Protocol Title:

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

Protocol Number: D-FR-52014-245

Compound: Triptorelin pamoate (embonate) salt (IPN52014)

Short Title: Effects of triptorelin when given every 6-months under the skin to adult males with cancer in the prostate

Study Phase: III

Sponsor Name: Ipsen Pharma SAS

Legal Registered Address:

Ipsen Pharma SAS
65, quai Georges Gorse
92100 Boulogne Billancourt, France

Regulatory Authority Identifier Number(s)

EudraCT: 2021-005719-29

Date: 04 December 2023
Version number: 3.0
Amendment Number: 2

Sponsor Signatory:

PPD

Date

Medical Monitor Name and Contact Information:

PPD

Ipsen Bioscience, Inc.
1 Main Street
Cambridge, Massachusetts 02142
United States
Email: PPD

Principal Investigator Signature Page

I have read and agree to Protocol D-FR-52014-245 entitled An open-label, multicentre, single arm study to assess the efficacy and safety of triptorelin 6-month formulation administered subcutaneously in participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue with Amendment 2. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: [ ]

TITLE: [PRINCIPAL] INVESTIGATOR SIGNATURE:

DATE:

OFFICE: [ ]
[ ]
[ ]
[ ]
[ ]

PROTOCOL AMENDMENT SUMMARY OF CHANGES

	DOCUMENT HISTORY		
Document	**Version**	**Date**	**Status**
Amendment 2	3.0	04 December 2023	Effective
Amendment 1	2.0	13 September 2022	Superseded
Original Protocol	1.0	16 March 2022	Superseded

The detail of Amendment 1 is provided in Appendix 10.6.

Amendment 2 (04 December 2023)

This amendment is considered to be non-substantial based on the criteria set forth in Directive 2001/20/EC because it neither significantly impacts the safety or rights of participants or on the reliability and robustness of the data generated in the clinical trial.

Overall Rationale for the Amendment:

Protocol updated to clarify study procedures, as well as the inclusion of minor additions/updates to comply with protocol template guidance.

Summary change table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikeout text (WAS column). Minor formatting and editing are not included.

Section	WAS (Version 2.0, 13 SEPTEMBER 2022)	IS (Version 3.0, 04 DECEMBER 2023)	Rationale
Sponsor Signatory	Sponsor Signatory: PPD Medical Monitor Name and Contact Information: PPD	Sponsor Signatory: PPD Medical Monitor Name and Contact Information: PPD	Change in sponsor personnel

Section	WAS (Version 2.0, 13 SEPTEMBER 2022)	IS (Version 3.0, 04 DECEMBER 2023)	Rationale
	PPD Ipsen Bioscience, Inc. 1 Main Street Cambridge, Massachusetts 02142 United States Email: PPD	PPD Ipsen Bioscience, Inc. 1 Main Street Cambridge, Massachusetts 02142 United States Email: PPD	
7.1.1 Temporary Discontinuation	In case of ~~suspected or confirmed COVID-19 (SARS-CoV-2) infection~~, the intervention administration may be temporarily postponed depending on the participant clinical presentation.	In case of **clinical study disruption due to a regional or national emergency declared by a government agency**, the intervention administration may be temporarily postponed depending on the participant clinical presentation.	Minor additions/updates to comply with protocol template guidance.
7.3 Lost to Follow-up	A participant will be considered lost to follow-up if ~~he~~ repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. (…) • Should the participant continue to be unreachable, ~~he will be considered to have withdrawn from the study~~. • Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not receive study intervention. ~~Public~~ sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.	A participant will be considered lost to follow-up if **the participant** repeatedly fails to return for scheduled visits and is unable to be contacted by the study site **until the end of the study**. (…) • Should the participant continue to be unreachable, **attempts to make contact should continue until study closure and participant might be confirmed as lost to follow up at the time of study closure**. • Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not receive study intervention. **All** sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be	Minor additions/updates to comply with protocol template guidance.

Section	WAS (Version 2.0, 13 SEPTEMBER 2022)	IS (Version 3.0, 04 DECEMBER 2023)	Rationale
		considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.	
Section 8 Study Assessments and Procedures	• ~~Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.~~	(…) **• In the event of a significant study-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.** (…)	Minor additions/updates to comply with protocol template guidance.
Section 8.4 Adverse Events and Serious Adverse Events and Other Safety Reporting	~~AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate).~~ The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs and SAEs during the study (see Section 7).	The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs and SAEs during the study (see Section 7). **This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative)**.	Minor additions/updates to comply with protocol template guidance.
Section 8.4.5 Pregnancy	(…) •If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form~~s (Pregnancy Notification Form – paper form)~~ and submit it to the sponsor within 24 hours via email of learning of the female partner of male participant becoming pregnant (after obtaining the necessary signed informed consent from the female partner).	(…) • If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours via email of learning of the female partner of male participant becoming pregnant (after obtaining the necessary signed informed consent from the female partner). **• While pregnancy itself is not considered to be and AE or SAE, a**ny pregnancy complication or elective termination of a	Minor additions/updates to comply with protocol template guidance.

Section	WAS (Version 2.0, 13 SEPTEMBER 2022)	IS (Version 3.0, 04 DECEMBER 2023)	Rationale
	• ~~A~~ny pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.	pregnancy for medical reasons will be reported as an AE or SAE.	
Section 8.4.8 Reporting of Study Intervention Errors Including Misuse/ abuse	• Study intervention errors and uses outside of what is foreseen in the protocol will be recorded in the eCRF irrespective of whether associated with an AE/SAE or not. ~~It will also be documented in the~~ AE section of the ~~eCRF if associated with an AE. It will be reported in the safety database only if associated with an SAE~~.	• Study intervention errors and uses outside of what is foreseen in the protocol, **such as misuse, abuse or overdose,** will be recorded **on** the **appropriate** eCRF **page** irrespective of whether associated with an AE/SAE or not, **within 24 hours of investigator or qualified designees' awareness**. **If an** AE/**SAE is associated with this study intervention error, it should be documented in the AE/SAE** section of the eCRF. **Please refer to Sections 6.7 and 10.3.1.**	Minor additions/updates to comply with protocol template guidance.
Section 10.1.5 Dissemination of Clinical Study Data	~~• The sponsor seeks to publish the results of its clinical trials in biomedical journals, whatever the outcome. Clinical trial results may also be presented at international congresses as posters or oral presentations.~~ • Protocol and result ~~summary~~ will be made publicly available on the United States ~~Clinical Trials Registry~~ (ClinicalTrials.gov) and for studies run in the EU/EEA on the EU Clinical Trials Register (www.clinicaltrialsregister.eu). The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation.	• Protocol **information** and **final study** result will be made publicly available on the United States **website** (ClinicalTrials.gov) and for studies run in the EU/EEA on the EU Clinical Trials Register (www.clinicaltrialsregister.eu) **or EU Clinical Trials Portal (https://euclinicaltrials.eu/home)**. The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation. **• A lay language protocol synopsis and a summary of the study will be made available on the EU Clinical Trials Portal (https://euclinicaltrials.eu/home) and/or Sponsor website.**	Minor additions/updates to comply with protocol template guidance.

Section	WAS (Version 2.0, 13 SEPTEMBER 2022)	IS (Version 3.0, 04 DECEMBER 2023)	Rationale
Section 10.1.9 Publication Policy	• The results of this study may be published or presented at scientific meetings. If this is foreseen, ~~t~~he investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.	**• The sponsor seeks to publish the results of these clinical trials in biomedical journals, whatever the outcome. Clinical trial results may also be presented at international congresses as posters or oral presentations.** • The results of this study may be published or presented at scientific meetings. If this is foreseen, **the investigator should discuss specific publication concepts, including data to be covered, target congress/journal and proposed authors, with the sponsor for agreement before initiation. T**he investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.	Minor additions/updates to comply with protocol template guidance.
Section 10.3.2 Definition of SAEs	e. Is a congenital ~~anomaly~~/birth defect f. Other situations: Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias,	e. Is a congenital **abnormality**/birth defect f. Other situations: Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias,	Deletion of the statement about the seriousness assessment of COVID-19 adverse events. This means that COVID-19 is no longer to be reported as a serious adverse event unless the occurrence of COVID-19 meets the defined seriousness criteria.

Section	WAS (Version 2.0, 13 SEPTEMBER 2022)	IS (Version 3.0, 04 DECEMBER 2023)	Rationale
	convulsions or development of intervention dependency or intervention abuse. ~~A suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection must be reported as serious (seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation).~~	convulsions or development of intervention dependency or intervention abuse.	
Section 10.3.4 Reporting of SAEs	• The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool. (…) • ~~Contacts for~~ SAE ~~reporting can~~ be ~~found on the SAE form and the cover sheet~~. SAE Reporting to the sponsor via paper • ~~Contacts for~~ SAE ~~reporting can~~ be ~~found on the SAE form and the cover sheet~~.	• The primary mechanism for reporting an SAE **in English language** to the sponsor will be the electronic data collection tool. (…) • SAE report **should** be sent to adverse.events@ipsen.com. SAE Reporting to sponsor via paper **data collection tool** • SAE report **should** be sent to adverse.events@ipsen.com.	Minor additions/updates to comply with protocol template guidance.
Section 10.5.1.7 Adverse Event Reporting	~~As per the protocol (Appendix 10.3.2),~~ ~~a~~ll COVID-19 cases (suspected or confirmed) should be ~~considered as SAEs~~. "~~Other medically significant" should be selected as seriousness criterium if no other seriousness criteria are present (e.g. hospitalisation).~~ Details can be collected by site staff via telephone call as per the rules relating to use of telemedicine in the protocol (Appendix 10.5.2).	**A**ll COVID-19 cases (suspected or confirmed) should be **seriousness assessed based on the reported seriousness criteria. If no seriousness criteria is reported by the investigator, the COVID-19 event/case will be collected and recorded as nonserious**. Details can be collected by site staff via telephone call as per the rules relating to use of telemedicine in the protocol (Appendix 10.5.2).	Amended for consistency with Section 10.3.2.

Section	WAS (Version 2.0, 13 SEPTEMBER 2022)	IS (Version 3.0, 04 DECEMBER 2023)	Rationale
Section 10.5.2 Specific Rules Related to Use of Telemedicine	~~Note that further information about measures adopted for the COVID-19 situation to cover SAE reporting and temporary discontinuations are found in Sections 10.3.4 and 7.1.1, respectively.~~		Amended for consistency with Sections 10.3.2 and 10.5.1.7.

Other documents impacted:

Informed consent form	Yes ☐	No ☒
Case report form (CRF)	Yes ☐	No ☒
Statistical analysis plan (SAP)	Yes ☐	No ☒

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LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
AE	Adverse event
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EoS	End of study
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICF	Informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LH	Luteinizing hormone
LHRH	Luteinizing hormone releasing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI-CTC	National Cancer Institute – Common Toxicity Criteria
PP	Per protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SoA	Schedule of activities
TEAE	Treatment emergent adverse event

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Short Title: Effects of triptorelin when given every 6-months under the skin to adult males with cancer in the prostate

Rationale:

Triptorelin is an agonist analogue of natural gonadotropin-releasing hormone (GnRH). The principal modification consists of substitution of natural glycine in position 6 by a D-amino acid (D-tryptophan) leading to improved receptor binding affinity and a longer activity time. The GnRH analogues, of which triptorelin belongs to, are used in the treatment of prostate cancer. Triptorelin is available on the market for more than 30 years under different formulations: 1-month, 3-months and 6-months. Clinical studies have shown that triptorelin 6-month formulation (22.5 mg) administered intramuscularly rapidly induces and maintains castration in patients with locally advanced or metastatic prostate cancer [Lundström 2009, Breul 2017]. Since 2009, different authorities, including those in Europe, have approved the aforementioned formulation and route of administration which is currently prescribed by many physicians for the treatment of advanced prostate cancer. Although intramuscular injection is mostly used, physicians prefer subcutaneous administration, as this method has less theoretical interactions with some medications patients may take for cardiovascular morbidities. Considering the patient age (elderly), as well as their body mass index (obese versus frail) and co-morbidities (requiring some to take concomitant medications (e.g. oral anticoagulants)), the subcutaneous administration of any injectable is considered more convenient for the patient. Positive outcomes from a previous clinical study performed with the triptorelin 3-month formulation manufactured by Ipsen (already marketed for intramuscular administration) and administered subcutaneously [Lebret 2015] has led to the registration and commercialisation of this new route of administration in Europe and worldwide.

The present study will assess the efficacy and safety of the 6-month triptorelin formulation (22.5 mg) administered subcutaneously (twice a year) in participants with locally advanced and/or metastatic prostate cancer previously treated and castrated by a GnRH analogue.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously in maintaining serum testosterone castrate levels in participants with advanced prostate cancer previously treated and castrated with a GnRH analogue.	• Percentage of participants maintaining castrate levels of serum testosterone during the study (maintenance of castration defined as testosterone <1.735 nmol/L (50 ng/dL) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337)
Secondary	
• To evaluate the efficacy of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously on castration	• Percentage of participants castrated at each timepoint on Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337, (castration defined as testosterone <1.735 nmol/L (50 ng/dL)
• To evaluate the efficacy of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously on testosterone levels <0.694 nmol/L (20 ng/dL)	• Percentage of participants with a serum testosterone level <0.694 nmol/L (20 ng/dL) during the study • Percentage of participants with a serum testosterone level <0.694 nmol/L (20 ng/dL) at each timepoint on Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337
• To demonstrate the effect of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously to suppress the 'acute-on-chronic' effect following the administration of the second dose	• Percentage of participants castrated, on Day 3 and Day 7 after each injection administered on Day 1 and Day 169 (castration defined as testosterone <1.735 nmol/L (50 ng/dL))
• To demonstrate the effect of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously in the maintenance of PSA	• Percent change in PSA from baseline (prior to injection) at Day 169 and Day 337 (Percent change in PSA defined as the absolute value of difference between the PSA values at Day 169 and Day 337 and the baseline value divided by the baseline value)
• To demonstrate the safety profile of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously	• Incidence of TEAEs (including local tolerability) throughout the study i.e. up to Day 337 • Change from baseline in clinical safety laboratory parameters (blood chemistry and haematology) at Day 337 • Change from baseline in physical examination at Day 169 and Day 337 • Change from baseline in ECG at Day 337 • Change from baseline in vital signs (blood pressure and heart rate) at each visit up to Day 337

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

The primary estimand for the primary endpoint is described below. The treatment will be triptorelin 6-month formulation administered subcutaneously. The population will comprise participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue as specified in the inclusion and exclusion criteria (Sections 5.1 and 5.2), respectively, that have received two scheduled treatment intervention doses (i.e. Day 1 and Day 169) and have completed all visits for measurement of testosterone.

The variable for the primary estimand will be castration maintenance rate during the study, which is defined as percentage of participants castrated (testosterone <1.735 nmol/L (50 ng/dL)) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337, with two complete study intervention administrations. Secondary estimands include analyses without using the visit window and/or using the ITT population where missing data will be considered a non-responder maybe conducted. Further details of the estimand will be specified in the statistical analysis plan (SAP).

Overall Design:

This is a phase III, multicentre, open-label, non-comparative, repeated dose study to evaluate the efficacy and safety of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously in participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue. Approximately 145 adult male participants will be enrolled in the study. All enrolled participants will receive a subcutaneous injection of triptorelin embonate 22.5 mg 6-month formulation on Day 1 and Day 169.

Note: participants must receive study intervention on Day 1 in accordance with the treatment schedule of their previously received GnRH analogue therapy.

Intervention Groups and Duration:

Triptorelin embonate 22.5 mg (6-month formulation), subcutaneous injection on Day 1 and Day 169.

Visit Frequency:

The study will consist of a Screening period (up to 28 days before enrolment), first open-label injection of the study intervention on Day 1. Following the first treatment, visits will occur on Day 3, Day 7, Day 29, Day 85, Day 141, Day 169 (second injection), Day 171, Day 175, Day 253, Day 309 and Day 337 for efficacy and safety assessments. (Note: if necessary, participants can request home visits, except for visits where study intervention is to be administered).

Participants will receive two injections of triptorelin embonate 22.5 mg (6-month formulation) during the study period before they attend the end of study (EoS) visit on Day 337.

Study Participant Duration:

Participants are expected to participate in this study for 52 weeks, including up to 4 weeks for screening.

Number of Participants:

Approximately 145 participants are planned to be assigned to study intervention.

Statistical Methods:

Sample Size Determination

This single-arm study is designed to demonstrate that the percentage of participants remaining castrated (maintenance of castration defined as testosterone <1.735 nmol/L (50 ng/dL) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337) during the study is greater than 90%. Considering an observed castration maintenance in 97% of participants, 130 eligible

participants are required to demonstrate the efficacy of the triptorelin 6-month formulation with approximately 90% power and a one-sided alpha of 0.025 using an exact binomial test. The objective will be achieved if the lower bound of the 95% confidence interval (CI) of the observed rate is greater than 90%.

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

Efficacy Analyses

Due to the single-arm nature of the study, all statistical analyses will be descriptive with quantitative data summarised as mean, standard deviation (SD), median, quartiles, 95% CIs and range. Qualitative data will be summarised as frequency counts and percentages. The 95% CIs will be calculated following the Clopper-Pearson method. The descriptive statistics of treatment effects and corresponding 95% CIs for the primary endpoint and secondary endpoints will be presented.

Missing castration level data during the study will be imputed by multiple imputation. Further details of the efficacy analyses will be specified in the SAP.

Safety Analyses

All adverse events, treatment-emergent adverse events and serious adverse events will be summarised and tabulated by system organ class and preferred term, including severity and relationship to test product.

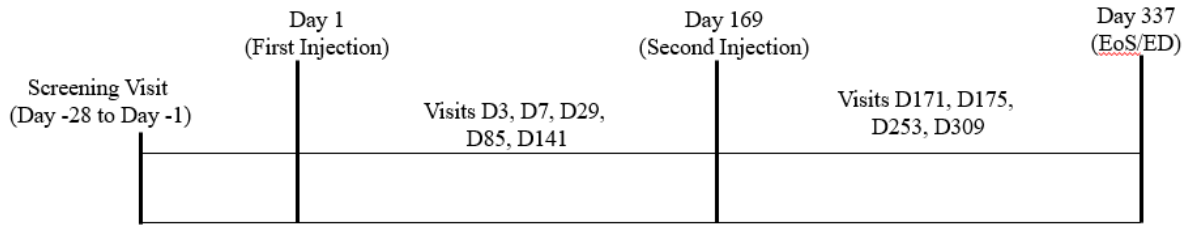
Values of laboratory parameters and vital signs at baseline, on treatment and the change from baseline to on-treatment levels will be described.

The Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0 or higher) classification will be used to classify adverse events (AEs) and laboratory abnormalities. The CTCAE grade by participant will be tabulated and listed.

1.2 Schema

The study schema is shown in Figure 1.

Figure 1 Study Schema



D=day; ED=early discontinuation; EoS=end of study
Participants will receive a subcutaneous injection of triptorelin embonate 22.5 mg (6-month formulation) on Day 1 and Day 169.

1.3 Schedule of Activities

Study assessments to be performed are outlined in Table 1. If the Coronavirus Disease 2019 (COVID-19) pandemic prevents participants from coming to the site, participants can have their study visit assessments performed remotely as judged appropriate by the investigator. This must be discussed with the sponsor before being implemented. In such a case, the investigator will perform a telemedicine visit and will make every effort, where applicable, to contact the participant's general practitioner or specialist physician to ensure all important medical

information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol-planned assessments is provided in Appendix 10.5. Such document will be filed in the trial master file.

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before Day 1)	Intervention Period											EoS/ ED	Section for further details
End of week	-	-	Week 1	Week 1	Week 4	Week 12	Week 20	Week 24	Week 25	Week 25	Week 36	Week 44	Week 48	
Day [a]	Day -28 to Day -1	Day 1	Day 3	Day 7	Day 29	Day 85	Day 141	Day 169	Day 171	Day 175	Day 253	Day 309	Day 337	
Visit window			Day 3 after first inj	Day 7 after first inj	±3 days	±3 days	±3 days	±3 days	Day 3 after last inj	Day 7 after last inj	±3 days	±3 days	±3 days	
Informed consent	X													10.1.3
Inclusion and exclusion criteria	X													5.1 & 5.2
Demography	X													
Full physical examination including body weight	X [b]	X						X					X	8.3.1
Medical and surgical history	X													
Prior disease-specific treatment	X													
Electrocardiogram [c]	X												X	8.3.3
Vital signs	X	X			X	X	X	X			X	X	X	8.3.2
Imaging scan [e]	X													8.3.4
ECOG score	X												X	10.4
Injection triptorelin 6M		X						X						6.1
Blood samples for testosterone	X [d]	X [d]	X	X	X	X	X	X [d]	X	X	X	X	X	8.2
Blood samples for PSA		X						X					X	8.2
Blood samples for laboratory safety tests [f]	X												X	8.3.5
Local tolerance [g]		X						X						8.3.6

Procedure	Screening (up to 28 days before Day 1)	Intervention Period											EoS/ ED	Section for further details
End of week	-	-	Week 1	Week 1	Week 4	Week 12	Week 20	Week 24	Week 25	Week 25	Week 36	Week 44	Week 48	
Day [a]	Day -28 to Day -1	Day 1	Day 3	Day 7	Day 29	Day 85	Day 141	Day 169	Day 171	Day 175	Day 253	Day 309	Day 337	
Visit window			Day 3 after first inj	Day 7 after first inj	±3 days	±3 days	±3 days	±3 days	Day 3 after last inj	Day 7 after last inj	±3 days	±3 days	±3 days	
Previous (excluding disease-specific) and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	6.8
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	8.4

Abbreviations: 6M=6-month formulation; AE=adverse event; ALT=alanine aminotransaminase; AST=aspartate aminotransaminase; eCRF=electronic case report form; ECG=electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EoS=end of study; Hb=haemoglobin, inj=injection; M=month; PSA=prostate-specific antigen WBC=white blood cell

a If necessary, participants can request home visits, except for visits where study intervention is to be administered.
b Height to be collected at screening only.
c ECG to be assessed as clinically indicated at any other time during the study as required.
d All testosterone assessments to be performed using the central laboratory, except at screening. At screening, testosterone to be assessed up to 7 days prior to Day 1 using the local laboratory. On Day 1 and Day 169, samples for testosterone to be collected pre-dose.
e An imaging scan is not required if performed within 6 months of study screening.
f Haematology (WBC and differential count, platelet count, Hb), blood chemistry (creatinine, glucose, ALT, AST, alkaline phosphatase, total and conjugated bilirubin). Glucose: Non-fasting levels in all participants.
g Injection site to be specifically checked for local site injection reactions 2 hours after study intervention administration. Any local reaction AEs will be collected on the eCRF.

2 INTRODUCTION

Triptorelin is an agonist analogue of natural GnRH. The principal modification consists of substitution of natural glycine in position 6 by a D-amino acid (D-tryptophan). Clinical and animal studies have provided positive results of triptorelin's action in hormone-dependent disorders such as prostate cancer, endometriosis, central precocious puberty, uterine fibromyomas, in vitro fertilisation and breast cancer.

2.1 Study Rationale

Clinical studies have shown the triptorelin embonate 22.5 mg 6-month formulation rapidly induces and maintains castration in patients with locally advanced or metastatic prostate cancer [Lundström 2009, Breul 2017]. The marketing-approved and recommended route of administration of triptorelin 6-month formulation is intramuscular injection in patients with prostate cancer. Although intramuscular injection of triptorelin sustained-release 6-month formulation offers the advantage of reduced frequency of injection and a lower rate of injection site reactions [Lundström 2009], both patients and doctors find a subcutaneous route of administration more convenient. In addition, some patients, such as those receiving anticoagulants, are more at risk of haematomas or excessive bleeding with an intramuscular route compared with a subcutaneous one [Bithell 1993]. Positive outcomes from a previous clinical study performed with the triptorelin 3-month formulation manufactured by Ipsen (already marketed for intramuscular administration) administered subcutaneously [Lebret 2015] has led to the registration and commercialisation of this new route of administration in Europe and worldwide.

The present study will assess the efficacy and safety, including local tolerability, of repeat treatment with the 6-month formulation of triptorelin embonate 22.5 mg administered subcutaneously in participants with locally advanced and/or metastatic prostate cancer previously treated and castrated by a GnRH analogue.

2.2 Background

Prostate cancer is the second most common cancer in the male population and thus the sixth cause of death from cancer in men over 50 in the western world [Sung 2021]. Prostate cancer is androgen dependent, with most patients initially responding to androgen deprivation therapy (ADT). However, after 1 to 2 years of treatment, advanced prostate cancer eventually progresses to castration resistant prostate cancer.

Androgen receptor signalling plays an important role in the development of prostate cancer. Gonadotropin-releasing hormone, also known as luteinizing hormone releasing hormone (LHRH) is released in a pulsatile manner by the hypothalamus and stimulates the pituitary to release in pulses the gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH stimulates the production of testosterone by the testis; however, approximately 5% of circulating testosterone is independently produced by the adrenal glands. FSH plays a role in the regulation of spermatogenesis.

Since the pioneering studies of Huggins and Hodges [1941, 1941a] in the 1940's about the role played by the testicular androgen development and progression of prostate cancer cells, the mainstay of treatment for advanced prostate cancer has been androgen deprivation by bilateral orchiectomy and/or oestrogen therapy. The limitations of these therapeutic modalities led to the development of GnRH analogues, which have made pharmacological castration the preferred option among many patients with metastatic disease [Filicori 1994].

The therapeutic activity of the GnRH agonists is achieved via pituitary down-regulation of their own receptors achieved by continuous and chronic administration, providing almost complete suppression of LH and FSH secretion leading to suppression of testicular function.

Subcutaneous injection of triptorelin 11.25 mg (3-month formulation) has been evaluated in an open-label, single-arm study where treatment was administered twice over a 6-month period [Lebret 2015]. Results showed subcutaneous injection of triptorelin was well tolerated and maintained castration for up to 6 months, similarly, to results from studies with triptorelin administered intramuscularly. Furthermore, results from a clinical study with triptorelin embonate 22.5 mg (6-month formulation) administered twice subcutaneously over a 1-year period in participants with advanced prostate cancer who were non-castrated, showed induction and maintenance of castration (i.e. serum testosterone <1.735 nmol/L) in the majority of participants (82.6%) (data on file). Subcutaneous injection of triptorelin 22.5 mg was also well tolerated, with mild to moderate injection site AEs reported in 5.0% of participants.

A more detailed description of the product, including further details on administration procedures and dosage are provided in Section 6.

2.3 Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and expected adverse events (AEs) of triptorelin may be found in the approved Summary of Product Characteristics.

2.3.1 Risk Assessment

A risk assessment for this study is provided in Table 2.

Table 2 Study Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Triptorelin		
There is no major known nonclinical risk associated with the study intervention Clinical risks associated with the study intervention may include: • hot flushes • erectile dysfunction • loss of libido • impaired physical activities • metabolic syndrome • cardiovascular events • anxiety/depression • decreased bone mineral density • risk of abortion or foetal abnormality [a] For a full list of adverse events and safety concerns with the product, please refer to the locally approved SmPC	See approved SmPC	**Participant selection:** Participants with significant medical conditions will be excluded from the study (see Section 5.1 and 5.2). **Participant monitoring:** During the study, there will be close monitoring of the participants for safety including local tolerability (see Section 8.3.6) **Withdrawal criteria:** Participants who become at risk due to any AE or medical condition will be withdrawn from the study intervention.
Study Procedures		
There are no specific risks related to the study design or procedures.	All procedures requested for the study are commonly used in clinical practice and the design does not create any specific risk or delay possible therapeutic option for participants	Not applicable

Abbreviations: SmPC=Summary of Product Characteristics
a Pregnancy is highly unlikely in this study population. However, reproductive risks are listed for completeness for female partners of participants who may become pregnant.

2.3.2 Benefit Assessment

To date the triptorelin 6-month formulation given intramuscularly has already proven its efficacy and safety leading to the registration and commercialisation in Europe and worldwide. Based on existing data from previous clinical studies with triptorelin embonate 22.5 mg (6-month formulation) as a subcutaneous injection and the triptorelin 3-month formulation (from intramuscular to subcutaneous) as presented in Section 2.2, it is expected that efficacy will be maintained (i.e. maintenance of castration) while demonstrating the same safety profile as the other triptorelin formulations.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants, the potential risks identified in association with the administration of the triptorelin 6-month formulation during the study are justified by the anticipated benefits to patients with prostate cancer.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously in maintaining serum testosterone castrate levels in participants with advanced prostate cancer previously treated and castrated with a GnRH analogue	• Percentage of participants maintaining castrate levels of serum testosterone during the study (maintenance of castration defined as testosterone <1.735 nmol/L (50 ng/dL) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337)
Secondary	
• To evaluate the efficacy of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously on castration	• Percentage of participants castrated at each timepoint on Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337 (castration defined as testosterone <1.735 nmol/L (50 ng/dL))
• To evaluate the efficacy of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously on testosterone levels <0.694 nmol/L (20 ng/dL)	• Percentage of participants with a serum testosterone level <0.694 nmol/L (20 ng/dL) during the study • Percentage of participants with a serum testosterone level <0.69 nmol/L (20 ng/dL) at each timepoint on Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337
• To demonstrate the effect of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously to suppress the 'acute-on-chronic' effect following the administration of the second dose	• Percentage of participants castrated on Day 3 and Day 7 after each injection administered on Day 1 and Day 169 (castration defined as testosterone <1.735 nmol/L (50 ng/dL))
• To demonstrate the effect of triptorelin embonate 22.5 mg 6-month formulation administered subcutaneously in the maintenance of PSA	• Percent change in PSA from baseline (prior to injection) at Day 169 and Day 337 (Percent change in PSA defined as the absolute value of difference between the PSA values at Day 169 and Day 337 and the baseline value divided by the baseline value)
• To demonstrate the safety profile of triptorelin embonate 22.5mg 6-month formulation administered subcutaneously	• Incidence of TEAEs (including local tolerability) throughout the study i.e. up to Day 337 • Change from baseline in clinical safety laboratory parameters (blood chemistry and haematology) at Day 337 • Change from baseline in physical examination at Day 169 and Day 337 • Change from baseline in ECG at Day 337 • Change from baseline in vital signs (blood pressure and heart rate) at each visit up to Day 337

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

The primary estimand for the primary endpoint is described below. The treatment will be triptorelin 6-month formulation administered subcutaneously. The population will comprise

participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue as specified in the inclusion and exclusion criteria (Sections 5.1 and 5.2), respectively, that have received two scheduled treatment intervention doses (i.e. Day 1 and Day 169) and have completed all visits for measurement of testosterone.

The variable for the primary estimand will be castration maintenance rate during the study, which is defined as percentage of participants castrated (testosterone <1.735 nmol/L (50 ng/dL)) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337, with two complete study intervention administrations. Secondary estimands include analyses without using the visit window and/or using the ITT population where missing data will be considered a non-responder maybe conducted. Further details of the estimand will be specified in the SAP.

4 STUDY DESIGN

4.1 Overall Design

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

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

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

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

The study design is illustrated in Figure 1.

4.2 Scientific Rationale for Study Design

This phase III, single-arm, open-label study will investigate the efficacy and safety of triptorelin 6-month formulation administered subcutaneously in participants with prostate cancer previously treated and castrated with a GnRH analogue.

The non-comparative, open-label clinical study design is acceptable as the primary endpoint will assess testosterone levels by the percentage of participants maintaining castrate levels of serum testosterone (defined as <1.735 nmol/L (50 ng/dL)) during the study (primary endpoint, as outlined in Table 3).

Assessment of testosterone is a well-established and a widely used efficacy parameter in studies investigating hormone deprivation therapies in patients with prostate cancer. Demonstration of testosterone castration <1.735 nmol/L (50 ng/dL) as an endpoint is also compliant with the European Medicines Agency (EMA) and European Association of Urology guidelines [Mottet 2021].

Some patients with prostate cancer, particularly those who are elderly and/or receiving anticoagulants, are at a higher risk of developing haematomas or excessive bleeding following intramuscular injection (see Summary of Product Characteristics). Thus, subcutaneous injection may be a better option.

As presented in Section 2.2, a clinical study was conducted with triptorelin embonate 22.5 mg (6-month formulation) administered subcutaneously in participants with advanced prostate cancer who were non-castrated. However, the primary endpoint regarding the maintenance rate of castration was not met, as maintenance of castration was not observed after the first injection in some participants but maintained for all participants after the second injection. The present study aims to assess whether castration maintenance is achieved via subcutaneous administration in participants already castrated at the beginning of the study. Thus, the outcomes of this study intend to fulfil an unmet need and improve treatment convenience.

4.3 Justification for Dose

For this intervention, the term "dose" refers to the subcutaneous injection of triptorelin embonate 22.5 mg (6-month formulation). Triptorelin embonate 22.5 mg is a sustained release formulation designed to deliver 22.5 mg of the active moiety over 6 months. In addition, results from clinical studies have shown the efficacy of 3-month (triptorelin 11.25 mg) formulation and 6-month formulation (22.5 mg) administered subcutaneously to induce and maintain castration in participants with locally advanced or metastatic hormone sensitive prostate cancer, as well as demonstrate a good safety profile (see Section 2.2).

4.4 End of Study Definition

The end of the study (EoS)/early discontinuation is defined as the date of the last visit of the last participant as shown in the SoA (Table 1).

A participant is considered to have completed the study if they have completed all phases of the study including the last visit.

Criteria for study intervention discontinuation and participant discontinuation/withdrawal from the study are described in Section 7.1 and Section 7.2, respectively. Loss to follow-up is described in Section 7.3.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

(1) Participant is male and must be 18 years of age inclusive, at the time of signing the informed consent.

(2) Participant has histologically or cytologically proven prostate cancer with rising PSA after failed local therapy or metastatic disease, or requiring radiotherapy, and be a candidate for long-term (i.e. >1 year) androgen deprivation therapy.

(3) Participant requires a GnRH analogue treatment for a minimum of 18 months, of which a minimum of 3 months of GnRH analogue treatment has already been provided prior to screening. (Note: participants must receive study intervention on Day 1 in accordance with the treatment schedule of their previously received GnRH analogue therapy).

(4) Has serum testosterone levels <1.735 nmol/L (50 ng/dL) at screening.

(5) Has Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1 (see Appendix 10.4).

(6) Has a life expectancy of >18 months.

(7) Male participants must agree that, if their partner is at risk of becoming pregnant (although highly unlikely in this study population), they will use an effective method of contraception. The participant must agree to use the contraception during the whole of the study and for 9 months after the last dose of study intervention.

(8) Capable of giving signed informed consent as described in Appendix 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

(1) Presence of another neoplastic lesion or brain metastases.

(2) Metastatic hormone-sensitive prostate cancer with high tumour burden

(3) Metastatic castration-resistant prostate cancer

(4) Any concomitant disorder or resulting therapy that is likely to interfere with participant compliance or with the study in the opinion of the investigator.

Prior/concomitant therapy

(5) Use of finasteride (Proscar®) or dutasteride (Avodart®/Avolve®) within the past 6 months

(6) Planned intermittent scheme of GnRH analogue

(7) At the time of screening, planned use of any chemotherapy for prostate cancer during the study

(8) Prior hypophysectomy or adrenalectomy

Prior/concurrent clinical study experience

(9) Participation in another study with an experimental drug within 3 months before signing informed consent or within five half-lives of the investigational drug (whichever was the longer), or any other type of medical research.

Diagnostic assessments

(10) Severe kidney or liver failure (creatinine >2 times the normal range, aspartate aminotransferase and alanine aminotransferase >3 times the normal range)

Other exclusions

(11) Any concomitant disorder or resulting therapy that is likely to interfere with participant's compliance, the subcutaneous administration of the drug or with the study in the opinion of the investigator.

(12) Previous history of QT prolongation or concomitant use of medicinal products known to prolong the QT interval or with a known risk of torsades de pointes

(13) Known hypersensitivity to triptorelin or any of its excipients, GnRH, other GnRH agonist/analogues.

(14) Known active use of recreational drug or alcohol dependence in the opinion of the investigator

(15) Inability to give informed consent or to comply fully with the protocol.

5.3 Lifestyle Considerations

Participants will be advised to avoid chronic alcohol use and smoking during the study.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes date of informed consent, demography, reason for screen failure, eligibility criteria and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. The informed consent process is described in Section 10.1.3.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

Table 4 Study Intervention Administered

Intervention Name	Triptorelin embonate
Intervention Description	A PR formulation of triptorelin pamoate 6-month formulation in D,L-lactide-co-glycolide polymers for single subcutaneous injection
Type	Drug
Dose Formulation	A white to slightly yellow freeze-dried cake or powder supplied in a single 6 mL glass vial
Unit Dose Strength(s)	22.5 mg
Dosage Level(s)	Single dose delivered on Day 1 and Day 169
Route of Administration	Subcutaneous injection
Use	Experimental
IMP and NIMP/AxMP.	IMP
Sourcing	Manufactured by Debiopharm and provided centrally by the sponsor [a]
Packaging and Labelling	Study intervention will be provided in a box containing one vial, one ampoule, one sterile injection kit with one syringe and three needles (one for reconstitution, one for subcutaneous injection and one to be retained in the kit for reconciliation). Each box will be labelled as required per country requirement.
Storage requirements	To be stored in the outer carton at a temperature below 25°C in a dry place, protected from freezing
Current Name	Decapeptyl®, Pamorelin®, Diphereline®

Abbreviations: IMP=investigational medicinal product; PR=prolonged release
a The triptorelin vial is manufactured by Debiopharm.

6.2 Preparation, Handling, Storage and Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants screened in the study and who meet the eligibility criteria may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- The sponsor will provide guidance on the destruction of unused study intervention. If destruction is authorised to take place at the investigational site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy and any special instructions provided by the sponsor. All destruction must be adequately documented.

Further guidance and information for the receipt, preparation, management and disposal/return of the study intervention are provided in the "Investigational Medicinal Product Handling Manual".

The investigator or an approved representative (e.g. pharmacist) will ensure that triptorelin is reconstituted and dispensed by a member of staff specifically authorised by the Investigator and trained for the investigational medicinal product reconstitution and administration.

The suspension for injection must be reconstituted using an aseptic technique and only using the ampoule of solvent for injection.

The solvent should be drawn into the syringe provided using the reconstitution needle (20 G, without safety device) and transferred to the vial containing the powder. The suspension should be reconstituted by swirling the vial gently from side to side for long enough until a homogeneous, milky suspension is formed. Do not invert the vial.

It is important to check there is no unsuspended powder in the vial. The suspension obtained should then be drawn back into the syringe, without inverting the vial. The reconstitution needle should then be changed, and the subcutaneous injection needle (20 G, with safety device) used to administer the product.

As the product is a suspension, the injection should be administered for a single use immediately after reconstitution to prevent precipitation.

At each dispensation (at scheduled and unscheduled visits, if applicable), treatment number(s) will be assigned by the Interactive Web Response System (IWRS). The IWRS will also manage all logistical aspects of the study intervention (e.g. replacement, drug supplies and expiry dates) and the recording of drug accountability/destruction. This service provides the investigator, investigational site coordinators and project team members with a service that is available 24 hours a day, 7 days a week. Additional details may be found in the IWRS reference manual provided to each investigational site. In case of technical or dispensation queries, a 24-hour helpline is available. If a participant discontinues the study before any intake of study intervention, his assigned treatment number(s) will not be reused.

In addition to the information provided in the IWRS, drug accountability paper records will be maintained by the investigator.

6.3 Measures to Minimize Bias: Randomisation and Blinding

6.3.1 Randomisation

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

6.3.2 Maintenance of blinding

This is an open-label study, therefore no procedure for blinding is applicable.

6.4 Study Intervention Compliance

The participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered and volume at the site will be recorded in the source documents and in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff.

6.5 Dose Modification

Not applicable. No dose modifications are to be performed in the study.

6.6 Continued Access to Study Intervention after the End of the Study

The participants will not receive any additional study intervention following the end of the study.

6.7 Treatment of Overdose

The pharmaceutical properties of triptorelin 6-month formulation and its mode of administration make accidental or intentional overdose unlikely. There is no experience of overdose from clinical studies (for more information see the summary of package characteristics). If overdose occurs, this should be managed symptomatically.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities (at least up to the Day 337 (Week 48) visit).
- Document the quantity of the excess dose as well as the duration of the overdose. See Section 10.3.1 for reporting requirements concerning overdose. If overdose occurs, symptomatic management is indicated.

6.8 Concomitant Therapy

Any medication or vaccine (including over the counter prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant has taken within the last 2 months before or during triptorelin administration must be recorded on the eCRF along with:

- Generic or trade name
- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The following concomitant medications are not permitted during the study:

- Finasteride or dutasteride
- Abiraterone
- Medications which are known to affect the metabolism and/or secretion of androgenic hormones: ketoconazole, aminoglutethimide, oestrogens.
- Systemic or inhaled corticosteroids (topical application permitted).
- Any herbal products previous used within 1 month prior to study start or plan to be used during the study, which are known to have cytotoxic effect or affect the metabolism and/or secretion of androgenic hormones.
- Medications known to prolong QT interval (class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics).

The following concomitant medications are permitted during this study, but they must be monitored closely, and every effort should be made to keep their dose and dose regimen constant throughout the course of the study:

- Enzalutamide, apalutamide or darolutamide

- Analgesics: are allowed when necessary for pain relief.
- Anticonvulsants (e.g phenobarbital): long-term therapy may have additional risk for osteoporosis
- Other medications: any treatment which is considered necessary for the participant's welfare, may be given at the discretion of the investigator.

Other procedures: any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded, including the date, indication, description of the procedure(s), and any clinical findings.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.8.

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

If participants are lost to follow-up, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.1.1 Temporary Discontinuation

In case of clinical study disruption due to a regional or national emergency declared by a government agency, the intervention administration may be temporarily postponed depending on the participant clinical presentation. In some cases, the investigator may request a participant be retested before the study intervention administration is resumed.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and for any further evaluations that need to be completed.
- The reason for discontinuation will be recorded in the eCRF.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent.
- If the participant requests to discontinue the study intervention, they will be asked to be followed for the study procedures.
- If the participant withdraws consent for any further contact, the investigator will explain in the medical records as to whether the withdrawal is only from further receipt of study intervention or also from study procedures. This information must be entered in the eCRF.
- If a participant withdraws from the study, he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- A participant will be withdrawn from the study if they have inadequate testosterone suppression (defined as >50 ng/dL detected at least 30 days after the first administration of study intervention and on two consecutive measurements at least 2 weeks apart, at either a scheduled or unscheduled study visit).

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site until the end of the study.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The site should counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, attempts to make contact should continue until study closure and participant might be confirmed as lost to follow up at the time of study closure.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not receive study intervention. All sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA. Protocol waivers and exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Table 1).
- In the event of a significant study-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- The maximum amount of blood for study purposes collected from each participant over the duration of the study will not exceed 153 mL.
- Repeat or unscheduled samples may be taken for safety reasons or in case of technical issues with the samples.

8.1 Demography

Age, sex and, according to individual country regulations/requirements and if authorised in the country, race/ethnicity will be collected. The collection of these data is needed to establish if there are potential clinical important racial/ethnic-based differences in the anticipated effects of the intervention.

8.2 Efficacy Assessments

Efficacy will be assessed in this study based on testosterone and PSA concentrations.

Approximately 148 mL of blood will be collected from all participants for measurement of testosterone and PSA. Serum, or plasma samples used to evaluate testosterone or PSA will be divided into two aliquots (one primary and one back-up).

Further instructions for the collection, handling and shipment of biological samples will be provided by the sponsor and described in the Study Laboratory Manual.

Note: No exploratory analyses are planned for this study. However, residual plasma and serum samples may also be used for exploratory analyses. This could include using leftover plasma and serum samples for pharmacokinetic analyses or additional investigations (i.e. long-term stability, reproducibility, bioanalytical method cross-validation). If required, exploratory analyses related to pharmacokinetics and additional investigations will be captured in a separate report.

8.2.1 Testosterone

Blood samples for the determination of testosterone serum concentrations will be collected at the timepoints indicated in the SoA (Table 1). Testosterone will be assessed centrally by a third-party vendor, as described in the Study Laboratory Manual. Serum will be analysed to determine concentrations of testosterone using a validated, specific and sensitive liquid chromatography tandem mass spectrometry methods.

At screening, testosterone will be assessed up to 7 days prior to Day 1 using the local laboratory.

8.2.2 Prostate-specific Antigen

PSA will be assessed centrally, as described in the Study Laboratory Manual.

Blood samples for the determination of PSA plasma concentrations will be collected at the timepoints indicated in the SoA (Table 1).

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any clinically significant physical examination findings (abnormalities) observed during the study participation will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until clinically stable.

8.3.2 Vital Signs

Blood pressure, temperature, respiratory rate and heart rate will be assessed with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after 5 minutes rest in supine position. Absolute values and change from Baseline will be analysed. Any clinically significant vital signs will be recorded as AEs.

8.3.3 Electrocardiograms

A 12-lead ECG analysis will be included as a safety evaluation/endpoint in this study at timepoints described in Table 1.

A single 12-lead ECG will be recorded so that the different ECG intervals (RR, PR, QRS, QT, QTcF) can be measured automatically. The ECG will be recorded with the participant in supine position after five minutes of rest until four regular consecutive complexes are available.

Based on investigator judgement, any abnormal ECG results will be repeated twice (10 minutes apart) to confirm the abnormal finding. Any clinically significant abnormalities will be recorded as AEs.

8.3.4 Imaging Scan

An imaging scan for the prostate gland or the whole body (only, if necessary, based on investigator's judgement) will be performed as described in the SoA (Table 1) to confirm disease stage prior to study entry. An imaging scan is not required if performed within 6 months of study screening.

An imaging scan could be magnetic resonance imaging (MRI), positron emission tomography with or without MRI or any other imaging modality which is standard of care at the institute. An ultrasonography cannot be considered as a reliable method for staging.

8.3.5 Clinical Safety Laboratory Assessments

- See Appendix 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. Assessments will be analysed by the local laboratory.

- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease, are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 168 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the sponsor notified.
    - All protocol-required laboratory tests, as defined in Appendix 10.2, must be conducted in accordance with each local laboratory practice and the SoA (Section 1.3).
    - If laboratory values from non-protocol specified laboratory tests performed at the study site laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3.6 Local Tolerance

Local tolerance will be assessed 2 hours after injection. After the single subcutaneous injection of the triptorelin 6-month formulation, the injection site will be examined by a physician or designee and assessed for characteristics such as but not limited to tenderness, redness, bruising, erythema, swelling, rash, pain, itching, induration, haematoma, ulceration or necrosis. If present, the extent of erythema, haematoma, rash, ulceration or necrosis will be described. If any reactions meet the definition of a treatment-emergent adverse event (TEAE), they are to be reported in the eCRF as such.

8.4 Adverse Events (AEs) and Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs and SAEs during the study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorised representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until EoS at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE section of the case report form.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of awareness of the event, as indicated in

Appendix 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed up until resolution or stabilisation, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor's policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

All participants in this study are male. Participants in this study are chemically castrated and partner pregnancy is not an expected event. However, the investigator must instruct all male participants to inform the investigator immediately should their partner become pregnant.

- Details of all pregnancies in female partners of male participants will be collected from the signing of the ICF and until up to 9 months after the participants last dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours via email of learning of the female partner of male participant becoming pregnant (after obtaining the necessary signed informed consent from the female partner).
- While pregnancy itself is not considered to be and AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The pregnant female partner will be followed up to determine the outcome of the pregnancy unless consent is not given/withdrawn. The investigator will collect follow-up information on the participant's pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in a former study participant's pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

8.4.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.7 Adverse Events of Special Interest

Not applicable.

8.4.8 Reporting of Study Intervention Errors Including Misuse/abuse

- Medication errors are unintentional errors in the prescribing, storing, dispensing, preparing or administration of a study intervention (medicinal product) while under the control of a healthcare professional, participant or consumer.
- Misuse refers to situations where the study intervention is intentionally and inappropriately used not in accordance with the protocol.
- Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Study intervention errors and uses outside of what is foreseen in the protocol, such as misuse, abuse or overdose, will be recorded on the appropriate eCRF page irrespective of whether associated with an AE/SAE or not, within 24 hours of investigator or qualified designees' awareness. If an AE/SAE is associated with this study intervention error, it should be documented in the AE/SAE section of the eCRF. Please refer to Sections 6.7 and 10.3.1.

9 STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to the first participant being enrolled and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

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

Null hypothesis: percentage of participants castrated (serum level of testosterone <1.735 nmol/L) after 12 months is less than or equal to 90%.

Alternative hypothesis: percentage of participants castrated (serum level of testosterone <1.735 nmol/L) after 12 months is greater than 90%.

9.2 Sample Size Determination

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

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

9.3 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled Set	The enrolled set will contain all participants who were enrolled to study treatment. A participant will be considered as enrolled if he has signed the informed consent form and is assigned to treatment.
Safety Set	The safety set will contain all participants who receive at least one dose of study intervention.
Full Analysis Set	The full analysis set analysis set will contain all participants who signed an informed consent form and received two administrations of study intervention and completed all visits for testosterone measurement (Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337). Note, a participant will be included in the full analysis set if their testosterone measurement is ≥50 ng/dl before the end of treatment, end of study or withdrawn from study, whichever is earlier.
Per Protocol Set	The per protocol set will contain all participants from the full analysis set who did not experience any major protocol deviations that may interfere with efficacy evaluation.

9.4 Statistical Analyses

The SAP will be developed prior to the first participant entering the study and it will include a more technical and detailed description of the statistical analyses described in this section. This

section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Other endpoints as well as demographic, baseline characteristics and disposition will be detailed in the SAP.

9.4.1 Analysis of Demographics and Other Baseline Characteristics

Baseline and demographic information will be listed and summarised. For continuous variables, the summary will consist of descriptive statistics (number of participants, mean, SD, minimum, median, and maximum). For categorical variables, the summary will consist of number and percentage of subjects in each category.

Medical history and concurrent medical conditions will be summarised by system organ class and preferred term. Medication history and concomitant medications will be summarised by preferred term.

9.4.2 Efficacy Analyses

Due to the single-arm nature of the study, all statistical analyses will be descriptive with quantitative data summarised as mean, SD, median, quartiles, 95% CIs and range. Qualitative data will be summarised as frequency counts and percentages. The 95% CIs will be calculated following the Clopper-Pearson method. The descriptive statistics of treatment effects and corresponding 95% CIs for the primary endpoint and secondary endpoints will be presented.

Missing castration level data during the study will be imputed by multiple imputation. Further details of the efficacy analyses will be specified in the SAP.

9.4.3 Safety Analyse(s)

Safety analyses (AEs and laboratory analyses) will be performed using the safety population. Adverse events will be coded using MedDRA (Version 24.1 or higher if available). Severity will be graded according to the National Cancer Institute (NCI)-CTCAE Version 5.0 or higher.

All AEs will be classified by MedDRA (latest version) preferred term and system organ class.

A TEAE is defined as any AE that occurs during the treatment period of the study if:

- it was not present prior to receiving the first dose of study intervention, or
- it was present prior to receiving the first dose of study intervention but the intensity increased during the active phase of the study.

Summary statistics (mean, median, SD and range as appropriate) will be presented for vital signs, blood pressure, heart rate, ECG variables, clinical laboratory tests etc. at each assessment, with change from Baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented for the number and percentage of participants with low, normal or high values and normal or abnormal examinations.

Summary incidence tables will be provided, classified by body system, preferred term and associated NCI-CTCAE worst grade. Dose delays and dose interruptions will be listed by cycle. Summaries of events that resulted in dose modifications (e.g. delay) will also be provided.

Haematological and biochemical toxicities will be recorded and graded according to the NCI-CTCAE criteria, where available. The NCI-CTCAE grade 3 and 4 haematology and biochemistry variables by participant and by cycle will be listed as SAEs. For white blood cells, neutrophils, platelets and haemoglobin, with associated grade 3 or 4 toxicities, nadir and day to nadir will be calculated. All AEs and SAEs must be captured in the relevant databases.

9.5 Interim Analyses

No interim analyses are planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations such as Regulation European Union (EU) 536/2014
- The protocol, protocol amendments, ICF, Investigator Brochure and other relevant documents (e.g. any participant recruitment materials) must be approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The protocol and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to applicable local regulations, ICH guidelines and the IRB/IEC requirements/procedures.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

10.1.3 Informed Consent Process

- The ICF and any participant recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. They must be approved prior to use as described in Section 10.1.1.
- The investigator or his/her authorised representative will explain to the potential participant or their legally authorised representative the nature and objectives of the study and possible risks and benefits associated with the participation. They will answer all questions regarding the study.

- Participants or their legally authorised representative, when applicable must be informed that their participation is voluntary.
- The investigator or his/her authorised representative will obtain written informed consent from each participant or the legally authorised representative, when applicable, before any study-specific procedure is performed. The investigator will retain the original of each participant's signed ICF.
- A copy of the signed ICF(s) must be provided to the participant or their legally authorised representative.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. If changes to the ICF do not apply to all participants, this will be communicated to the IRB/IEC with a rationale. IRB/IEC approval must be received before implementation as required by local regulations.
- The ICF will contain a separate section that addresses the use of all data and remaining material after analysis from mandatory samples for optional future research. These data and biosamples may only be used for future research and analysis to advance science and public health, including in order to:
  - understand and evaluate the study drug and/or other drugs
  - better understand the studied disease and associated health problems,
  - develop new drugs and find new ways to detect, treat, prevent or cure health problems,
  - plan new studies or improve scientific analysis methods,
  - publish research results in scientific journals or use them for educational purposes,
  - conduct additional statistical analysis.
- Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. A specific consent will be required to document a participant's agreement to allow any data and remaining specimens to be used for future research.
- If a pregnancy is reported for a female partner of a male participant during the study, the partner will be asked to sign appropriate consent for the sponsor to follow the outcome of the pregnancy.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 4 weeks, to be determined on a study-by-study basis, but in any case, should not be longer than 4 weeks from the previous ICF signature date.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his medical records may be examined by the sponsor's auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor will ensure that appropriate organisational and technical arrangements are implemented to comply with the applicable rules on the protection of personal data.
- In the event of a potential data security breach concerning personal data processed on behalf of the sponsor, the data protection officer must be informed without undue delay and no later than 24 hours from the discovery of the event. The data protection officer will evaluate the event and notify the Data Protection Authorities within 72 hours, if required. Corrective actions and preventive actions will be implemented to mitigate the possible adverse effects. Affected study participants will be informed accordingly. Ipsen Data Protection Officer can be contacted by email: dataprivacy@ipsen.com.
- When permitted by local regulation, the ICF will contain a separate section that addresses the remote access by the study monitors to source documents/data for the purpose of source data verification. A specific consent will be required to document a participant's agreement.

10.1.5 Dissemination of Clinical Study Data

- Protocol information and final study result will be made publicly available on the United States website (ClinicalTrials.gov) and for studies run in the EU/EEA on the EU Clinical Trials Register (www.clinicaltrialsregister.eu) or EU Clinical Trials Portal (https://euclinicaltrials.eu/home). The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation.
- A lay language protocol synopsis and a summary of the study will be made available on the EU Clinical Trials Portal (https://euclinicaltrials.eu/home) and/or Sponsor website.
- A clinical study report will be prepared if at least one participant has signed informed consent and received intervention, regardless of whether the study is completed or prematurely terminated. The clinical study report may be disclosed according to regulatory requirements.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the eCRF.
- All entries in the eCRF will be made under the e-signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections, and provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing, and inspection by domestic and foreign regulatory authorities.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as Risk

Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organisations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study should be retained by the investigator according to the ICH-GCP guidelines, to local regulations, or as specified in the study agreement, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source documents/data and their location will be documented in a specific form.
- The investigator must maintain accurate documentation that supports the information entered in the eCRF. Source data must be attributable, legible, contemporaneous, original, accurate and complete.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements. When permitted by local regulation and guidance, study monitors will access remotely to source documents/data to conduct source data verification, while maintaining appropriate security measures and ensuring the protection of the data. This will be described in the monitoring plan or equivalent.

10.1.8 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants or the actual date on which the first participant was enrolled.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication Policy

- The sponsor seeks to publish the results of these clinical trials in biomedical journals, whatever the outcome. Clinical trial results may also be presented at international congresses as posters or oral presentations.
- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator should discuss specific publication concepts, including data to be covered, target congress/journal and proposed authors, with the sponsor for agreement before initiation. The investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix: Clinical Laboratory Tests

- Refer to SoA Section 1.3 for details of visits.
- The tests detailed in Table 5 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Tests

Parameters	Screening	Intervention Period	EoS/ED
Haematology	X		X
Platelet Count	X		X
Haemoglobin	X		X
White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Others	X		X
Clinical Chemistry			
Creatinine	X		X
Glucose (non-fasting)	X		X
Aspartate Aminotransferase	X		X
Alanine Aminotransferase	X		X
Alkaline phosphatase	X		X
Bilirubin (total and conjugated)	X		X

EoS=end of study; ED=early discontinuation
Note: All parameters will be analysed locally. The preparation and storage of samples will be performed per each local laboratory practice.

Investigators must document their review of each laboratory safety report.

10.3 Appendix: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital abnormality /birth defect

f. Other situations:

Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the required forms.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study using the National Cancer Institute - Common Toxicity Criteria for AEs (NCI-CTCAE) (version 5.0 or higher).

Where:

- **Grade 1**: Mild; symptoms do not alter the participant's normal functioning.
- **Grade 2**: Moderate; symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the participant.
- **Grade 3**: Severe; symptoms definitely hazardous to wellbeing or causing significant impairment of function or incapacitation.
- **Grade 4**: Life-threatening; any event that places the participant at immediate risk of death from the event as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- **Grade 5**: Death related to AE

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the eCRF.
- The investigator or qualified designee will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE in English language to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours of awareness of the event. The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- SAE report should be sent to adverse.events@ipsen.com.

SAE Reporting to sponsor via paper data collection tool
• The site will email the SAE form or fax the cover sheet and SAE form to the sponsor if the electronic data collection tool is unavailable. It must be retrospectively recorded as soon as the electronic data collection tool becomes available. • SAE report should be sent to adverse.events@ipsen.com.

10.4 Appendix: ECOG Performance Scale

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

10.5 Appendix: Temporary Measures and Procedures Related to COVID-19 Pandemic

This appendix is intended to provide temporary measures to manage study assessments that cannot be done in compliance with the current protocol version because of the COVID-19 pandemic.

The implementation of the below measures must be in line with applicable country regulation or national temporary COVID-19 measures guidance and must remain temporary until the situation resolves, at which point the protocol assessments will return to those specified in the current approved protocol effective at that time. The temporary measures may remain in place for different periods of time per country/site.

The temporary measures specified in this appendix must be reported as "protocol deviation related to COVID-19" and must still be documented and reported to the IEC/IRB and/or Health Authorities, based on the regulatory requirements applicable at your country/site, in addition to any deviation to the current protocol.

Investigators will determine the appropriateness of starting or continuing study intervention on a participant-by-participant basis, depending on the ability to conduct safety monitoring and provide sites with an adequate supply of study intervention, in accordance with local requirements.

The following guidelines were adapted using suggestions from the TransCelerate publication "Beyond COVID-19: Modernizing Clinical Trial Conduct" published by TransCelerate Biopharma Inc. July 2020, which was influenced by Food and Drug Administration (FDA) and EMA guidance issued for conduct and management of clinical studies during the COVID-19 pandemic.

10.5.1 Specific Guidance for Study Visits and Assessments

10.5.1.1 Study Schedule

If the COVID-19 pandemic prevents participants from coming to the site, apart from the mandatory site visits for screening assessments and for days of study intervention administrations (Days 1 and 169) as per the protocol (Section 1.3), participants can have their study visit assessments performed remotely as judged appropriate by the investigator. This must be discussed with the sponsor (or sponsor delegate) before being implemented. In such a case, the investigator will perform a telemedicine visit and will make every effort to collect all important medical information and safety event(s) occurring since the last visit. Guidance on how to collect protocol-planned assessments is provided below.

10.5.1.2 Screening and Enrolment

Participants can be rescreened within 4 weeks according to the protocol (Section 10.1.3). However, if a participant tests positive for COVID-19 during the screening period, this should be escalated to the sponsor (or sponsor delegate). In exceptional circumstances, where a participant starts screening procedures, which are then delayed due to COVID-19 (for example testing positive for COVID-19), the participant might continue with the screening assessments after a negative COVID-19 test is confirmed and all eligibility criteria are met prior to enrolment, even if this is outside the normal 28-day screening window, after discussion with the sponsor.

10.5.1.3 Informed Consent (including Re-consent)

As per guidelines issued by the FDA in the United States and in line with guidance in other countries, the use of electronic signatures is authorised to obtain the participant's or legal guardian's informed consent. In such a case, the IRB need to be notified of the use of electronic

informed consent signature and the accepted electronic formats need to be clearly documented. This is not meant to replace the important discussion between the participant, legal guardian, investigator and site staff. Such a discussion must still occur and be part of a screening visit (in-person, by telemedicine, or home health visit). A clearly documented process on how participants are contacted virtually to explain the study and close monitoring needs to be in place.

Screening visit and assessments (apart from informed consent as described above) must be performed on site.

10.5.1.4 Dosing Visits

In case of dosing visits delayed due to COVID-19 (e.g. temporary closure of the site, participant unable to travel, etc.)

- Dosing visits may be delayed due to COVID-19. These delays are not permitted by the protocol. Any potential delay of dosing must be escalated to the sponsor and discussed between the investigator and the sponsor.

In case of suspected COVID-19 infection

- The administration of study intervention may be temporarily discontinued depending on the participant's clinical presentation. In some cases, the investigator may request a participant be retested before the administration of study intervention is resumed.
- In all cases, the investigator must ensure that the participant receives appropriate medical follow-up. It will be in the investigator's medical judgement to assess the benefits and risks before restarting study intervention. If a participant has temporarily interrupted study intervention, the decision to restart participants on study intervention will be managed on an individual case basis in discussion with the sponsor (or sponsor delegate) and investigator.

In case of confirmed COVID-19 infection

- Participants who present with COVID-19 positive-confirmed infection should be placed on immediate study intervention delay as per institutional guidelines [Curigliano 2020]. Any suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection should be considered serious and be immediately reported to the sponsor.
- Since there is lack of data on risk/benefit analysis of the study intervention and COVID-19 infection, in the absence of a confirmatory negative COVID-19 PCR test in an asymptomatic participant, it is in the investigator's medical judgement to assess the benefit and risks of restarting study intervention. The management of participants following temporary interruption of the study intervention and decision to restart participants on study intervention will be managed on an individual participant basis in discussion with the sponsor and investigator.

10.5.1.5 Testosterone Assessments

Study home nursing is encouraged to ensure the collection of the testosterone samples. These samples will be then sent to the Central Laboratory as planned. Where a study home nursing solution is possible, vital signs will be collected at the same time as testosterone sample collection.

10.5.1.6 Concomitant Medications and Procedures

Details can be collected by site staff via telephone call as per the rules relating to use of telemedicine below. COVID-19 vaccines and or medication shall be reported as concomitant medication.

10.5.1.7 Adverse Event Reporting

All COVID-19 cases (suspected or confirmed) should be seriousness assessed based on the reported seriousness criteria. If no seriousness criteria is reported by the investigator, the COVID-19 event/case will be collected and recorded as nonserious.

Details can be collected by site staff via telephone call as per the rules relating to use of telemedicine in the protocol (Appendix 10.5.2).

10.5.2 Specific Rules Relating to Use of Telemedicine

The form of telemedicine used (phone call or use of a platform), the legal and privacy protection of the participant, as well as details of the verification of the identity of the participant and site personnel conducting the assessment should be documented at site level and should be available for review by the monitor.

10.5.3 Guidance on COVID-19 Vaccine and/or Medications

Currently available COVID-19 vaccines for age appropriate participants do not contain a live virus, therefore, they are permitted during the study. Future approved COVID-19 vaccines will be assessed by the sponsor.

Participants may receive COVID-19 vaccinations if they have no contraindications to any component of the specific vaccine. However, they should be counselled by the investigator about benefit/risk of getting the vaccination based on their individual health conditions, as well as with the healthcare physician administrating the vaccination, about the unknown vaccine safety profile and effectiveness in immunocompromised populations, as well as the potential for insufficient immune responses, and the need to continue to follow all current guidance to protect themselves against COVID-19.

The co-administration of the COVID-19 vaccines with the study intervention has not been studied. Based on the lack of evidence, the following recent guidance for cancer patients participating in oncology studies is recommended [Desai 2021]:

- It is recommended to avoid administration of study intervention within 48 to 72 hours of vaccination to minimise confusion and/or inaccurate attribution of AE causation.
- Investigator discretion is necessary to ascertain the benefit/risk to taking the vaccine while taking into consideration of the participant's clinical condition. COVID-19 vaccines and/or medications shall be reported as concomitant medication.

10.6 Appendix: Protocol Amendment History

The Protocol Amendment Summary of Changes table for the current amendment is located directly before the Table of Contents.

10.6.1 Amendment 1: (13 September 2022)

Section	WAS (Version 1.0, 16 MARCH 2022)	IS (Version 2.0, 13 SEPTEMBER 2022)	Rationale
Sponsor Signatory	Sponsor Signatory: PPD	Sponsor Signatory: PPD	Change in company personnel.
Sponsor Signatory	Medical Monitor Name and Contact Information: PPD ~~Ipsen Bioinnovation~~ ~~102 Park Drive~~ ~~Milton Park, Oxfordshire~~ ~~OX14 4RY~~ ~~United Kingdom~~ Email: PPD	Medical Monitor Name and Contact Information: PPD **Ipsen Bioscience, Inc.** **1 Main Street** **Cambridge, Massachusetts 02142** **United States** Email: PPD	Change in company personnel.
Synopsis and 3 / Objectives and Endpoints	The primary ~~efficacy~~ estimand is described below. The treatment will be triptorelin 6-month formulation administered subcutaneously. The population will comprise participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue as specified in the inclusion and exclusion criteria (Sections 5.1 and 5.2), respectively. The variable for the primary estimand will be castration maintenance rate during the study, which is defined as percentage of participants castrated (testosterone <1.735 nmol/L (50 ng/dL)) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337. ~~The reasons for participant withdrawal from the study will be separate intercurrent events. Employing a hypothetical strategy, missing data dependent~~	The primary estimand for **the primary endpoint** is described below. The treatment will be triptorelin 6-month formulation administered subcutaneously. The population will comprise participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue as specified in the inclusion and exclusion criteria (Sections 5.1 and 5.2), respectively, **that have received two scheduled treatment intervention doses (i.e. Day 1 and Day 169) and have completed all visits for measurement of testosterone.** The variable for the primary estimand will be castration maintenance rate during the	Modified to provide clarification of the primary and secondary estimands for the primary endpoint.

Section	WAS (Version 1.0, 16 MARCH 2022)	IS (Version 2.0, 13 SEPTEMBER 2022)	Rationale
	~~on intercurrent events will be imputed by multiple imputation.~~ Further details of the estimand will be specified in the statistical analysis plan (SAP).	study, which is defined as percentage of participants castrated (testosterone <1.735 nmol/L (50 ng/dL)) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337, **with two complete study intervention administrations. Secondary estimands include analyses without using the visit window and/or using the ITT population where missing data will be considered a non-responder maybe conducted.** The reasons for participant withdrawal from the study will be separate intercurrent events. Employing a hypothetical strategy, missing data dependent on intercurrent events will be imputed by multiple imputation. Further details of the estimand will be specified in the statistical analysis plan (SAP).	
Synopsis / Overall Design	Approximately ~~153~~ adult male participants will be enrolled in the study.	Approximately **145** adult male participants will be enrolled in the study.	Planned participants adjusted to account for decrease in drop out rate from 15% to 10%.
Synopsis / Number of Participants	Approximately ~~153~~ participants are planned to be assigned to study intervention.	Approximately **145** participants are planned to be assigned to study intervention.	Planned participants adjusted to account for decrease in drop out rate from 15% to 10%.

Section	WAS (Version 1.0, 16 MARCH 2022)	IS (Version 2.0, 13 SEPTEMBER 2022)	Rationale
Synopsis / Statistical Methods (Sample Size Determination)	Considering a drop-out rate of ~~15~~%, ~~153~~ participants will be included in the study.	Considering a drop-out rate of **10%**, **145** participants will be included in the study.	Drop-out rate reduced, and planned participants adjusted to account for decrease in drop-out rate.
4.1 / Overall Design	Approximately ~~153~~ participants will be assigned to triptorelin embonate 22.5 mg (6-month formulation) to be administered on Day 1 and Day 169.	Approximately **145** participants will be assigned to triptorelin embonate 22.5 mg (6-month formulation) to be administered on Day 1 and Day 169.	Planned participants adjusted to account for decrease in drop-out rate from 15% to 10%.
4.2 / Scientific Rationale for Study Design	The non-comparative, open-label clinical study design is acceptable as the primary ~~efficacy~~ endpoint will assess testosterone levels by the percentage of participants maintaining castrate levels of serum testosterone (defined as <1.735 nmol/L (50 ng/dL)) during the study (primary endpoint, as outlined in Table 3).	The non-comparative, open-label clinical study design is acceptable as the primary endpoint will assess testosterone levels by the percentage of participants maintaining castrate levels of serum testosterone (defined as <1.735 nmol/L (50 ng/dL)) during the study (primary endpoint, as outlined in Table 3).	Amended for consistency with changes made in Section 3.
4.4 / End of Study Definition	~~The overall duration of the study (from first participant in, to last participant out) will be approximately 52 weeks. The study will be considered to have ended after the last participant has completed the last visit (on Day 337 (Week 48)) in the study.~~		Removed to provide better clarity, as text did not clearly describe the end of study definition, but individual participation.
5.2 / Exclusion Criteria	~~U~~se of any ~~other therapy~~ for prostate cancer during the study ~~(e.g. chemotherapy)~~	**At the time of screening, planned use of any chemotherapy** for prostate cancer during the study	Modified to avoid exclusion of eligible participants.

Section	WAS (Version 1.0, 16 MARCH 2022)	IS (Version 2.0, 13 SEPTEMBER 2022)	Rationale
6.8 / Concomitant Therapy	•Finasteride or dutasteride •Medications which are known to affect the metabolism and/or secretion of androgenic hormones: ketoconazole, aminoglutethimide, oestrogens. •Systemic or inhaled corticosteroids (topical application permitted). •~~Cytotoxic chemotherapy or abiraterone~~	•Finasteride or dutasteride •**Abiraterone** •Medications which are known to affect the metabolism and/or secretion of androgenic hormones: ketoconazole, aminoglutethimide, oestrogens. •Systemic or inhaled corticosteroids (topical application permitted).	Modified to avoid exclusion of eligible participants.
7.2 / Participant Discontinuation / Withdrawal from the Study		• **A participant will be withdrawn from the study if they have inadequate testosterone suppression (defined as >50 ng/dL detected at least 30 days after the first administration of study intervention and on two consecutive measurements at least 2 weeks apart, at either a scheduled or unscheduled study visit).**	Clarification added to provide guidance for participants who have lack of efficacy during the study.
8 / Study Assessments and Procedures	The maximum amount of blood collected from each participant over the duration of the study, ~~including any extra assessments that may be required,~~ will not exceed ~~65~~ mL.	The maximum amount of blood **for study purposes** collected from each participant over the duration of the study will not exceed **153** mL.	Blood volume to be collected over the whole duration of the study increased to accommodate requirements needed for testing at the central laboratory.

Section	WAS (Version 1.0, 16 MARCH 2022)	IS (Version 2.0, 13 SEPTEMBER 2022)	Rationale
8.2 / Efficacy Assessments	Approximately ~~60~~ mL of blood will be collected from all participants for measurement of testosterone and PSA.	Approximately 148 mL of blood will be collected from all participants for measurement of testosterone and PSA.	Blood volume to be collected over the whole duration of the study increased to accommodate requirements needed for testing at the central laboratory.
9.1 / Statistical Hypothesis	The primary objective of this study is to evaluate the efficacy triptorelin embonate 22.5 mg (6-month formulation) administered subcutaneously in maintaining serum testosterone castrate levels.	The primary objective of this study is to evaluate the efficacy triptorelin embonate 22.5 mg (6-month formulation) administered subcutaneously in maintaining serum testosterone castrate levels **during the study (maintenance of castration defined as testosterone <1.735 nmol/L (50 ng/dL) at Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337) with two complete study intervention administrations.**	Modified to provide clarification of the primary endpoint.
9.2 / Sample Size Determination	Considering a drop-out rate of ~~15~~%, ~~153~~ participants will be included in the study.	Considering a drop-out rate of **10%**, **145** participants will be included in the study.	Planned participants adjusted to account for decrease in drop-out rate from 15% to 10%.

Section	WAS (Version 1.0, 16 MARCH 2022)		IS (Version 2.0, 13 SEPTEMBER 2022)		Rationale
9.3 / Analysis Sets	Full Analysis Set	The full analysis set analysis set will contain all participants who signed an informed consent form and receive ~~at least one~~ administration of study intervention ~~and have a serum testosterone level <1.735 nmol/L (50 ng/dL) on Day 1 (pre-dose measurement)~~.	Full Analysis Set	The full analysis set analysis set will contain all participants who signed an informed consent form and received **two** administrations of study intervention and **completed all visits for testosterone measurement (Day 29, Day 85, Day 141, Day 169, Day 253, Day 309 and Day 337). Note, a participant will be included in the full analysis set if their testosterone measurement is ≥50 ng/dl before the end of treatment, end of study or withdrawn from study, whichever is earlier.**	Clarification of full analysis set definition.

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Sponsor Signatory:

PPD

05/12/2023

Date

Medical Monitor Name and Contact Information:

PPD

Ipsen Bioscience, Inc.
1 Main Street
Cambridge, Massachusetts 02142
United States
Email: PPD

Principal Investigator Signature Page

I have read and agree to Protocol D-FR-52014-245 entitled An open-label, multicentre, single arm study to assess the efficacy and safety of triptorelin 6-month formulation administered subcutaneously in participants with locally advanced and/or metastatic prostate cancer previously treated and castrated with a GnRH analogue with Amendment 2. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: [ ] PPD

TITLE: [PRINCIPAL] INVESTIGATOR

SIGNA PPD

DATE: PPD

OFFICE: [ ] PPD
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Triptoswitch PA 2

Final Audit Report 2023-12-05

Created:	2023-12-05 (Central European Time)
By:	PPD
Status:	Signed
Transaction ID:	PPD

"Triptoswitch PA 2" History

Document created by PPD
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Signer PPD entered name at signing as PPD
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PPD has agreed to the terms of use and to do business electronically with IPSEN PHARMA SAS.
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