Based on the criteria presented in Attachment 2, markedly abnormal ECG parameters will be identified at each visit.

4.2.8 Vital Signs Evaluations

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, and 168. Additionally vital signs parameters will be measured at follow-up any unscheduled visits for both Groups 1 and 2 (subjects not entered in Stage 3). For subjects entered in Stage 3, vital signs parameters are additionally measured at the final assessment, occurring 1 week after last Stage 3 visit or ≥28 days after last injection for EW(Early Withdrawal). This is in accordance with the schedule of events (Section 0). 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 blood pressure (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 6.9.2). 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. Blood pressure 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, blood pressure and pulse rate should preferably be measured in the same arm at each visit.

Based on the criteria presented in Attachment 2, markedly abnormal vital signs measurements will be identified at each visit.

4.2.9 Predictive Effect of Cardiac Biomarkers

To assess the predictive effect of cardiac biomarkers for new cardiovascular (CV) events, the following parameters will be collected at Stage 1 (Day 0) and Stage 2 (Day 28, Day 42, Day 84, Day 126, Day 168):

- N-terminal pro-B-type natriuretic peptide (NTproBNP)
- D-dimer
- C-reactive protein (CRP)
- high-sensitivity troponin (hsTn)

4.3 Other Measures

4.3.1 Physical Examination

A physical examination will be performed at the timepoints specified in **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 5.3.2.3). 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.

4.3.2 Subject Disposition

Subject disposition data will be included on the 'Informed Consent at Screening visit (visit 1)', 'Subject Eligibility at Screening visit (visit 1)', 'Subject Eligibility at Day 0', 'End of Treatment – Core Study at End of Treatment – Core Study' and 'End of Study – Core Study at End of Study – Core Study' CRF pages when a subject completed or discontinued from the study, along with date and time of informed consent. The following data will be summarized:

- Number of subjects screened and screen failed (with the reasons);
- Number of subjects assigned treatment group;
- Number of subjects completed the study;
- Number of subjects prematurely discontinued\withdrawn (with the reasons);
- The analysis sets defined in Section 3 will be summarised.

4.3.3 Protocol Violations

Protocol violations are defined as violations that might affect the efficacy or treatment of a subject, and lead to the exclusion of subjects from the analysis sets defined in Section 3.

The following protocol deviations lead to the exclusion from the defined analysis sets:

- Subject did not provide informed consent.
- Subject was not allocated to one of the treatment groups.
- Subject did not take at least one dose of the study medication.
- Prohibited Concomitant Medication received.
- Study visit was outside the permitted window.

The eligibility of all subjects for entry into the study was assessed at Visit 1 Day -6 to -1. A subject should have met all of the inclusion, and none of the exclusion criteria before entry into the study.

The inclusion criteria comprise the following:

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.

The exclusion criteria comprise the following:

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 exceedingly 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 5 α-reductase inhibitor treatment etc. (Spironolactone is a permitted concomitant treatment).
      ii. GnRH analogues, androgen receptor antagonists
      iii. Androgen synthesis inhibitors (e.g., abiraterone)
      iv. 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 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 liver metastases

4.3.4 Demographics

The following demographic characteristics data will be collected on the 'Demography at Screening visit (Visit 1)' eCRF page at Screening Visit 1 Day -6 to -1:

- Year of birth
- Age
- Sex
- Race
- Ethnicity
- Country
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

Weight, height and BMI will be collected on the 'Demography - Post Screening at Day 0, Day 28, Day 42, Day 84, Day 126, Day 168. Additionally, Demography will be assessed on Follow Up Visit, Unscheduled_visit' for both Groups 1 and 2 (subjects not entered in Stage 3). During Stage 2 these assessments will be performed on the day of the maintenance dose. For subjects entered in Stage 3, demography parameters are additionally measured at the final assessment, i.e., occurring 1 week after last Stage 3 visit or ≥28 days after last injection for EW (Early Withdrawal). This is in accordance with the schedule of events table 16 (in Protocol).

Age (in years) at Screening will be recorded as a whole integer.

Weight will be measured and recorded in kilograms (kg). Height will be measured in centimetres at the screening visit (Visit 1) only.

Missing demography data will not be imputed.

The analysis will be summarised for Safety, Intention-To-Treat & Per-Protocol populations as defined in Section 3.

4.3.5 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.

4.3.5.1 Coding of Medical History Terms

The medical history term (Investigator term) is assigned to the LLT, and a PT will be classified by a HLT, a HLGT and a SOC according to the MedDRA thesaurus, Version 25.0.

Although there can be multiple SOCs for a PT, each PT will be linked with one SOC, namely the primary SOC which is automatically assigned by MedDRA via one HLT, HLGT route.

The following coding data will be presented:

- LLT
- PT
- Coding data per primary SOC:
  - HLT
  - HLGT

Medical history will be reported on a per-subject basis. This means that even if a subject suffered the same clinical event repeatedly (i.e., events mapped to the same PT) the event will be counted only once and the earliest date will be regarded as start date of the event and the latest date will be regarded as stop date of the event.

The same rule for counting applies for PTs mapped to the same HLT and for HLTs mapped to the same HLGT and for HLGTs mapped to the same SOC.

4.3.6 Prior and Concomitant Medications

Concomitant medications include all medications that a subject used at any stage during the study. Any medication started prior to or any time after the first study medication administration, thus after the Baseline visit, will be included.

Concomitant medications data will be collected throughout the study on the 'Prior and concomitant Medication and Therapy' CRF page.

Missing concomitant medications data will be handled according to the rules specified in Section 5.3.2.4.

Any concomitant therapies and medications administered during the trial must 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.

4.3.6.1 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

4.3.6.2 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

4.3.6.3 Coding of Concomitant Medication Terms

Concomitant medications are classified according to active drug substance using WHODD GLOBAL B3 Version Sep 2020.

The WHO-DD drug identity (ID) has 11 characters. The preferred name, for example, the salt/ester of the substance is defined by the first 8 characters, and the WHO-DD name is defined by the 11 characters.

In addition, the Anatomical Therapeutic Chemical (ATC) classes are assigned to the drug ID. An ATC code has 7 characters. The first character gives the anatomical main group (1st level), the first 3 characters give the therapeutic main group (2nd level), the first 4 characters give the therapeutic subgroup (3rd level), the first 5 characters give a further level therapeutic subgroup (4th level), whereas the 7 characters give the subgroup for the chemical substance. In this study, ATC codes are defined to the 4th level.

Although there can be multiple ATC classes for a drug, each drug will be linked with one ATC class which will be assigned manually during the coding process, based on information about the indication and route in relation to the study therapeutic area. This one ATC class will be indicated as the 'primary' ATC class, and only the primary class will be presented.

4.3.7 Treatment Compliance and Drug Accountability

Dose, site, visit, date, injection type and whether visit was attended and whether treatment was received will be recorded.

4.3.8 Pharmacokinetics

It is planned that a separate PK SAP will be developed to provide a detailed description of the PK analysis based on the Pharmacokinetic (PK) Analysis set. The current SAP will only present general information as per the study protocol. It should be noted that the Pharmacokinetic Analysis set presented in the current SAP is solely for general information purposes and will not be utilized for any analysis described in this document

4.3.8.1 Pharmacokinetic variables

Pharmacokinetic parameters will be generated using Phoenix WinNonlin Version 8.1 or higher for evaluation [1].

Data from participants who have sufficient concentrations to derive at least one PK parameter will be analysed. This analysis will include the parameters shown in **Error! Reference source not found.**.

Table 16 Pharmacokinetic Parameters

PK parameter	Description	Unit
AUC_{0-t}	Area under the concentration time-curve from time zero up to the last quantifiable concentration at time point t (C_t), calculated using the linear up/log down trapezoidal rule.	ng*h/mL
AUC_{0-t1}	Area under the concentration time-curve from time zero up to the concentration at time point t1 after which the concentrations start to rise again towards a second peak, calculated using the linear up/log down trapezoidal rule. t1 will be determined after review of the concentration-time profiles (immediate release component of total observed AUC).	ng*h/mL
AUC_{t1-t}	Area under the concentration time-curve from time point t1 up to the concentration at time point t (slow release component of total observed AUC), calculated using the linear up/log down trapezoidal rule.	ng*h/mL
$AUC_{0-\infty}$	Area under the concentration time-curve from time zero up to infinity (∞),calculated using the linear up/log down trapezoidal rule.	ng*h/mL
C_{max}	Maximum plasma concentration	ng/mL
$C_{max,0-t1}$	Maximum plasma concentration after administration from zero up to time point t1	ng/mL
$C_{max,t1-t}$	Maximum plasma concentration after administration from time point t1 up to time point 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
t_{last}	Time of the last quantifiable concentration	h
λ_z	Apparent terminal elimination rate constant	1/h
$t_{½}$	Apparent terminal plasma half-life, calculated as: ln 2 / λ_z	h

h= hours; PK= Pharmacokinetic

Actual sampling times (relative to the IM injection of teverelix TFA at time zero will be used for the calculation of all PK parameters, and all calculations will be made using non-rounded raw data. Where the actual sampling time is not recorded, the nominal sampling time will be used. Concentrations below the lower limit of quantification (LLOQ) will be taken as zero for calculation of concentration summary statistics and PK parameters.

A PK profile for a subject may be excluded from the PK analysis if the subject did not receive active treatment or had insufficient concentration data. Missing data will be excluded from the PK analysis. Removal of anomalous data (outliers) will be considered on an individual basis and reasons provided with an assessment of the impact on the study. Special consideration will be given to the estimation of λ_z and corresponding $t_{1/2}$ values. Three or more points will be required within the terminal phase for λ_z and $t_{1/2}$ to be estimated. The following additional variables will be tabulated to aid identification of potentially unreliable estimates of $t_{1/2}$ and $AUC_{0-\infty}$:

#pts	the number of data points used in the calculation of λ_z.
Rsq	the goodness of fit statistic for the terminal elimination phase. Note, if Rsq is less than 0.8, the $t_{1/2}$ will not be reported as the estimate will be classed as unreliable.
λ_z_lower	the lower limit on time for values included in the calculation of λ_z.
λ_z_upper	the upper limit on time for values included in the calculation of λ_z.
λ_z_period	estimated as (λ_z_upper - λ_z_lower) / $t_{1/2}$; values < 2 would indicate that λ_z and corresponding $t_{1/2}$ estimates are potentially unreliable **Error! Reference source not found.**.
$\%AUC_{ext}$	the percentage of $AUC_{0-\infty}$ that is due to extrapolation from C_t to infinity; values for $AUC_{0-\infty}$ will be classed as potentially unreliable if more than 20% of the total $AUC_{0-\infty}$ will be extrapolated **Error! Reference source not found.**.

4.3.8.2 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 time point.

Blood is drawn for PK analysis according to the schedule in **Error! Reference source not found.** where time points 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:

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

All PK parameters analysis will be described with details in a separate SAP.

Table 17 presents the pharmacokinetic timepoints at which the blood samples will be collected.

Table 17 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 visit[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

4.3.9 Pharmacodynamics

The following parameters will be investigated:

- T
- LH
- FSH
- PSA or hs PSA

Table 18 **Error! Reference source not found.**below **Error! Reference source not found.**presents the PD blood sampling schedule for the study.

Table 18 Pharmacodynamic Blood Sampling Schedule

	Day 0 (pre-dose)	24h	48h	72h	Day 4	Day 7	Day 10
T (local)							
T (central)	O	O	O	O	O	O	O
LH	O	O	O	O	O	O	O
FSH	O	O	O	O	O	O	O
PSA	O					O	

	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 visit[d]
T (local)			O		O	O	
T (central)	O	O	O	O	O		O
LH	O	O	O	O	O		O
FSH	O	O	O	O	O		O
PSA		O	O	O	O		O

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 who enter Stage 3

5. Statistical Methodology

5.1 General Statistical Methods

5.1.1 General Information

All analysis data sets, and output will be produced by the Biostatistics Department of Quanticate Ltd using the SAS® system Version 9.4 or higher.

5.1.2 Default Descriptive Statistics and Data Rules

In general, all continuous measures will be summarised descriptively, including number of available values, mean, standard deviation (SD), median, 1st quartile (for primary and secondary efficacy measures), 3rd quartile (for primary and secondary efficacy measures), minimum, maximum, and 95% confidence interval (CI) for the mean (for primary and secondary efficacy measures) if appropriate. Minimum and maximum values will be presented to the same decimal precision as the raw values, the 1st quartile, median, mean, 3rd quartile and 95% CI to one more, and the standard deviation, to two more decimal places than the raw values. Ordinal ratings may be handled as continuous data if appropriate.

Categorical data will be presented by frequency and percentage. All percentages will be presented to one decimal place except for values of 100%.

For AEs reported on a per-subject basis, medical history and concomitant medications, the denominator for the percentage calculation will be the number of subjects in each treatment arm. A subject will be considered at risk if the subject is in the Safety/FAS analysis set and entered the respective study period.

Unless otherwise specified, if reporting by visit, percentages are calculated using the number of subjects in the corresponding treatment group with non-missing data at that visit as the denominator, and if reporting overall, the denominator is the number of subjects in the given treatment group and population.

5.2 Hypotheses and Decision Rules

The approach for testing the hypothesis, if any, will solely rely on utilizing confidence intervals.

5.3 Handling of Missing Data

5.3.1 Efficacy Endpoints

Missing efficacy data will not be replaced.

5.3.2 Other Endpoints

5.3.2.1 Laboratory Data

If a laboratory reports a concentration as unquantifiable (too low), they will set the value to 0. If a laboratory reports a concentration as unquantifiable (too high), they will set the value to the upper limit for that value. Values for samples that are not technically evaluable will be set to missing by the laboratory.

5.3.2.2 Exposure

If the start of treatment date is missing, the latest possible date of all the pre-dose assessments, up to and including Randomization will be imputed as the start of treatment date.

If the end of treatment date is missing, the latest possible time of all the post-dose assessments will be imputed as the end of treatment date.

5.3.2.3 Adverse Events

Missing and/or incomplete dates/times for AEs are imputed in a manner to ensure a conservative approach to treatment period if the missing/partial dates cannot definitively exclude the treatment period, taking additionally into account that the start date/time should not be after the stop date/time. Stop dates/times will not be imputed if the AE is ongoing.

This will be done as follows:

When the day of onset of an AE is missing:

- If month and year of onset of an AE is the same as the month and year of date of first administration of the study drug, then the missing day is imputed as the day of date of first administration of the study drug.
- Otherwise, the missing day is imputed as 1st of the month.

When the day and month of onset of an AE are missing:

- If the year of onset of an AE is the same as the year of date of the first administration of the study drug, then the missing day and month are imputed as the day and month of date of first administration of the study drug.
- Otherwise, the missing day and month are imputed as January 1st .

If onset date is completely missing:

- If AE end date is on/after the date of first administration of the study drug, then onset date is set to date of first administration of the study drug.
- If AE end day or month are missing, then day will be imputed as last day of the month and month will be imputed as December:
    - If imputed end date is on or after the date of first administration of the study drug, then onset date is set to date of first administration of the study drug and AE is considered as treatment emergent.
    - If AE end date is prior to the date of first administration of the study drug, then onset date is not imputed, and AE is not considered as treatment emergent.

The imputation method will only be used to determine treatment emergence and to determine the time of the event relative to the first administration of study medication.

A worst-case approach will be followed in the event of missing intensity or causality data. If the intensity is missing, ‘Severe’ will be imputed. If causality data is missing, ‘Related to study medication’ will be imputed.

In the event that no coding information is available for a specific AE, the AE will be presented as an ‘Uncodable Event’ in summary tables.

5.3.2.4 Concomitant Medications

Missing concomitant medication dates will be handled in a similar fashion as described for AEs in Section 4.3.6.

5.4 Windowing Conventions

Table 19 presents the visit windows that will be used to assign assessments to a nominal visit.

Table 19 Visit Windows

Stage	Group	Visit	Visit Label	Visit Day	Visit Window
Screening	1 and 2	V1 – Screening (D -6 to -1)	Screening	Day -6 to -1	Day -6 to -1
1	1 and 2	V2 – Day 0	Baseline	0	
1	1 and 2	V3 – Day 1	D1	1	
1	1 and 2	V4 – Day 2	D2	2	
1	1 and 2	V5 – Day 3	D3	3	
1	1 and 2	V6 – Day 4	D4	4	
1	1 and 2	V7 – Day 7	D7	7	
1	1 and 2	V8 – Day 10	D10	10	±1 day from planned day
1	1 and 2	V9 – Day 12	D12	12	±1 day from planned day
1	1 and 2	V10 – Day 14	D14	14	±1 day from planned day
1	1 and 2	V11 – Day 21	D21	21	±1 days from planned day
2	1 and 2	V12 – Day 28	D28	28	±3 days from planned day
2	1 and 2	V13 – Day 35	D35	35	±3 days from planned day
2	1 and 2	V14 – Day 42	D42	42	±3 days from planned day

2	1 and 2	V15 – Day 77	D77	77	±3 days from planned day
2	1 and 2	V16 – Day 84	D84	84	±3 days from planned day
2	1 and 2	V17 – Day 119	D119	119	±3 days from planned day
2	1 and 2	V18 – Day 126	D126	126	±3 days from planned day
2	1 and 2	V19 – Day 161	D161	161	±3 days from planned day
2	1 and 2	V20 – Day 168	D168	168	±3 days from planned day
3	2 only	V21 – Day 203	D203	203	±3 days from planned day
3	2 only	V22 – Day 210	D210	210	±3 days from planned day
3	2 only	V23 – Day 217	D217	217	±3 days from planned day
3	2 only	V24 – Day 224[b]	D224 [b]	224 [b]	±3 days from planned day
3	2 only	V25 – Day 231	D231 [b]	D231 [b]	±3 days from planned day
3	2 only	V26 – Day 238	D238[b]	D238 [b]	±3 days from

						planned day
3		2 only	V27 – Day 245	D245 [b]	D245 [b]	±3 days from planned day
3	2 only	V28 – Day 252	D252	D252	±3 days from planned day	
Follow-up		1 and 2 (not entered in Stage 3[a])	V21 – 28 days after last dose	Follow-up	28 days after last dose	±3 days from planned day
Final Assessment		2 only (entered in Stage 3)		Final Assessment	1 week after last Stage 3 visit or >28 days after last injection for EW	

[a] Subjects not entered in Stage 3 will have follow- up, Subjects who entered stage 3 will have final assessments.

[b] 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).

5.5 Schedule of Events

The Study Day of an event/assessment will be calculated relative to the first study medication administration at Baseline. The Study Day of events/assessments occurring before, at or after the first administration will be calculated as follows:

Study Day = (Date of event/assessment - Date of first study medication administration)

6. Statistical Analyses

Both Group 1 and Group 2 outputs will be displayed and analysed separately. Combined totals of the groups will be displayed for completeness, but not analysed.

6.1 Subject Disposition

Subject Disposition will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of subjects with data. Percentages will not be provided for number of patients enrolled; only the total number of subjects enrolled will be presented. The number of subjects who completed the study, the number of subjects who prematurely discontinued, number of subjects screened but not enrolled (Screen Failures), and the primary reason for withdrawal will be reported. The absolute counts (n) and percentages (%) will be presented for Safety set, Intention-to-treat set, and Per-protocol set.

6.2 Protocol Violations

Protocol Violations will be summarised by absolute counts (n) and percentages (%). Percentages will be based on the number of subjects with data.

6.3 Demographics

Demographics include collected and derived, continuous and categorical variables. Categorical variables will be summarised by absolute counts (n) and percentages (%) and continuous variables will be summarised as specified in Section 5.1.25.1.2.

6.4 Prostate Cancer Diagnosis

Prostate cancer diagnosis, Gleason Score and TNM will each be summarised in a separate table. Qualitative parameters will be summarised by absolute counts (n) and percentages (%). Percentages will be based on the number of subjects with data.

6.5 Medical History

Medical History will be listed only.

6.6 Prior and Concomitant Medication

Prior medications and concomitant medications will be summarised separately. Both will be summarised by absolute counts (n) and percentages (%). Percentages will be calculated based on the number of subjects at risk for the specific treatment group. ATC Code Levels 2 and 4 and associated Preferred Terms will be presented.

6.7 Treatment Compliance

Treatment Compliance includes derived continuous and categorical variables. Continuous variables will be summarised by the number of subjects, minimum, median, mean, SD, and maximum.

Compliance will be calculated as the percentage separately for Intramuscular and Subcutaneous, the formula to be used is:

Compliance = (Number of dose administered / Number of dose planned) x 100%

6.8 Efficacy Analyses

The efficacy endpoints will include collected and derived, continuous and categorical variables. Continuous variables will be summarised as detailed in Section 5.1.2.

The primary analysis will be performed on the per-protocol (PP) population. In addition, a sensitivity analysis will be prepared in the intention-to-treat (ITT) population. All efficacy assessments on the PP population will be repeated for the ITT population.

The primary analysis is carried out on the PP population as there is no comparator and therefore no risk of bias towards one group. Also, due to the study design, it is not expected that there will be many protocol violations. Furthermore, it is not preferable for subjects who fail to attend the Day 28 visit to get their test to be included as non-responders in the primary response rate. If the response rate is below 90% in the ITT population but above in the PP, this will be considered in the interpretation of the results.

The following SAS code chooses the exact/Clopper-Pearson CI for the proportion of responders with two possible ways of extracting the data.

```
ods output binomialcls=<data out1>;
proc freq data=<data in> order= formatted; /* choose the correct order
option to specify which is the responder. See SAS documentation for
further details if required */
      table <responder variable> / bin(cl=exact);
      output out=<data out2>(keep=_bin_ xl_bin xu_bin) bin ;
run;
ods output close;
```

6.8.1 Primary Efficacy Analysis

Proportion of participants achieving castration level with serum T <0.5 ng/mL or 1.73 nmol/L at Day 28.
Descriptive statistics, including proportion, Clopper-Pearson confidence interval (CI), and absolute frequencies will be calculated

Sensitivity Analyses on Primary Endpoint

Proportion of participants achieving castration level with serum T <0.5 ng/mL or 1.73 nmol/L at Day 28 will be repeated on the ITT analysis set as a sensitivity analysis for the Primary endpoint.

6.8.2 Secondary Efficacy Analyses

1. Proportion of participants achieving castration level with serum T <0.2 ng/mL or 0.6394 nmol/L at Day 28 will be analysed as mentioned in the Section 5.1.2 for both ITT and PP Population.

2. Proportion of participants achieving castration level with serum T <0.5 ng/mL or 1.73 nmol/L at Day 42 will be analysed as mentioned in the Section 5.1.2 for both ITT and PP Population.

3. Proportion of participants achieving castration level with serum T <0.2 ng/mL or 0.6394 nmol/L at Day 42 will be analysed as mentioned in the Section 5.1.2 for both ITT and PP Population.

4. Proportion of participants achieving castration level with serum T <0.5 ng/mL or 1.73 nmol/L across treatment period from Day 28 until Day 168 will be analysed as mentioned in the Section 5.1.2 for both ITT and PP population.
   Note: Castration level is defined as the observed percentage of participants who have T concentrations <0.5 ng/mL (1.73 nmol/L) at all scheduled visits.

   Descriptive statistics with proportion, its Clopper-Pearson confidence interval (CI) and absolute frequencies.

5. Proportion of participants achieving castration level with serum T <0.2 ng/mL or 0.6394 nmol/L across treatment period from Day 28 until Day 168 will be analysed as mentioned in Section 5.1.2 for both ITT and PP population.

6. Time to T levels falling below castration level (<0.5 ng/mL [1.73 nmol/L]) for the first time. First time castrate serum level (<0.5 ng/mL [1.73 nmol/L]) will be defined as the analysis event. Analysis will be done from Day 1 to the end of the study.
   The following censoring rules will be used for this analysis:
   - Patients who did not achieve castrate serum T levels with central lab during the study period will be censored at their last serum T level assessment.
   - Patients who leave the trial without achieving castrate serum T levels will be censored at their last serum T level assessment.

7. Time to (first) overstep of T castration level after achieving castration will be analysed using the Kaplan-Meier method.
   First time overstep of T castration level will be defined as the analysis event. Analysis will be done from the day of achieving castration T level to the end of the study. Only patients who achieved castration serum T levels will be analysed for both ITT and PP Population. Day of achieving castration T level will be defined as Day 1 for this analysis.
   The following censoring rules will be used for this analysis:
   - Patients with stable T level will be censored at their last available measure.
   - Patients who fail to maintain castration T level will be censored at the day of failure.
   - Patients who leave the trial for reasons other than a non-castrate serum T level will be censored at their last serum T level assessment.

   Note: Overstep of T castration level is defined as the first instance of T levels being above castration level after a patient has achieved castration.

8. Time for serum T levels to be > 0.5 ng/mL after final, Day 168 injection will be analysed using the Kaplan-Meier method.
   First time noncastrate serum T levels will be defined as the analysis event. Analysis will be done from Day 168 to the end of the observation. Only patients with castrate serum T levels at Day 168 will be analysed for both ITT and PP Population.
   The following censoring rules will be used for this analysis:
   - Patients who achieve and maintain castrate serum T levels with central lab from Day 168 through the end of the study period will be censored at their last serum T level assessment.
   - Patients who leave the trial for reasons other than a non-castrate serum T level will be censored at their last serum T level assessment.

9. Proportion of participants achieving castration level for LH (LH <1.1 U/L) at Day 28 Descriptive statistics with proportion, will be analysed as mentioned in Section 5.1.2 for both ITT and PP population.

10. Proportion of participants with effective LH castration level across treatment period from Day 28 until Day 168. Descriptive statistics with proportion, will be analysed as mentioned in Section 5.1.2 for both ITT and PP population.

11. Time to LH levels falling below castration level (LH <1.1 U/L) for the first time will be analysed using the Kaplan-Meier method.
    First time LH levels falling below castration level (LH <1.1 U/L) will be defined as the analysis event. Analysis will be done from Day 1 to the end of the study.
    The following censoring rules will be used for this analysis:
    - Patients who did not achieve castration LH level during the study period will be censored at their last LH level assessment.
    - Patients who leave the trial without achieving castration LH level will be censored at their last LH level assessment.

12. Time to (first) overstep of LH castration level after achieving castration will be analysed using the Kaplan-Meier method. First time overstep of LH castration level will be defined as the analysis event. Analysis will be done from day of achivieng castration LH level to the end of the study. Only patients who achieved castration LH level will be analysed for both ITT and PP Population. Day of achiving castration LH level will be defined as Day 1 for this analysis.
    The following censoring rules will be used for this analysis:
    - Patients with stable LH level will be censored at their last available measure.
    - Patients who leave the trial for reasons other than a non-castrate serum T level will be censored at their last LH assessment.

13. Changes from baseline in PD parameters over time will be analysed as mentioned in Section 5.1.2 for both ITT and PP Population.

14. Confirmed PSA Response Rate will be analysed as mentioned Section 5.1.2 for both ITT and PP Population
    Note: Confirmed PSA Response rate is defined as patients who have a > 50% reduction at day 14 followed with confirmation at day 28

15. PSA Response Rate at day 28 will be analysed as mentioned Section 5.1.2 for both ITT and PP Population

16. Number of participants with a PSA response of ≥50% reduction at the Day 168 visit will be analysed as mentioned in Section 5.1.2 both ITT and PP Population.

17. Number of participants with PSA response of ≥80% reduction at the Day 168 visit will be analysed as mentioned in Section 5.1.2 for both ITT and PP Population.

18. Percent change from baseline in serum PSA concentration at each visit will be analysed as mentioned Section 5.1.2 for both ITT and PP Population.

19. Mean serum PSA concentration at each visit will be analysed as mentioned Section 5.1.2 for both ITT and PP Population.

20. PSA Levels at each visit will be analysed as mentioned Section 5.1.2 for both ITT and PP Population

21. Mean nadir PSA up to Day 168. To analyse this, for each subject the lowest PSA result will be taken from all collected PSA data up to Day 168 and the descriptive statistic of the lowest PSA level recorded during that time will be presented for both ITT and PP Population.

22. Time to nadir PSA level will be analysed as mentioned Section 5.1.2 for both ITT and PP Population.

23. Percent change from baseline in Serum LH concentration at each visit will be analysed as mentioned Section 5.1.2 for both ITT and PP Population

24. Mean serum LH concentration at each visit will be analysed as mentioned Section 5.1.2 for both ITT and PP Population.

25. LH Levels at each visit will be analysed as mentioned Section 5.1.2 for both ITT and PP Population.

26. Mean serum T concentration at each visit will be analysed as mentioned Section 5.1.2 for both ITT and PP Population.

27. Percent change from baseline in Serum FSH concentration at each visit will be analysed as mentioned Section 5.1.2 for both ITT and PP Population

28. Mean serum FSH concentration at each visit will be analysed as mentioned Section 5.1.2 for both ITT and PP Population.

29. FSH Levels at each visit will be analysed as mentioned Section 5.1.2 for both ITT and PP Population.

6.8.3 Supplementary FDA Recommended Efficacy Analyses

Supplementary analysis will be conducted utilizing the Kaplan-Meier technique to estimate the proportion of patients who achieve and maintain castrate T levels (<0.5 ng/mL or 1.73 nmol/L) from Day 28 through the end of the treatment period using the ITT population.

Treatment failure [non-castrate serum T levels (≥0.5 ng/mL or 1.73 nmol/L) with central lab] will be defined as the analysis event.

The following patients will be considered as experiencing an event

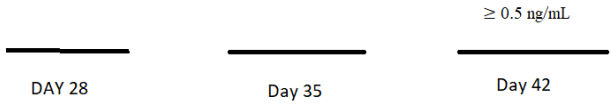
1. Patients who did not achieve castrate serum T levels (<0.5 ng/mL or 1.73 nmol/L) by Day 28. Day 28 will be considered as the day of event.
2. Patients who successfully achieve a castrate serum T level by Day 28 but fail to maintain it throughout the treatment period. Day of failure (day of sampling) will be considered as the day of event.

The following patients will not be considered as having experienced an event:

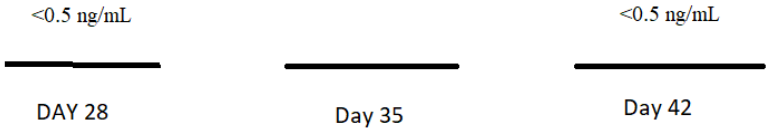
1 Patients who achieve and maintain castrate serum T levels with central lab from Day 28 through the end of the treatment period.
2 Patients who leave the trial for reasons other than a non-castrate serum T levels.

Censoring and handling of missing data rules will be used for this analysis:

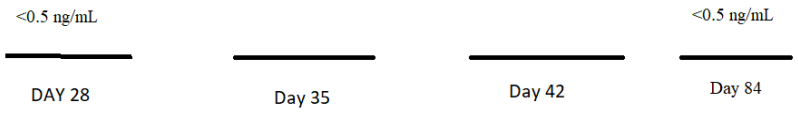
1. Patients who achieve and maintain castrate serum T levels with central lab from Day 28 through the end of the treatment period will be censored at their last serum T level assessment.
2. Patients who leave the trial for reasons other than a non-castrate serum T level will be censored at their last serum T level assessment.
3. Patients with one or more consecutive missing serum T levels and a non-castrate serum T level after the missing time point(s) will be considered to have had an event (treatment failure) at the first missing time point. For example: if the subject's data is missing for Days 28 and 35 and having a non - castrate T levels (≥ 0.5 ng/mL) on Day 42 we should consider that the subjects had an event on day 28.



4. Patients with castrate serum T levels immediately before and after a single missing serum T level will not be considered to have had an event (treatment failure) at the missing time point. For example: if the subjects have castrate T levels (<0.5 ng/mL) for Days 28 and 42 but data on day 35 is missing will not be considered to have had an event on day 35.



5. Patients with two or more consecutive missing serum T levels and castrate serum T levels immediately before and after the missing time points will be censored at their last T level before the missing data. For example: if the subjects have missing castrate T levels (<0.5 ng/mL) for Days 35, 42 but have data on day 28 and 84 the data on Day 28 will be censored.



Time to event will be calculated as: **(*date of event - date of Day 28) + 1*.**

The presentation of the results will include the median by Kaplan-Meier function, 95% CI for Kaplan-Meier median and the Kaplan-Meier survival curve. The proportion of participants achieving castration level with serum T <0.5 ng/mL or 1.73 nmol/L across the treatment period from Day 28

to Day 168, along with Clopper-Pearson CI of the proportion will be presented for both ITT and PP Population at each assessment point.

Sensitivity Analyses on Supplementary FDA Recommended Efficacy Analyses

Two sensitivity analysis will be performed. In the first sensitivity analysis the definition of treatment failures will be expanded and include following patients as treatment failures (patients with event):

1. Patients who did not achieve castrate serum T levels (<0.5 ng/mL or 1.73 nmol/L) by Day 28.
2. Patients who successfully achieve a castrate serum T level by Day 28 but fail to maintain it throughout the treatment period.
3. All the patients who leave the trial will be considered to have had an event at their last serum T level assessment.
4. Patients with two or more consecutive missing T levels (regardless of T levels before and after those missing time points). They will be considered to have had an event at the first missing time point.

In the second sensitivity analysis the ITT population will be changed to the population of patients who have received any dose of IMP and have a non-missing central lab serum T record at Day 28 except for patients who received concomitant medications and herbal supplements that could possibly affect T levels.

6.9 Safety Analyses

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.

6.9.1 Exposure to Study Medication

Exposure to Study Medication will include derived continuous and categorical variables. Categorical variables will be summarised by absolute counts (n) and percentages (%). Percentages will be based on the number of subjects with data.

6.9.2 Adverse Events

All AEs will be coded by MedDRA terminology and summarised by preferred term (PT) and system organ class (SOC). Frequencies of AEs will be presented by absolute and relative frequencies to the number of participants experiencing an event and the number of events for each SOC and PT.

All AEs, serious AEs, TEAEs, serious TEAEs, treatment-related AEs will be summarised in a single output.

Separate summaries will be produced for serious AEs, TEAEs and treatment-related AEs (see Section 4.2.3 for treatment-related AE definition).

EuDRA CT serious AEs and EuDRA CT non-serious treatment-emergent AEs summaries will also be presented.

6.9.2.1 Injection Site Reactions

Pain, Tenderness, Erythema/Redness and Swelling and their grade will be summarised at each visit and overall, for Stage 1, Stage 2 and final assessments..

6.9.3 Clinical Laboratory Parameters

Clinical Laboratory Parameters include collected and derived quantitative and qualitative parameters. Parameters will be grouped by category (see Table 14 in Section 4.2.6). Qualitative parameters will be summarised by absolute counts (n) and percentages (%). Percentages will be based on the number of subjects with data.

Haematology and Biochemistry will have separate tables for Summary, Shift for normal ranges and shift for qualitative measures.

Urinalysis parameters will be summarised.

6.9.4 Electrocardiogram (ECG) Parameters

ECG Parameters include collected and derived quantitative and qualitative parameters. Qualitative parameters will be summarised by absolute counts (n) and percentages (%). Percentages will be based on the number of subjects with data.

The number and % of patients with markedly abnormal results will be presented for each visit. The Investigators overall assessment will be summarised as a categorical variable along with the shift from baseline in the investigator's overall assessment.

6.9.5 Vital Signs

Vital Signs include collected and derived continuous and categorical variables. Categorical variables will be summarised by absolute counts (n) and percentages (%). Percentages will be based on the number of subjects with data.

The results and changes from baseline for each vital signs parameter will be summarised at each visit.

The number and percentage of participants with markedly abnormal vital signs results at each visit will also be presented.

6.9.6 Physical Examination

Any physical examination findings will be listed. The number of participants with a physical examination finding will be summarized by absolute counts (n) and percentages (%) by visit. Percentages will be based on the number of participants with data.

6.9.7 Predictive Effect of Cardiac Biomarkers

It is planned that the biomarker parameters (N-terminal pro-B-type natriuretic peptide (NTproBNP), D-dimer, C-reactive protein (CRP), high-sensitivity troponin (hsTn)) will include collected and derived quantitative parameters only. The results, changes from the baseline, and percent change from the baseline for each biomarker parameter will be summarized at each visit.
If any qualitative parameters are collected, they will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of subjects with data.
All collected biomarker parameters will be listed.

7. Changes to the Planned Analyses

7.1 Changes to the Analyses Described in the Study Protocol and Protocol Amendments

Changes were made to the analysis defintions related to “Mean time to” events, which are now labelled as “Time to” events and will not contain the mean. This was changed due to the decision to use Kaplan-Meier methods of analyses for these, where the mean is not a suitable output in the presence of censoring.
After discussion with the FDA, a new Supplementary FDA Recommended Efficacy Analyses was added to the SAP.
The following analyses were also added:

PSA:

- PSA level at each visit
- Confirmed PSA Response Rate - defined as > 50% reduction in PSA from baseline at Day 14 followed with confirmation at Day 28
- PSA response rate at Day 28

FSH:

- FSH Level at each visit
- Percent Change From Baseline In Serum Concentrations Of FSH

LH:

- LH Level at each visit
- Percent Change From Baseline In Serum Concentrations Of Luteinizing Hormone

7.2 Changes from the Statistical Analysis Plan Version 1.0

No changes will be made to Version 1.0 of the SAP after database lock. Any changes to the planned analyses occurring after unblinding will be described and justified in the Clinical Study Report (CSR).

8. Attachments

Attachment 1 List of Tables, Listings and Figures

Please see Attachment 1: “ANT-1111-02 Output Shells Version 1.0.”

Attachment 2 Markedly Abnormal Laboratory Ranges

Please see Attachment 2: “Attachment 2 Markedly Abnormal Ranges AECTCAE Revised”.