Protocol Title:
A multicentre, open-label, single-arm study to investigate the efficacy and safety of triptorelin pamoate 22.5 mg 6-month formulation in Chinese patients with locally advanced or metastatic prostate cancer

Protocol Number: D-CN-52014-237

Compound: Triptorelin pamoate (embonate) salt (IPN52014)

Short Title: Effects of triptorelin pamoate 6-month when given to adult Chinese participants with advanced cancer in the prostate

Study Phase: IIIb

Sponsor Name: Ipsen Pharma

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Regulatory Authority Identifier Number(s)
Not applicable

Date: 08 March 2024

Version Number: 4.0
Amendment Number: 3

Sponsor Signatory:

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Principal Investigator Signature Page

I have read and agree to Protocol D-CN-52014-237 entitled "A multicentre, open-label, single-arm study to investigate the efficacy and safety of triptorelin pamoate 22.5 mg 6-month formulation in Chinese patients with locally advanced or metastatic prostate cancer" with protocol Amendment #3. 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 3	4.0	08 March 2024	Effective
Amendment 2	3.0	07 April 2022	Superseded
Amendment 1	2.0	11 November 2021	Superseded
Original Protocol	1.0	31 July 2019	Superseded

Amendment 3 (08 March 2024)

Overall Rationale for the Amendment:

Protocol was updated to clarify ambiguous wording/text in the protocol and the safety/full analysis set.

Summary change table from previous version of the protocol

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

Section	Was (Version 3.0, 07 April 2022)	Is (Version 4.0, 08 March 2024)	Rationale
Sponsor Signatory and Medical Monitor Name and Contact Information Page	Sponsor Signatory: PPD Medical Development Director R&D Shanghai Innovation Hub Ipsen (Shanghai) ~~No. 2306 International Capital Plaza~~ ~~No. 1318 North Sichuan Road~~ Shanghai 200080~~0~~ China Medical Monitor Name and Contact Information: PPD Medical Development Director R&D Shanghai Innovation Hub Ipsen (Shanghai) ~~No. 2306 International Capital Plaza~~ ~~No. 1318 North Sichuan Road~~ Shanghai 200080~~0~~ China Telephone:PPD	Sponsor Signatory: PPD Medical Development Director R&D Shanghai Innovation Hub Ipsen (Shanghai) **Unit 01, 15th Floor** **No.218, Xujiahui Road** **Huangpu District** Shanghai 200**01** China Medical Monitor Name and Contact Information: PPD Medical Development Director R&D Shanghai Innovation Hub Ipsen (Shanghai) **Unit 01, 15th Floor** **No.218, Xujiahui Road** **Huangpu District** Shanghai 200**01** China Telephone:PPD	Change of sponsor personnel.
1.3 Schedule of Activities (Table 1 and Table 2)	Footnote "d" Table 1 and Footnote "e" Table 2: Injection site to be specifically checked 2 hours after injection for local reactions on Day 1. After Day 1 any local reaction AEs to be collected on the CRF in the same manner as other AEs.	Footnote "d" Table 1 and Footnote "e" Table 2: Injection site to be specifically checked 2 hours **±15 minutes** after injection for local reactions on Day 1. After Day 1 any local reaction AEs to be collected on the CRF in the same manner as other AEs.	Reasonable time window is allowed for applicability.

Section	Was (Version 3.0, 07 April 2022)	Is (Version 4.0, 08 March 2024)	Rationale
1.3 Schedule of Activities (Table 2)	Footnote "c": Sampling on Day 1. PK time sampling windows: • Pre-dose (≤30 mins) prior to study drug injection • 1h, 2h, 3h post-dose ±5 mins • 4h, 6h, 8h post-dose ±15 mins • 12h post-dose ±30 mins • 24h post-dose ±1 hour • 48h post-dose ±2 hours • ~~120~~h post-dose ±3 hours • 168h post-dose ±4 hours • Day 15 (2 weeks post-dose) ±24 hours • Day 22 (3 weeks post-dose) ±24 hours • Day 29, 57, 85, 113, 141, 169 = clinic visit time windows (±3 days)	Footnote "c": Sampling on Day 1. PK time sampling windows: • Pre-dose (≤30 mins) prior to study drug injection • 1h, 2h, 3h post-dose ±5 mins • 4h, 6h, 8h post-dose ±15 mins • 12h post-dose ±30 mins • 24h post-dose ±1 hour • 48h post-dose ±2 hours • **96**h post-dose ±3 hours • 168h post-dose ±4 hours • Day 15 (2 weeks post-dose) ±24 hours • Day 22 (3 weeks post-dose) ±24 hours • Day 29, 57, 85, 113, 141, 169 = clinic visit time windows (±3 days)	Typo correction.
5.2 Exclusion Criteria	3. 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 ~~as per Pharmacovigilance Risk Assessment Committee (PRAC) recommendations~~.	3**a**. 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	The label of the used medicinal products will be referred per clinical practice.
5.2 Exclusion Criteria	4. Metastatic hormone-sensitive prostate cancer with high tumour burden.	4**a**. Metastatic hormone-sensitive prostate cancer with high tumour burden. **(Note: high tumour burden: presence of visceral metastases and/or at least four bone lesions with at least one lesion outside the vertebral column and/or pelvis per CHAARTED study (Kyriakopoulos 2018).**	Definition of high tumour burden added for clarification.

Section	Was (Version 3.0, 07 April 2022)	Is (Version 4.0, 08 March 2024)	Rationale
5.2 Exclusion Criteria	7. Previous hormone therapy (including abiraterone) for prostate cancer within 6 months prior to study ~~start~~. 8. Previous cytotoxic chemotherapy treatment within 6 months prior to study ~~start~~. 9. Use of finasteride or dutasteride within 2 months prior to study ~~start~~. 14. Participation in another study with an investigational drug or treatment within 3 months prior to study ~~entry~~ or within 5 drug half-lives of the investigational drug (whichever is the longer).	7**a**. Previous hormone therapy (including abiraterone) for prostate cancer within 6 months prior to study **screening**. 8**a**. Previous cytotoxic chemotherapy treatment within 6 months prior to study **screening**. 9**a**. Use of finasteride or dutasteride within 2 months prior to study **screening.** 14**a**. Participation in another study with an investigational drug or treatment within 3 months prior to study **screening** or within 5 drug half-lives of the investigational drug (whichever is the longer).	Clarification of exclusion criteria for consistency within the protocol.
5.2 Exclusion Criteria	11. Any current use or use within 6 months prior to treatment start of medications which are known to affect the metabolism and/or secretion of androgenic hormones: ketoconazole, aminoglutethimide, oestrogens and antiandrogens.	11**a**. Any current use or use within 6 months prior to treatment start of medications which are known to affect the metabolism and/or secretion of androgenic hormones: ketoconazole, aminoglutethimide, oestrogens and antiandrogens. **Note: antiandrogen: enzalutamide, apalutamide or darolutamide is allowed (if required per investigator's clinical judgement) due to no interference on the metabolism and/or secretion of androgenic hormones.**	Clarification added to allow new generation androgen receptor inhibitors considering as they are not anticipated to affect the metabolism and/or secretion of androgenic hormones.
5.2 Exclusion Criteria	12. ~~S~~ystemic or inhaled corticosteroids (topical application permitted).	12a. **Current use of** systemic or inhaled corticosteroids (topical application permitted).	Clarification of corticosteroid use during the study.
6.2 Preparation, Handling, Storage and Accountability	The reconstitution needle should then be changed, and the injection needle (20 G, with safety device) used to administer the product.	The reconstitution needle should then be changed, and the injection needle (20 G, with**out** safety device) used to administer the product.	Typo correction.

Section	Was (Version 3.0, 07 April 2022)	Is (Version 4.0, 08 March 2024)	Rationale
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 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.
8.3.2 Vital Signs	Blood pressure, temperature, respiratory rate and heart rate will be assessed as outlined in the SoA (Section 1.3) 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.	Blood pressure, temperature, respiratory rate and heart rate will be assessed as outlined in the SoA (Section 1.3) with an automated device **(if possible)** so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after 5 minutes rest in supine **or seated** position.	Clarification added to allow flexibility for respiratory rate and position for blood pressure and heart rate per clinical practice.
8.3.4 Magnetic Resonance Imaging Scan	A magnetic resonance imaging (MRI) scan for prostate gland or the whole body ~~(~~only if necessary, based on investigator's judgement) will be performed as described in the SoA (Table 1 and Table 2) to confirm disease stage prior to study entry.	A magnetic resonance imaging (MRI) scan for prostate gland or the whole body**,** only if necessary **(**based on investigator's judgement**),** will be performed as described in the SoA (Table 1 and Table 2) to confirm disease stage prior to study entry.	Clarification for consistency with SoA Table 1 and Table 2 footnote "g" and "h", respectively.
9.3 Analysis Sets	Safety Set: The safety set will contain all participants who receive ~~at least one~~ dose of study intervention. Full Analysis Set: ~~A~~ll treated participants ~~having at least one baseline and at least one post baseline assessment of the primary efficacy endpoint~~.	Safety Set: The safety set will contain all participants who receive **the single** dose of study intervention. Full Analysis Set: **The FAS will contain a**ll treated participants **who complete the study or is a treatment failure**. **Completing the study is defined as having serum testosterone measurement at baseline, Day 29 and Day 169. Treatment failure is defined as escaping castration (testosterone level ≥50 ng/dL) at any assessments on and after Day 29 during the study, or premature discontinuation from the intervention period**	Clarification of the safety and full analysis sets.

Section	Was (Version 3.0, 07 April 2022)	Is (Version 4.0, 08 March 2024)	Rationale
		due to drug-related reasons (adverse event or death).	
10.1.5 Dissemination of Clinical Study Data	• Protocol and result summary will be made publicly available on the US 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 and result summary will be made publicly available on the US Clinical Trials Registry (ClinicalTrials.gov). The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation.	Clarification for studies conducted in China.

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
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
CA	Competent authority
CI	Confidence interval
C_{max}	Maximum concentration
CRF/eCRF	Case report form/electronic case report form
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
CRO	Contract research organisation
CSR	Clinical study report
ECG	Electrocardiogram
EDC	Electronic data capture
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GnRH	Gonadotropin-releasing hormone
Hb	Haemoglobin
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
i.m.	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IVF	In vitro fertilisation
ITT	Intention-to-treat
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LH	Luteinising hormone

ABBREVIATION	Wording Definition
LHRH	Luteinising hormone-releasing hormone
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Non-compartmental analysis
NCI-CTCAE	National Cancer Institute – Common Toxicity Criteria for Adverse Events
NOS	Not otherwise specified
PD	Pharmacodynamics
PK	Pharmacokinetics
PLGA	Poly(1actide-CO-glycolide)
PP	Per Protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PSA	Prostate specific antigen
PT	Preferred term
SAE	Serious adverse event
SAS®	Statistical Analysis Software
SD	Standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
t_{cast}	Time to castration
t_{max}	Time to peak serum/plasma concentration
TNM	Tumour, lymph nodes, metastases
ULN	Upper limit of normal
US	United States of America
WBC	White blood cells
WHO	World Health Organisation
WHODRUG	WHO Drug Dictionary

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A multicentre, open-label, single-arm study to investigate the efficacy and safety of triptorelin pamoate 22.5 mg 6-month formulation in Chinese patients with locally advanced or metastatic prostate cancer

Short Title:

Effects of triptorelin pamoate 6-month when given to adult Chinese participants with advanced cancer in the prostate

Rationale:

The 6-month triptorelin formulation (22.5 mg) has been evaluated in a multicentre, non-comparative Phase III study in participants with advanced prostate cancer, conducted between July 2006 and August 2007 [Lundstrom 2009]. The results from the study have shown that the new triptorelin 6-month formulation (22.5 mg) rapidly induces and maintains castration in participants with locally advanced or metastatic prostate cancer. In the intention-to-treat (ITT) population, 97.5% (117/120) of participants were castrated (testosterone level <50 ng/dL) on Day 29, and 93.0% (107/115) of participants maintained castration from Week 8 (Day 57) to end of Week 48. The efficacy results of the 6-month formulation have been reviewed with those obtained in previous studies with the marketed triptorelin 1- and 3-month formulations. Results show that the rate of castration achieved with the 6-month formulation on Day 29, after the first triptorelin injection, was comparable to those with the 1-month and 3-month formulations [Breul 2017].

In terms of local tolerance at the injection site, intramuscular triptorelin injections were well tolerated as confirmed in the phase III study where injection site reactions were assessed by active questioning: 6.7% participants with injection-site reactions reported as adverse events (AEs), which is lower than for other 6-month gonadotropin-releasing hormone (GnRH) formulations [Lundstrom 2009]. In a pooled analysis, very few (<5%) local adverse reactions at the injection site have been reported in clinical studies with all triptorelin sustained-release formulations (1-, 3- and 6 month) [Breul 2017].

The advantage of the sustained-release 6-month triptorelin pamoate formulation is that the reduced frequency of injections will provide greater convenience to both the participants and the physician and it may also improve the participant acceptability and compliance with the injection schedule.

The present study will assess the efficacy and safety of the sustained-release 6-month triptorelin pamoate formulation in Chinese participants with locally advanced or metastatic prostate cancer for confirming the registration of this product in China. At the same time, triptorelin pharmacokinetics (PK) and testosterone pharmacodynamics (PD) will be assessed in in this study population.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of triptorelin pamoate 22.5 mg 6-month formulation in achieving castrate levels of testosterone	• Percentage of participants achieving castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) on Day 29
• To evaluate the efficacy of triptorelin pamoate 22.5 mg 6-month formulation in maintaining the castrate levels of serum testosterone	• Percentage of participants maintaining the castrate levels from Week 8 to Week 24
Secondary	
• To assess the safety profile including local tolerability of triptorelin pamoate 22.5 mg 6-month formulation	• Incidence of TEAEs (including local tolerability) throughout the study i.e., up to Week 24 • Change from baseline in clinical safety laboratory parameters (blood chemistry and haematology) at Week 24 • Change from baseline in physical examination at Day 1, Week 12 and Week 24 • Change from baseline in ECG at Week 4 and Week 24 • Change from baseline in vital signs (blood pressure and heart rate) at each visit up to Week 24
• To demonstrate the effect of triptorelin pamoate 22.5 mg 6-month formulation on PSA response	• Percent change in PSA from baseline (prior to injection) at Week 12 and Week 24 (Percent change in PSA is defined as the absolute value of difference between the PSA values at Week 12 and Week 24 and the baseline value divided by the baseline value)
• To assess the PK of triptorelin pamoate 22.5 mg 6-month formulation in a subset of 12 participants	• PK parameters for dosing interval up to 24 weeks: ○ t_{max}, ○ C_{max}, ○ AUC_{0-169} ○ AUC_{last}
• To assess the PD of testosterone in a subset of 12 participants	• PD parameters for dosing interval up to 24 weeks: ○ t_{max}, ○ C_{max} ○ t_{cast}
• To assess the PK of triptorelin pamoate 22.5 mg 6-month formulation for all participants	• Sparse plasma concentrations of triptorelin at pre-dose and at Week 4, 8, 12, 16, 20 and 24
• To assess the PD of testosterone for all participants	• Sparse serum concentrations of testosterone at pre-dose and at Week 4, 8, 12, 16, 20 and 24
Exploratory	
• To evaluate the PK/PD relationship between the PK of triptorelin pamoate 22.5 mg 6-month and testosterone concentration versus time profiles (PD)	

AUC_{0-169}=area under the plasma concentration time curve from time 0 to the visit on Day 169; AUC_{last}=area under the plasma concentration time curve from time 0 to the last quantifiable concentration; C_{max}=maximum concentration; ECG=electrocardiogram; PD=pharmacodynamics; PK=pharmacokinetics; PSA=prostate specific antigen; t_{cast}=time to castration; TEAE=treatment-emergent adverse event; t_{max}=time to peak serum/plasma concentration
Note: A list of laboratory parameters to be assessed during the study are presented in Appendix 10.2.

Overall Design:

This is a prospective, interventional, multicentre, open-label phase IIIb, single-arm study with a treatment period of 24 weeks for each participant. A total of 195 Chinese adult participants with locally advanced or metastatic prostate cancer will be enrolled in the study. All enrolled participants will receive one intramuscular (i.m.) injection of the 6-month formulation containing 22.5 mg triptorelin pamoate on Day 1.

Intervention Groups and Duration:

Triptorelin pamoate 22.5 mg (6-month formulation), i.m. injection, single dose on Day 1.

Visit Frequency:

This study will consist of a 4-week screening period, a single open-label administration of the study intervention on Day 1. Following treatment, visits will occur on Day 2, Day 3, Day 5, Day 8, Day 15, Day 22 in a subset of 12 participants, and for all participants on Day 29, Day 57, Day 85, Day 113, Day 141 and Day 169.

Study Participant Duration:

Participants are expected to participate in this study for 24 weeks.

Number of Participants:

Approximately 195 participants (including a rich sampling pharmacokinetic/pharmacodynamic subset of 12 participants) are planned to be assigned to study intervention.

Statistical Methods:

Sample Size Determination

The sample size was estimated based on data from the previous Study DEB-TRI6M-301, 97.5% of participants achieving castration on Day 29 and 93% of participants maintaining castration from Week 8 to Week 24.

Sample size is calculated to fulfil the co-primary efficacy criteria of this study, which is to assess the proportion of participants achieving castrate levels of testosterone on Day 29 and the proportion of participants maintaining the castrate levels of serum testosterone from Week 8 to end of Week 24.

For an exact binomial test of a proportion with a two-sided nominal significance level of 0.05 and null proportion of 85%, a sample size of 165 participants has an exact power of 88.3% when the true proportion is 93% (of participants maintaining castration from Week 8 to Week 24). This sample size of 165 participants has a power >99.9% when the true proportion is 97.5% (of participants achieving castrate testosterone levels). Exact two-sided 95% CI for a binomial proportion was computed by statistical analysis software (SAS) using the exact binomial distributions.

Assuming the dropout rate will be around 15%, a sample size of 195 participants with locally advanced or metastatic prostate cancer in total is planned for this study.

Primary Analysis

The analysis sets for the primary and secondary efficacy endpoints will be the full analysis set (FAS) and the per protocol (PP) set.

Co-primary endpoints will be tabulated with two-sided 95% confidence interval (95% CI) using the Clopper-Pearson exact method.

Secondary Analyses

Prostate-specific antigen (PSA) percent change from pre-treatment Day 1 will be reported at Week 12 and Week 24, using descriptive statistics. The PK (triptorelin) and PD (testosterone) metrics will be reported as descriptive statistics.

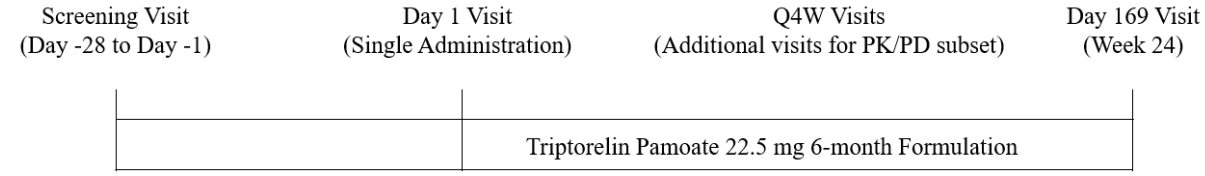
For the analysis of safety, any participant who receives the single dose of triptorelin will be analysed (Safety population). The incidence of AEs as per National Cancer Institute – Common Toxicity Criteria (NCI-CTCAE) Version 5.0 grading will be summarised by System Organ Class (SOC), preferred term (PT) severity and relationship to study drug. Adverse events will be coded using Medical Dictionary of Drug Regulatory Activities (MedDRA) Version 24.1 (or higher if available) prior to analysis. Changes from baseline in clinical laboratory tests, physical examinations, electrocardiogram (ECG) and vital signs will be summarised using descriptive statistics.

The data will be summarised with the descriptive statistics (i.e. N, means, standard deviation, minimum, maximum, median) for the continuous variables and with counts and percentages for the categorical variables. In addition, for PK endpoints, the geometric mean, the standard deviation of the geometric mean, and geometric coefficient of variance% will be presented.

1.2 Schema

The study schema is shown in Figure 1.

Figure 1 Study Schema



PD=pharmacodynamic; PK=pharmacokinetic; Q4W=every 4 weeks

1.3 Schedule of Activities (SoA)

The schedule of activities during the study is summarised for all participants in Table 1, except the PK/PD subset of 12 participants which is summarised in Table 2.

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 will be provided to the investigator in a separate document. Such document will be filed in the trial master file. Independent ethics committees (IECs)/institutional review boards (IRBs) will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

Table 1 Schedule of Activities for All Participants Except the Pharmacokinetic/Pharmacodynamic Subset

Procedure	**Screening**	**Intervention Period**						**EoS/EW**
End of Week	**-**	**-**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**
Day	**D-28 to D-1**	**D1**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**
Visit Window	-	-	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Informed consent	X							
Eligibility	X	X						
Demography	X							
Medical and surgical history	X							
Physical examination [f]	X	X [a]			X			X
MRI scan [g]	X							
Disease-specific medical history	X							
Prior disease-specific treatment	X							
Body weight	X							X
Vital signs	X	X [a]	X	X	X	X	X	X
12-lead electrocardiogram[b]	X		X					X
ECOG Score	X							
Injection triptorelin 6M		X						
Blood samples for triptorelin PK		X [a]	X	X	X	X	X	X
Blood sample for testosterone PD [h]	X	X [a, e]	X	X	X	X	X	X
Blood samples for PSA [h]	X	X [a, e]			X			X
Blood samples [c] laboratory safety tests	X	X [a, e]						X
Local tolerance [d]		X						
Previous (excluding disease-specific) and concomitant medication	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X

6M=6-month formulation, AE=adverse event, ALT=alanine aminotransaminase, AST=aspartate aminotransaminase, CRF=case report form, D=day; ECG=electrocardiography; ECOG=Eastern Cooperative Oncology Group, EoS/EW=end of study/early withdrawal, Hb=haemoglobin, M1b=distant metastasis bone(s), MRI=magnetic resonance imaging; PD=pharmacodynamic, PK=pharmacokinetics, PSA=prostate-specific antigen, WBC=white blood cell.

a Assessment or blood sampling to be performed prior to study intervention injection. PK Predose sampling window (≤30 minutes).
b ECG to be assessed as clinically indicated at any other time in the study as required.
c Haematology (WBC, platelet count, Hb), Blood Chemistry (creatinine, glucose, ALT, AST, alkaline phosphatase, bilirubin (total and conjugated)) will be tested at the local laboratory. Glucose: fasting levels in all participants at Screening visit, fasting levels on Days 1 and 169. Fasting is not necessary for diabetic participants.
d Injection site to be specifically checked 2 hours ±15 minutes after injection for local reactions on Day 1. After Day 1, any local reaction AE to be collected on the CRF in the same manner as other AEs.
e Measurement of testosterone, PSA and laboratory safety tests for analysis purposes only and not for eligibility. The screening testosterone, PSA and safety laboratory test results will be used for eligibility.
f Complete physical examination to be performed (or brief physical examination based on investigator judgement). Participants, particularly those with M1b status, should be advised regarding clinical signs suggestive of spinal cord compression.
g Scan for prostate gland or the whole body, only if necessary, based on investigator's judgement. An MRI scan is not required if performed within 1 month of screening.
h Testosterone and PSA testing will be performed at the central laboratory.
See Appendix 10.5 for ECOG performance scale.

Table 2 Schedule of Assessments for the Pharmacokinetic/Pharmacodynamic Subset of Participants

Procedures	**Screening**	**Intervention Period**												**EoS/EW**
End of Week	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**
Day	**D-28 to D-1**	**D1**	**D2**	**D3**	**D5**	**D8**	**D15**	**D22**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**
Visit Window									±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Informed consent	X													
Eligibility	X	X												
Demography	X													
Medical and surgical history	X													
Physical examination [g]	X	X [a]									X			X
MRI scan [h]	X													
Disease-specific medical history	X													
Prior disease-specific treatment	X													
Body weight	X													X
Vital signs	X	X [a]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram[b]	X								X					X
ECOG Score	X													
Injection triptorelin 6M		X												
Blood sample for triptorelin PK		X [c]	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for testosterone PD [i]	X	X [a, f]	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for PSA [i]	X	X [a, f]									X			X
Blood samples for [d] laboratory safety tests	X	X [a, f]												X
Local tolerance [e]		X												

Procedures	Screening	Intervention Period												EoS/EW
End of Week	-	-	-	-	-	-	-	-	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**
Day	**D-28 to D-1**	**D1**	**D2**	**D3**	**D5**	**D8**	**D15**	**D22**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**
Visit Window									±3 days	±3 days	±3 days	±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	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

6M=6-month formulation, AE=adverse event, ALT=alanine aminotransaminase, AST=aspartate aminotransaminase, CRF=case report form, D=day; ECG=electrocardiography; ECOG=Eastern Cooperative Oncology Group, EoS/EW=end of study/early withdrawal; h=hours; Hb=haemoglobin, M1b=distant metastasis bone(s); MRI=magnetic resonance imaging; PD=pharmacodynamic, PK=pharmacokinetics, PSA=prostate-specific antigen, WBC=white blood cell.

a Assessment or blood sampling to be performed prior to study intervention injection.

b ECG to be assessed as clinically indicated at any other time in the study as required.

c Sampling on Day 1. PK time sampling windows:
- Pre-dose (≤30 mins) prior to study drug injection
- 1h, 2h, 3h post-dose ±5 mins
- 4h, 6h, 8h post-dose ±15 mins
- 12h post-dose ±30 mins
- 24h post-dose ±1 hour
- 48h post-dose ±2 hours
- 96h post-dose ±3 hours
- 168h post-dose ±4 hours
- Day 15 (2 weeks post-dose) ±24 hours
- Day 22 (3 weeks post-dose) ±24 hours
- Day 29, 57, 85, 113, 141, 169 = clinic visit time windows (±3 days)

d Haematology (WBC, platelet count, Hb), Blood Chemistry (creatinine, glucose, ALT, AST, alkaline phosphatase, bilirubin (total and conjugated) will be tested at the local laboratory. Glucose: Fasting levels in all participants at Screening visit, fasting levels on Days 1 and 169. Fasting is not necessary for diabetic participants.

e Injection site to be specifically checked 2 hours ±15 minutes after injection for local reactions on Day 1. After Day 1 any local reaction AEs to be collected on the CRF in the same manner as other AEs.

f Measurement of testosterone, PSA and laboratory safety tests for analysis purposes only and not for eligibility. The screening testosterone, PSA and safety laboratory test results will be used for eligibility.

g Complete physical examination to be performed (or brief physical examination based on investigator judgement). Participants, particularly those with M1b status, should be advised regarding clinical signs suggestive of spinal cord compression.

h Scan for prostate gland or the whole body, only if necessary, based on investigator's judgement. An MRI scan is not required if performed within 1 month of screening.

i Testosterone and PSA testing will be performed at the central laboratory.

See Appendix 10.5 for ECOG performance scale.

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

Results from a global phase III study have shown that the new triptorelin 6-month formulation (22.5 mg) was well tolerated and rapidly induced and maintained castration in participants with locally advanced or metastatic prostate cancer [Lundstrom 2009].

The advantage of the sustained-release 6-month triptorelin pamoate formulation is that the reduced frequency of injections will provide greater convenience to both the patient and the physician and may also improve patient acceptability and compliance with the injection schedule.

The present study will assess the efficacy and safety of the sustained-release 6-month triptorelin pamoate formulation in Chinese participants with locally advanced or metastatic prostate cancer for confirming the registration of this product in China. In addition, triptorelin pharmacokinetics (PK) and testosterone pharmacodynamics (PD) will be assessed in the study population.

2.2 Background

Prostate cancer is one of the most commonly occurring malignancies in the male population and thus the second cause of death from cancer in men over 50 in the western world. In most patients, it is an androgen-dependent tumour at initial presentation.

Growth of the prostatic tissue is regulated by a network of hormones in which androgens play a major role. Gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone releasing hormone (LHRH), released in a pulsatile manner by the hypothalamus, stimulates the pituitary to release in pulses the gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH stimulates the production of testicular testosterone; 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 regulatory role played by the testicular androgens in the growth of prostate cancer cells, the mainstay of treatment for advanced prostate cancer was for decades androgen deprivation by bilateral orchiectomy and/or oestrogen therapy. The limitations of these therapeutic modalities led to the development of GnRH agonists, which have made medical castration the preferred option among many patients with metastatic disease [Filicori 1994]. The efficacy and safety of these agents is now well established, and GnRH agonists are not associated with an increased risk of cardiovascular disease.

The therapeutic activity of the GnRH agonists is through 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.

Achievement of castration levels of testosterone is generally obtained around one month after start of therapy. Of note, long term endocrine status and evolution of advanced prostate cancer treated with GnRH agonists are similar to those observed after surgical castration [Parmar 1987, DeSy 1988, Botto 1987] but in contrast to surgical castration, treatment with GnRH agonists initially results in a markedly, albeit temporary (~2 weeks), increase of gonadal androgen

release (flare-up phenomenon). The initial rise in testosterone may cause a temporary worsening of symptoms including increase in bone pain within the first days of treatment; for these reasons, GnRH agonists are contraindicated for use in patients presenting metastases with neurologic symptomatology, or other possible life-threatening metastases. The most significant side effects - hot flushes, decreased libido and erectile dysfunction - are linked to the pharmacological effect (castrate levels of testosterone) and are usually relatively mild and reversible upon cessation of therapy.

Since the discovery and synthesis of GnRH, many analogues of the native decapeptide have been synthesised in attempts to develop agonists with increased in vivo half-life and potency.

As shown in the amino acid sequences below, the major structural difference between the native decapeptide and the triptorelin agonist is the substitution of a different D-amino acid at position six, which is the hinge between the two active portions of the peptide. However, triptorelin retains the parts of the native decapeptide responsible for its biological activity.

Decapeptide	1 2 3 4 5 6 7 8 9 10 Glu-His-Trp-Ser-Tyr- Gly -Leu-Arg-Pro-Gly-NH2
Triptorelin	(pyro) Glu-His-Trp-Ser-Tyr- D-Trp -Leu-Arg-Pro-Gly-NH2

GnRH has a L-glycine at position six, whereas triptorelin has a D-tryptophan. The substitution of the D-amino acid increases resistance to cleavage by proteolytic enzymes and increases biological potency relative to the native decapeptide [Barron 1982]. Triptorelin, like other GnRH agonists, has a short half-life in vivo (t½=5 h), therefore, sustained-release dosage forms have been developed by combining the peptide with a biocompatible and biodegradable copolymer (lactide-glycolide). By modifying the molar ratio of lactic acid to glycolic acid, the peptide is released continuously over periods ranging from 28 days (1-month formulation) to 168 days (6-month formulation) following administration of a single intramuscular (i.m.) injection.

The 6-month triptorelin formulation (22.5 mg) has been evaluated in a multicentre, non-comparative phase III study in participants with advanced prostate cancer, conducted between July 2006 and August 2007 [Lundstrom 2009]. The results from the study have shown that the new triptorelin 6-month formulation (22.5 mg) rapidly induces and maintains castration in participants with locally advanced or metastatic prostate cancer. In the intention-to-treat (ITT) population, 97.5% (117/120) of participants were castrated (testosterone level <50 ng/dL) on Day 29, and 93.0% (107/115) of participants maintained castration from Week 8 (Day 57) to end of Week 48. The efficacy results of the 6-month formulation have been reviewed with those obtained in previous studies with the marketed triptorelin 1- and 3-month formulations. Results show that the rate of castration achieved with the 6-month formulation on Day 29, after the first triptorelin injection, was comparable to those with the 1-month and 3-month formulations [Breul 2017].

In terms of local tolerance at the injection site, intramuscular triptorelin injections were well tolerated and in the phase III study where injection site reactions were assessed by active questioning: 6.7% participants with injection-site reactions reported as adverse events (AEs), which is lower than for other 6-month GnRH formulations [Lundstrom 2009]. In a pooled analysis, very few (<5%) local adverse reactions at the injection site have been reported in clinical studies with all triptorelin sustained-release formulations (1-, 3- and 6-month) [Breul 2017].

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 reasonably expected AEs of triptorelin may be found in the IB.

2.3.1 Risk Assessment

A risk assessment for this study is provided in Table 3.

Table 3 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 in 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] See Section 8.3	See IB Section 6.6.1	**Participant selection:** Participants with significant medical conditions and at high risk of presenting treatment related SAEs and high-grade toxicity will be excluded from the study. **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 of unacceptable toxicity 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

IB=investigator's brochure; SAE=serious adverse event
a Pregnancy is not relevant 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

Based on the nonclinical and clinical data generated up to finalisation of the protocol, treatment with triptorelin 6-month formulation may maintain castrate levels of testosterone for a longer period, i.e. 6 months (24 weeks), thereby reducing the need for frequent injections, in Chinese participants with locally advanced or metastatic prostate cancer to a similar extent as in a previous global phase III study.

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 triptorelin are justified by the anticipated benefits that may be afforded to Chinese participants with locally advanced or metastatic prostate cancer.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of triptorelin pamoate 22.5 mg 6-month formulation in achieving castrate levels of testosterone	• Percentage of participants achieving castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) on Day 29
• To evaluate the efficacy of triptorelin pamoate 22.5 mg 6-month formulation in maintaining the castrate levels of serum testosterone	• Percentage of participants maintaining the castrate levels from Week 8 to Week 24
Secondary	
• To assess the safety profile including local tolerability of triptorelin pamoate 22.5 mg 6-month formulation	• Incidence of TEAEs (including local tolerability) throughout the study i.e., up to Week 24 • Change from baseline in clinical safety laboratory parameters (blood chemistry and haematology) at Week 24 • Change from baseline in physical examination at Day 1, Week 12 and Week 24 • Change from baseline in ECG at Week 4 and Week 24 • Change from baseline in vital signs (blood pressure and heart rate) at each visit up to Week 24
• To demonstrate the effect of triptorelin pamoate 22.5 mg 6-month formulation on PSA response	• Percent change in PSA from baseline (prior to injection) at Week 12 and Week 24 (percent change in PSA is defined as the absolute value of difference between the PSA values at Week 12 and Week 24 and the baseline value divided by the baseline value)
• To assess the PK of triptorelin pamoate 22.5 mg 6-month formulation in a subset of 12 participants	• PK parameters for dosing interval up to 24 weeks: o t_{max} o C_{max} o AUC_{0-169} o AUC_{last}
• To assess the PD of testosterone in a subset of 12 participants	• PD parameters for dosing interval up to 24 weeks: o t_{max} o C_{max} o t_{cast}
• To assess the PK of triptorelin pamoate 22.5 mg 6-month formulation for all participants	• Sparse plasma concentrations of triptorelin at pre-dose and post-dose at Weeks 4, 8, 12, 16, 20 and 24
• To assess the PD of testosterone for all participants	• Sparse serum concentrations of testosterone at pre-dose and post-dose at Weeks 4, 8, 12, 16, 20 and 24
Exploratory	
• To evaluate the PK/PD relationship between the PK of triptorelin pamoate 22.5 mg 6-month formulation and testosterone concentration versus time profiles (PD)	

AUC_{0-169}=area under the plasma concentration time curve from time 0 to the visit on Day 169; AUC_{last}=area under the plasma concentration time curve from time 0 to the last quantifiable concentration; C_{max}=maximum concentration;

ECG=electrocardiogram; PD=pharmacodynamics; PK=pharmacokinetics; PSA=prostate specific antigen; t_{cast}=time to castration; TEAE=treatment-emergent adverse event; t_{max}=time to peak serum/plasma concentration

Note: A list of laboratory parameters to be assessed during the study are presented in Appendix 10.2.

4 STUDY DESIGN

4.1 Overall Design

This is a prospective, interventional, multicentre, open-label phase IIIb, single-arm study with a treatment period of 24 weeks for each participant. A total of 195 Chinese adult participants with locally advanced or metastatic prostate cancer will be enrolled in the study. All enrolled participants will receive one i.m. injection of the 6-month formulation containing 22.5 mg triptorelin pamoate on Day 1.

This study will consist of a 4-week screening period, during which participants with advanced or metastatic prostate cancer will be screened for eligibility. On Day 1, eligible participants will receive a single open-label administration of the study intervention. Following treatment on Day 1, visits will occur on Day 2, Day 3, Day 5, Day 8, Day 15, Day 22 in a subset of 12 participants, and for all participants on Day 29, Day 57, Day 85, Day 113, Day 141 and Day 169. For more details on sampling schedule see the SoA (Table 1 and Table 2).

The maximum duration of the study is approximately 30 months from screening to the last study visit. Participants who complete all scheduled visits will be considered to have completed the study. Participants who complete the study will have final procedures and assessments performed at the final visit (Day 169). Participants who withdraw from the study before the completion of the Day 169 evaluation period 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 single-arm, phase III study will investigate the efficacy, safety and PK/PD of triptorelin 6-month formulation in Chinese adult males with locally advanced or metastatic prostate cancer.

According to data from China National Cancer Registration Institute, prostate cancer has become the most common tumour in male urinary malignancies since 2008. The incidence rate was approximately 9.80/100,000 in 2014 and ranks the sixth common malignancy in male malignant tumours. The mortality of prostate cancer is 4.22/100,000, and it is the 9th common cause of death in all male malignancies. The staging varies widely between China and Western developed countries. In China, only 30% of newly diagnosed patients are clinically localised, and the rest are locally advanced or extensively metastatic disease, who have lost the chance of radical treatment with poor prognosis [National Health Commission China 2019]. This study will enrol adult Chinese men with advanced prostate cancer.

The non-comparative, open-label clinical study design is acceptable as the efficacy of triptorelin will be assessed by the percentage of participants achieving castrate levels of serum testosterone (defined as <50 ng/dL or 1.735 nmol/L) on Day 29 and maintaining castrate levels of serum testosterone from Week 8 to Week 24 (co-primary endpoints). Studies conducted in Western countries have shown that the rate of castration achieved with the 6-month formulation on Day 29, after the first triptorelin injection, was comparable to those with the 1-month and 3-month formulations [Breul 2017]. No studies have evaluated the 6-month triptorelin formulation in Chinese men with locally advanced or metastatic prostate cancer, thus the outcomes of this study intend to fulfil an unmet need and provide treatment convivence for the patient and physician.

This study will evaluate the PK/PD profile of triptorelin 6-month formulation in this study population. The blood sample collection scheme was designed to collect the minimum number of blood samples to help provide useful PK/PD information of study treatment in Chinese men with locally advanced or metastatic prostate cancer.

4.3 Justification for Dose

For this intervention, the term "dose" refers to the i.m. injection of triptorelin 22.5 mg created to guarantee the release of a monthly dose of 3.75 mg over a 169-day period. In addition, results from a phase III study have shown the 6-month triptorelin 22.5 mg formulation to induce and maintain castration in participants with locally advanced or metastatic prostate cancer, as well as demonstrate a good safety profile [Lundstrom 2009].

4.4 End of Study Definition

The end of the study (EoS) is defined as the date of the last visit of the last participant in the study as shown in the SoA (Table 1 and Table 2).

The overall duration of the study (from first participant in, to last participant out) will be approximately 30 months. The study will be considered to have ended after the last participant has completed the last visit (at Week 24) in the study.

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 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.
2. Participant must be over 18 years of age, at the time of signing the informed consent.
3. Has a histologically or cytologically confirmed adenocarcinoma, locally advanced or metastatic prostate cancer, which is staged $T_{3-4}N_xM_0$ or $T_xN_1M_0$ or $T_xN_xM_1$ according to the TNM classification (Appendix 10.4). Or participant has PSA recurrence after curative treatment and be a candidate for androgen deprivation therapy (ADT).

   (Note: PSA recurrence after radical prostatectomy: PSA ≥0.2 ng/mL and rising, confirmed on a repeat test; PSA recurrence after radiation therapy: PSA increased 2 ng/mL than the lowest level.)
4. Has serum testosterone level >150 ng/dL (> 5.2 nmol/L).
5. Has expected survival time ≥12 months according to the investigator's assessment.
6. Has Eastern Cooperative Oncology Group (ECOG) performance status score ≤1 (see Appendix 10.5).
7. Has absence of another malignancy, other than local dermatological, for the previous 5 years.
8. Participant is male.
9. Male participants must agree that, if their partner is at risk of becoming pregnant, they will use an effective method of contraception. The participant must agree to use the contraception during the whole period of the study and for 9 months after the last dose of study intervention.

5.2 Exclusion Criteria

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

Medical conditions

1. Risk of a serious complication in the case of tumour flare (known or suspicion of vertebral metastases threatening spinal cord compression or significant obstructive uropathy).
2. Presence of another neoplastic lesion or brain metastases.

3a. 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.

4a. Metastatic hormone-sensitive prostate cancer with high tumour burden.

   (Note: high tumour burden: presence of visceral metastases and/or at least four bone lesions with at least one lesion outside the vertebral column and/or pelvis per CHAARTED study (Kyriakopoulos 2018).

5. Metastatic castration-resistant prostate cancer.

Prior/concomitant therapy

6. Previous surgical castration.

7a. Previous hormone therapy (including abiraterone) for prostate cancer within 6 months prior to study screening.

8a. Previous cytotoxic chemotherapy treatment within 6 months prior to study screening.

9a. Use of finasteride or dutasteride within 2 months prior to study screening.

10. Previous hypophysectomy or adrenalectomy.

11a. Any current use or use within 6 months prior to treatment start of medications which are known to affect the metabolism and/or secretion of androgenic hormones: ketoconazole, aminoglutethimide, oestrogens and antiandrogens.

Note: antiandrogen: enzalutamide, apalutamide or darolutamide is allowed (if required per investigator's clinical judgement) due to no interference on the metabolism and/or secretion of androgenic hormones.

12a. Current use of systemic or inhaled corticosteroids (topical application permitted).

13. Any previous use of traditional Chinese medicine or herbal products within 1 month prior to study screening or planned use during the study of products, which are known to have cytotoxic effect or affect the metabolism and/or secretion of androgenic hormones.

Prior/concurrent clinical study experience

14a. Participation in another study with an investigational drug or treatment within 3 months prior to study screening or within 5 drug half-lives of the investigational drug (whichever is the longer).

Diagnostic assessments

15. Severe kidney or liver impairment (creatinine >2 x upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >3 x ULN).

Other exclusions

16. Any concomitant disorder or resulting therapy that is likely to interfere with participant compliance, the i.m. administration of the drug or with the study in the opinion of the investigator.

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

18. Known active use of recreational drug or alcohol dependence in the opinion of the investigator.

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) will not be rescreened.

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

Study intervention is described in Table 5.

Table 5 Study intervention administered

Intervention Name	Triptorelin pamoate (embonate) salt
Intervention Description	A PR formulation of triptorelin pamoate 6-month formulation in D,L-lactide-co-glycolide polymers for single i.m injection
Type	Drug
Dose Formulation	A yellow freeze-dried cake or powder supplied in a single 6 mL glass vial
Unit Dose Strength(s)	22.5 mg (with release of a monthly dose of 3.75 mg over a 169-day period)
Dosage Level(s)	Single dose delivered on Day 1
Route of Administration	i.m. injection
Use	Experimental
IMP and NIMP/AxMP	IMP
Sourcing	Manufactured by Debiopharm and provided centrally by the sponsor
Packaging and Labelling	Study intervention will be provided in a box containing one vial, one ampoule and one blister containing one injection syringe and two injection needles. 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	Diphereline®

i.m.=intramuscular; IMP=investigational medicinal product; NIMP=non-investigational medicinal product; AxMP=auxiliary medicinal product; PR=prolonged release

6.2 Preparation, Handling, Storage and Accountability

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 IMP reconstitution and administration.

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

The instructions for reconstitution hereafter and in the leaflet provided with triptorelin must be strictly followed.

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 injection needle (20 G, without 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.

- 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".

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 procedures for blinding are applicable.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in 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 other than the person administering the study intervention.

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 product characteristics). If overdose occurs, this should be managed symptomatically.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.

- Closely monitor the participant for any AE/SAE and laboratory abnormalities (at least up to the Week 24 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.

6.8 Concomitant Therapy

Any medication (excluding prior disease-specific medications) or vaccine (including over the counter prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant had received within 2 months before triptorelin administration or receives during the study 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, frequency and route of administration

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

The following concomitant medications are not permitted during this study:

- Any treatment or procedure with a specific or potential effect on androgenic hormones be administered concomitantly to the study drug (will be considered as a protocol violation). Per investigator's clinical judgement, suggest offering short-term administration of an older generation androgen receptor antagonist to M1 participants starting study intervention to reduce the risk of the 'flare-up' phenomenon.
- Any medication which raises prolactin levels and those affecting pituitary secretion of gonadotropins
- All drugs mentioned as prohibited in the exclusion criteria:
  - 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, abiraterone.
  - Any traditional Chinese medicine or 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.
  - Concomitant use of medications known to prolong QT interval should not be given (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:

- 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 this study, there will only be one treatment cycle administered on Day 1 of the study, thus discontinuation of the study intervention is not applicable (i.e. no repeat cycles). In the event a participant is enrolled, but does not receive study intervention, the participant will not remain in the study and EoS/EW assessment will not be performed. Only the reason for discontinuation will be collected.

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 suspected or confirmed COVID-19 (SARS-CoV-2) infection, 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 intervention administration.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her 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, 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 follow-up 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 withdraws consent for any further contact, the investigator will explain in the medical records that the participant was also withdrawn from study procedures. This information must be entered in the eCRF.
- If a participant withdraws from the study, he/she 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 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 they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

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, he/she 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 enrolled, 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.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Table 1 and Table 2). Protocol waivers and exemptions are not allowed.
- 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.
- Adherence to the study design requirements, including those specified in the SoA (Table 1 and Table 2), 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 and Table 2)
- 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 95 mL for the PK/PD subset of participants and 60 mL for all other participants. Blood sampling should be taken at the same time of day during different visits.
- 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.

8.2 Efficacy Assessments

Efficacy will be assessed in this study using the surrogate PD markers for testosterone and PSA concentrations.

Approximately 26 mL of blood will be collected from all participants, and approximately 38 mL of blood from the PK/PD subset participants, for measurement of testosterone and PSA. Serum samples used to evaluate testosterone and 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.

8.2.1 Testosterone

Testosterone will be assessed by a third-party vendor, as described in the Laboratory Manual. Serum will be analysed to determine concentrations of testosterone using a validated, specific and sensitive liquid chromatography tandem mass spectrometry (LC-MS/MS) methods.

Blood samples for the determination of testosterone serum concentrations will be collected at the timepoints indicated in the SoA (Table 1 (all participants) and Table 2 (for the subset of 12 participants)).

Residual serum samples remaining from the analysis may also be retained by the sponsor for up to 5 years after completion of the study. This could include using leftover serum for long-term stability or reproducibility assessments.

Surplus serum samples can only be used in China. Surplus serum samples will be managed anonymously and will not be identifiable.

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 Table 1 (all participants) and Table 2 (for the subset of 12 participants).

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study specific evaluations. Participants will acknowledge and agree to the possible use of this information for the study by giving informed consent.

8.3.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the skin, and cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded. Body weight will be measured in underwear and without shoes.

A brief physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, abdomen (liver and spleen).

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

Any clinically significant physical examination findings (abnormalities) observed during the study 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.

In addition, participants, particularly those with M1b status, should be advised regarding clinical signs suggestive of spinal cord compression.

8.3.2 Vital Signs

Blood pressure, temperature, respiratory rate and heart rate will be assessed as outlined in the SoA (Section 1.3) with an automated device (if possible) so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after 5 minutes rest in supine or seated 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 and Table 2.

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.

Any clinically significant abnormalities will be recorded as AEs.

8.3.4 Magnetic Resonance Imaging Scan

A magnetic resonance imaging (MRI) scan for prostate gland or the whole body, only if necessary (based on investigator's judgement), will be performed as described in the SoA (Table 1 and Table 2) to confirm disease stage prior to study entry. An MRI scan is not required, if performed within 1 month of study screening.

8.3.5 Clinical Safety Laboratory Assessments

- All clinical laboratory safety tests (haematology and blood biochemistry) will be assessed locally.
- 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.
- 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 the laboratory manual 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.

Haematology blood samples (2 mL) will be collected in a potassium ethylenediaminetetraacetic acid tube. Blood biochemistry samples (3 mL) will be collected in an activator gel tube.

8.3.6 Local Tolerance

Local tolerance will be assessed 2 hours (±15 minutes) after injection. After the single injection of 6-month formulation triptorelin, the injection site will be examined by a physician or Medical Research Associate 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 and assessed quantitatively; this will at least include measurement of maximum length and maximum width. If any reactions meet the definition of a treatment-emergent adverse event (TEAE), they are to be reported in the eCRF as such (see Section 9.4.5).

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

The definitions of AEs and serious adverse events (SAEs) can be found in Appendix 10.3.

Adverse events 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 or SAEs, considered related to the study intervention or study procedures (see Section 7).

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 the 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 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, Institutional Review Boards (IRB)/Independent Ethics Committees (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 (SUSAR) 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. 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 forms (Pregnancy Notification Form– paper form) and submit it to the sponsor within 24 hours of learning of the female partner of male participant becoming pregnant (after obtaining the necessary signed informed consent from the female partner).
- 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 participant's pregnant female partner will be followed 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 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.

8.5 Pharmacokinetics

- Approximately 14 mL of blood will be collected from all participants, and approximately 40 mL of blood from the PK/PD subset participants, for measurement of plasma concentrations of triptorelin 6-month formulation as specified in the SoA (Section 1.3)

- Instructions for the collection, handling and shipment of biological samples will be provided by the sponsor and described in the study laboratory manual. The accurate date and time (24-hour clock time) of each sample collection must be recorded.
- Plasma samples will be used to evaluate the PK of triptorelin 6-month formulation. Each plasma sample will be divided into two aliquots (one primary and one backup). Samples collected for analyses of triptorelin concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- During the study, the nominal sample collection times may be changed, but the total number of samples will not increase. The exact dates and times of blood sample collection and study drug administration must be recorded in the eCRF.
- On predetermined dates, plasma samples will be shipped to the bioanalytical service provider under frozen conditions. For security reasons, the back-up aliquots will not be shipped until the primary aliquots have arrived. Upon receipt at the bioanalytical service provider, samples will be checked and stored until analysis.
- Plasma will be analysed to determine concentrations of triptorelin using a validated, specific and sensitive LC-MS/MS methods.
- Surplus plasma samples will be used in China and will not be shipped outside China. Surplus plasma samples will be managed anonymously and will not be identifiable.
- Residual plasma samples remaining from the analyses may also be retained by the sponsor for up to 5 years after completion of the study. This could include using leftover plasma for long-term stability or reproducibility assessments.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No statistical hypotheses are planned for this study.

9.2 Sample Size Determination

The sample size was estimated based on data from the previous Study DEB-TRI6M-301, 97.5% of participants achieving castration and 93% of participants maintaining castration from Week 8 to Week 24.

Sample size is calculated to fulfil the co-primary efficacy criteria of this study, which is to assess the proportion of participants achieving castrate levels of testosterone on Day 29 and the proportion of participants maintaining the castrate levels of serum testosterone from Week 8 to end of Week 24. A total of 195 participants with advanced prostate cancer will be enrolled to receive the triptorelin pamoate 22.5 mg 6-month formulation.

For an exact binomial test of a proportion with a two-sided nominal significance level of 0.05 and null proportion of 85%, a sample size of 165 participants has an exact power of 88.3% when the true proportion is 93% (of participants maintaining castration from Week 8 to Week 24). This sample size of 165 participants has a power >99.9% when the true proportion is 97.5% (of participants achieving castrate testosterone levels). Exact two-sided 95% confidence interval (CI) for a binomial proportion was computed by SAS using the exact binomial distributions.

Assuming the dropout rate will be around 15%, a sample size of 195 participants in total is planned for this study.

9.3 Analysis Sets

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

Participant Analysis Set	Description
Screened	All participants screened (i.e. who signed the informed consent).
Safety Set	The safety set will contain all participants who receive the single dose of study intervention.
Full Analysis Set	The FAS will contain all treated participants who complete the study or is a treatment failure. Completing the study is defined as having serum testosterone measurement at baseline, Day 29 and Day 169. Treatment failure is defined as escaping castration (testosterone level ≥50 ng/dL) at any assessments on and after Day 29 during the study, or premature discontinuation from the intervention period due to drug-related reasons (adverse event or death).
Per Protocol Set	All participants in the FAS who have no impacting major protocol deviations (i.e. that could potentially affect the primary efficacy endpoint outcome for the participant) as described in the protocol deviations document.
Rich PK Analysis set (for non-compartmental analysis)	Participants in the PK/PD subset who receive one dose of study intervention, have no major protocol deviations affecting the PK variables, and who have a sufficient number of plasma concentrations to estimate the main PK parameters (maximum observed plasma drug concentration (C_{max}), time to maximum observed drug concentration (t_{max}) and area under the plasma concentration time curve (AUC))
Population PK Analysis Set	All participants who received one dose of triptorelin and who have at least one triptorelin plasma concentration and no major protocol deviations affecting PK variables.

Participant Analysis Set	Description
Rich PD Analysis Set	all participants in the PK/PD subset who have a sufficient number of PD (testosterone) measurements to estimate the main PD parameters (maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}) and time to castration (t_{cast}))

FAS=full analysis set; PD=pharmacodynamic PK=pharmacokinetic

The efficacy analysis for the primary and secondary efficacy endpoints will be presented for the full analysis set (FAS) and per protocol (PP) population. The analysis of the safety data will be performed based on the safety set and analysis of PK and PD in the relevant PK analysis set

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalised before the first participant enters 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.

Statistical evaluation will be performed using Statistical Analysis System (SAS®) Version 9.4 (or higher if available).

9.4.1 General Considerations

9.4.1.1 Reasons for Exclusion from the Analyses

Any major protocol deviation will be described and listed and its impact on inclusion of any participant in each analysis population will be specified. The final list of protocol deviations impacting each analysis population will be reviewed prior to database lock. The list may be updated, up to the point of database lock, to include any additional major protocol deviations impacting inclusion in the PP set.

9.4.1.2 Significance Testing and Estimations

As this is a descriptive safety and efficacy study, no formal statistical testing will be carried out.

9.4.1.3 Statistical/Analytical Methods

Statistical analyses will be performed by an external CRO, managed by the sponsor's Biometry department.

Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant disease (predosing AEs and ongoing medical history, prior medications and therapies, etc.) will be presented for the FAS, PP and safety sets.

Participant Disposition and Withdrawals

The numbers and percentages of participants screened and included in each of the populations will be tabulated overall and by centre. The reasons for participant exclusions from each of the populations will also be tabulated. Primary reasons for discontinuation of study will be tabulated.

Adjustment for Country/Centre Effects

Descriptive analysis will be carried out to evaluate any possible centre effect.

9.4.2 Analysis of Primary Endpoints

The co-primary efficacy variables are

- percentage of participants achieving castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) and
- percentage of participants maintaining the castrate levels from Week 8 to Week 24.

The percentage of participants achieving castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) on Day 29 will be obtained as the number of participants with castrate levels at the visit, divided by the total number of participants on Day 29 in the considered population.

Percentage of participants maintaining the castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) from Week 8 to Week 24 will be calculated as the number of participants with castrate levels at all visits from Week 8 to Week 24, divided by the total number of assessable participants.

To derive the percentage of participants maintaining castration levels of testosterone, missing data will be handled as follows:

(a) In participants escaping castration at a certain visit, subsequent missing data is irrelevant.

(b) Participants maintaining castration up to a certain visit with missing data afterwards (drop-out due to non-drug-related reasons) will be excluded from the analysis.

(c) Participants maintaining castration up to a certain visit with missing data afterwards (drop-out due to drug-related reasons) will be treated as having escaped castration (failure).

(d) Missing data between two visits where castration levels are maintained will be handled as missing for that particular visit, and the participant will be considered to have maintained castration.

To derive the percentage of participants maintaining castrate levels of testosterone, assessable participants are defined as the total number of all participants having values at all visits and all participants having missing data according to the criteria a), c) and d) mentioned previously. Participants having missing data according to the criteria b) will be excluded from this calculation.

Co-primary endpoints will be tabulated with two-sided 95% (95% CI) using the Clopper-Pearson exact method.

9.4.3 Analysis of Secondary Endpoints

9.4.3.1 Prostate-Specific Antigen

The secondary efficacy variable is the percent change in PSA from baseline (prior to injection) measured at Week 12 and Week 24. Percent change in PSA is defined as the absolute value of difference between the PSA values at Week 12 and Week 24 and the baseline value divided by the baseline value.

PSA percent change from pre-treatment Day 1 will be reported at each subsequent visit, using descriptive statistics.

9.4.3.2 Pharmacokinetic and Pharmacodynamic Data Analysis

Description of Triptorelin and Testosterone Concentrations

Individual plasma or serum concentrations of triptorelin and testosterone will be listed and summarised by visit and time points using descriptive statistics for continuous variables (number of available observations, mean, median, SD, minimum, maximum, geometric mean, and geometric coefficient of variation (assuming log normally distributed data). Data will be

summarised for the PK/PD subset and overall. Individual and mean triptorelin and testosterone concentration time profiles, as well as spaghetti plots, will be generated.

Non-compartmental Analysis

The PK analysis of triptorelin plasma concentrations and testosterone serum concentrations of the rich sampling PK/PD subset will be performed by the non-compartmental analysis (NCA) approach using Phoenix WinNonlin PK program version 8.3 or higher. The following PK parameters will be calculated if warranted by the data:

- maximum observed concentration (C_{max})
- time to maximum observed blood concentration (t_{max})
- (for triptorelin only) area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration (AUC_{last})
- (for triptorelin only) area under the plasma concentration time curve from time 0 to the visit on day 169 (AUC_{0-169})
- (For testosterone only): time to castration t_{cast}

Additional PK parameters may be calculated if appropriate.

Descriptive statistics of PK and PD parameters will be presented for the rich PK analysis set for triptorelin and the rich PD analysis set for testosterone. PK and PD parameters will be summarised by, but not limited to, n, mean, SD, median, minimum, maximum, geometric SD, geometric mean, and geometric coefficient of variation except for t_{max} where only n, median, minimum and maximum values will be reported.

The NCA analysis will be described in a separate data analysis plan and reported in a standalone report.

Population Pharmacokinetic Analysis

Population pharmacokinetics (PopPK) modelling will be performed using concentrations obtained from all participants in order to describe the pharmacokinetics of triptorelin 6-month formulation in the prostate cancer population (if warranted by the data). In addition, quantification of the inter-participant variability on PK will be performed and an attempt to identify participant characteristics explaining the variability on PK will be made. Historical PK data from other studies may also be used to compare the PK profiles from this study against other populations. The PK model developed will be used to derive exposure metrics to perform an exploratory analysis with efficacy and safety endpoints (should any safety signal emerge). Should a trend be observed, PK/PD modelling will be performed to describe the relationship between exposure and efficacy and/or safety endpoints.

Population PK/PD analysis will be described in a separate data analysis plan and presented in a stand-alone report.

9.4.4 Analysis of Exploratory Endpoint

9.4.4.1 Pharmacokinetic/Pharmacodynamic Relationship

An exploratory analysis will be performed to assess the relationship between PK and PD endpoints. If a trend is shown, an attempt to build a PK/PD model using a population approach will be performed. The PopPK and PK/PD analyses will be described in a separate data analysis plan and reported in a standalone report.

9.4.5 Safety Analyses

Safety endpoints are indicated in Section 3.

All safety data will be included in the participant data listings. Analyses and summary tables will be based upon the safety set.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 (or higher if available) and will be classified by MedDRA preferred term and system organ class. Adverse event listings will be presented by participant, system organ class and PT.

The incidence of all TEAEs and SAEs will be tabulated overall. In addition, summary tables will be presented by maximum intensity and drug relationship.

A TEAE is defined as any AE that occurs during the active phase of the study (from study intervention injection to 24 weeks after injection) if it was not present prior to receiving study intervention, or:

- it was present prior to receiving IMP but the intensity increased during the active phase of the study.
- It became serious during the active phase of the study
- It was present prior to receiving the study intervention and the intensity was the same, but the causality changed to 'related to treatment' during the active phase of the study.

All TEAEs will be flagged in the AEs listings.

Haematological and biochemical toxicities will be recorded and graded according to the NCI CTCAE criteria, where available. The National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Grade 3 and 4 haematology and biochemistry variables by participant and by cycle will be listed.

Actual values and changes from baseline in clinical laboratory tests, physical examinations, vital signs and 12-lead ECG will be summarized using descriptive statistics at each visit. 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 using the worst on-treatment grade will be presented for the number and percentage of participants with NCI-CTCAE grades.

AEs reported by investigators using the NCI-CTCAE classification (Version 5.0 or higher) will be coded using MedDRA Version 24.1 (or higher if available).

Summary incidence tables will be provided, classified by SOC, PT and associated NCI/CTC worst grade. In the event of multiple occurrences of the same AEs being reported by the same participant, the maximum intensity (Grade 5 >Grade 4 >Grade 3 >Grade 2 >Grade 1 >missing >not applicable) will be chosen.

9.4.6 Subgroups Analyses

No subgroups analysis will be performed.

9.4.7 Other Analyses

Not applicable.

9.5 Interim Analyses

No interim analysis will be performed.

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 International Ethical Guidelines
  - International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations such as Regulation 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 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 combined with data from prostate cancer patients from other parts of the world. These data may only be used for 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.
- 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.

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/her personal study-related data will be used by the sponsor in accordance with local data protection law. 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/her 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

- 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 US Clinical Trials Registry (ClinicalTrials.gov). The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation.
- 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 CRF 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 CRF.
- All entries in the CRF 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 CRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the CRF.
- Guidance on completion of CRFs will be provided in CRF 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 CRF 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 CRF. 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 CRF 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 is enrolled.

Study/Site Termination

There are no formal rules for early termination of this study.

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 results of this study may be published or presented at scientific meetings. If this is foreseen, 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

- The tests detailed in Table 6 will be performed locally.
- 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.
- Refer to SoA Section 1.3 for details of visits.

Table 6 Protocol-Required Safety Laboratory Tests

Parameters	Screening	Intervention Period	EoS/EW
Haematology	X	X	X
Platelet Count	X	X	X
Haemoglobin	X	X	X
White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	X	X	X
Clinical Chemistry			
Creatinine	X	X	X
Glucose (fasted at screening and fasted on Day 1 and Day 169) [a]	X	X	X
Aspartate aminotransferase	X	X	X
Alanine aminotransferase	X	X	X
Alkaline phosphatase	X	X	X
Bilirubin (total and conjugated)	X	X	X

EoS=end of study; EW=early withdrawal
a Fasting not necessary for diabetic participants.
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 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, convulsions or development of intervention dependency or intervention abuse.

A suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection should be reported as serious if the event meets the defined seriousness criteria. If no seriousness criteria are reported by the investigator, the COVID-19 event will be collected and recorded as nonserious.

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 grading system.

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.
- New or updated information will be recorded in the CRF.
- 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 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).
- Contacts for SAE reporting can be found on the SAE form and the cover sheet.

SAE Reporting to sponsor via paper

- 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.

• Contacts for SAE reporting can be found on the SAE form and the cover sheet.

10.4 Appendix: American Joint Committee on Cancer (AJCC) TNM Staging System for Prostate Cancer

The treatment of prostatic carcinoma is predicated largely on the stage of the disease; accurate staging is therefore essential.

The TNM staging system classifies the disease according to the progression of the primary tumour, the spread to the regional lymph nodes, and the development of distant metastases (hence TNM). Each stage is further subdivided (e.g. T1-T4 and Tla-T4) to give more detailed information about progression within each category.

Primary Tumour (T)	**T**
Clinically inapparent tumour neither palpable nor visible by imaging:	**T1**
Tumour incidental histologic finding in 5% or less of tissue resected	**Tla**
Tumour incidental histologic finding in more than 5% of tissue resected	**Tl b**
Tumour identified by needle biopsy (e.g. because of elevated PSA)	**Tl c**
Tumour confined within prostate	**T2**
Tumour found in one or both lobes by needle biopsy, but not palpable, or reliably visible by imaging is classified as TIc	
Tumour involves one half on one lobe or less	**T2a**
Tumour involves more than one half of one lobe but not both lobes	**T2 b**
Tumour involves both lobes	**T2 c**
Tumour extends through the prostate capsule	**T3**
Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but T2.	
Extracapsular extension (unilateral or bilateral)	**T3a**
Tumour invades seminal vesicles	**T3b**
Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall	**T4**
Regional Lymph Nodes (N)	**N**
No regional lymph node metastasis	**NO**
Metastasis in regional lymph node(s)	**N1**
Distant metastasis (M)	**M**
No distant metastasis	**MO**
Distant metastasis	**M1**
Non-regional lymph node(s)	**Mla**
Bone(s)	**Mlh**
Other site(s) with or without bone disease	**Mlc**

10.5 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.

10.6 Appendix: Protocol Amendment History

10.6.1 Amendment 1: 11 November 2021

Overall Rationale for the Amendment:

Protocol was moved to a new template allowing clarifications and further instruction to the study design to be made.

Summary change table from previous version of the protocol

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

<table>
<tr><th>Section</th><th>Was (Version1.0, 31 July 2019)</th><th>Is (Version 2.0, 11 November 2021)</th><th>Rationale</th></tr>
<tr><td>Throughout</td><td></td><td>Protocol moved to new template. Not all changes are identified. Only major content changes or changes that impact the conduct of the study are included below in the amendment form.</td><td>New protocol template implemented</td></tr>
<tr><td>Throughout</td><td>~~Subject(s)~~</td><td>Participant(s)</td><td>New template terminology</td></tr>
<tr><td>1.1 / Synopsis (Objectives/ Endpoints)
&
3 / Objectives and Endpoints</td><td><table><tr><th>Primary Objective(s)</th><th>Primary Endpoint(s)</th></tr><tr><td>• To evaluate the efficacy of triptorelin pamoate 22.5 mg 6-month formulation in achieving castrate levels of testosterone ~~(<50 ng/dL or <1.735 nmol/L) on Day 29 (i.e. 28 days after study drug injection)~~</td><td>• Percentage of participants achieving castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) on Day 29 ~~(i.e. 28 days after first injection)~~</td></tr></table></td><td><table><tr><th>Primary Objectives(s)</th><th>Primary Endpoint(s)</th></tr><tr><td>• To evaluate the efficacy of triptorelin pamoate 22.5 mg 6-month formulation in achieving castrate levels of testosterone</td><td>• Percentage of participants achieving castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) on Day 29</td></tr></table></td><td>Objectives and endpoint presentation made consistent with new protocol template guidance</td></tr>
</table>

Section	Was (Version1.0, 31 July 2019)		Is (Version 2.0, 11 November 2021)		Rationale
	• To evaluate the efficacy of triptorelin pamoate 22.5 mg 6-month formulation in maintaining the castrate levels of serum testosterone ~~from Week 8 to end of Week 24 in participants with locally advanced or metastatic prostate cancer~~	• Percentage of participants maintaining the castrate levels from Week 8 to Week 24 ~~in participants with locally advanced or metastatic prostate cancer~~	• To evaluate the efficacy of triptorelin pamoate 22.5 mg 6-month formulation in maintaining the castrate levels of serum testosterone	• Percentage of participants maintaining the castrate levels from Week 8 to Week 24	

Section	Was (Version1.0, 31 July 2019)		Is (Version 2.0, 11 November 2021)		Rationale
1.1 / Synopsis (Objectives/ Endpoints) & 3 / Objectives and Endpoints	Secondary Objective(s)	Secondary Endpoint(s)	Secondary Objective(s)	Secondary Endpoint(s)	Objectives and endpoint presentation made consistent with new protocol template guidance
	• To assess the safety of triptorelin pamoate 22.5 mg 6-month formulation ~~over the study treatment period, i.e. from treatment start to 24 weeks~~	• ~~Adverse events~~ • ~~Physical examination, ECG and vital signs~~ • ~~Laboratory parameters (haematology and blood chemistry)~~	• To assess the safety **profile including local tolerability** of triptorelin pamoate 22.5 mg 6-month formulation	• **Incidence of TEAEs (including local tolerability) throughout the study, i.e up to Week 24** • **Change from baseline in clinical safety laboratory parameters (blood chemistry and haematology) at Week 24** • **Change from baseline in physical examination at Day 1, Week 12 and Week 24** • **Change from baseline in ECG at Week 4 and Week 24** • **Change from baseline in vital signs (blood pressure and heart rate) at each visit up to Week 24**	

Section	Was (Version1.0, 31 July 2019)		Is (Version 2.0, 11 November 2021)		Rationale
	Primary Objective(s)	Primary Endpoint(s)	Secondary Objective(s)	Secondary Endpoint(s)	
	• To ~~assess the change in prostate specific antigen (~~PSA~~) levels from baseline throughout treatment~~	• Change in PSA from baseline (prior to injection) ~~on~~ Week 12 and Week 24	• To **demonstrate the effect of triptorelin pamoate 22.5 mg 6-month formulation on** PSA **response**	• **Percent** change in PSA from baseline (prior to injection) **at** Week 12 and Week 24 **(Percent change in PSA is defined as the absolute value of difference between the PSA values at Week 12 and Week 24 and the baseline value divided by the baseline value)**	

<table>
<tr><th>Section</th><th>Was (Version1.0, 31 July 2019)</th><th>Is (Version 2.0, 11 November 2021)</th><th>Rationale</th></tr>
<tr><td rowspan="2">1.1 / Synopsis (Objectives/ Endpoints)
&
3 / Objectives and Endpoints</td><td>
<table>
<tr><th colspan="2">~~Secondary Pharmacokinetic/Pharmacodynamic in Subset of Participants~~</th></tr>
<tr><td>• To assess the PK of triptorelin pamoate 22.5 mg 6-month formulation</td><td>• ~~Triptorelin~~ PK parameters: ~~t~~t_{max}, C_{max}, AUC_{0-169} and AUC_{last}</td></tr>
<tr><td>• To ~~evaluate~~ the ~~PK/~~PD ~~relationship between the PK of triptorelin pamoate 22.5 mg 6-month and testosterone concentration versus time profiles (PD)~~</td><td>• ~~Testosterone~~ PD parameters: t_{max}, C_{max} and t_{cast}</td></tr>
</table>
</td><td>
<table>
<tr><th>Secondary Objective(s)</th><th>Secondary Endpoint(s)</th></tr>
<tr><td>• To assess the PK of triptorelin pamoate 22.5 mg 6-month formulation in a subset of 12 participants</td><td>• PK parameters for dosing interval up to 24 weeks:
○ t_{max}
○ C_{max}
○ AUC_{0-169}
○ AUC_{last}</td></tr>
<tr><td>• To assess the PD of testosterone in a subset of 12 participants</td><td>• PD parameters for dosing interval up to 24 weeks
○ t_{max}
○ C_{max}
○ t_{cast}</td></tr>
<tr><td>• To assess the PK of triptorelin pamoate 22.5 mg 6-month formulation for all participants</td><td>• Sparse plasma concentrations of triptorelin at pre-dose and at Weeks 4, 8, 12, 16, 20 and 24</td></tr>
<tr><td>• To assess the PD of testosterone for all participants</td><td>• Sparse serum concentrations of testosterone at pre-dose and at Weeks 4, 8, 12, 16, 20 and 24</td></tr>
</table>
</td><td rowspan="2">Objectives and endpoint presentation made consistent with new protocol template guidance</td></tr>
<tr><td></td><td>
<table>
<tr><th>Exploratory</th></tr>
<tr><td>• To evaluate the PK/PD relationship between the PK of triptorelin pamoate 22.5 mg 6-month formulation and testosterone concentration versus time profiles (PD)</td></tr>
</table>
</td></tr>
</table>

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
1.1 / Synopsis (Sample Size Determination)	Sample size is calculated to fulfil the co-primary efficacy criteria of this study, which is to assess the proportion of ~~subjects~~ achieving castrate levels of testosterone on Day 29 and the proportion of ~~subjects~~ maintaining the castrate levels of serum testosterone from Week 8 to end of Week 24. ~~A total of 195 subjects with advanced prostate cancer will be enrolled to receive the triptorelin pamoate 22.5 mg 6 month formulation.~~ […] Assuming the dropout rate will be around 15%, a sample size of 195 ~~subjects~~ in total is planned for this study.	Sample size is calculated to fulfil the co-primary efficacy criteria of this study, which is to assess the proportion of **participants** achieving castrate levels of testosterone on Day 29 and the proportion of **participants** maintaining the castrate levels of serum testosterone from Week 8 to end of Week 24. […] Assuming the dropout rate will be around 15%, a sample size of 195 **participants with locally advanced or metastatic prostate cancer** in total is planned for this study.	Removal of repetition in the text
1.1 / Synopsis (Primary Analysis) & 9.4.2 / Analysis of Primary Endpoints	~~The proportion of subjects who achieved castration levels of serum testosterone on Day 29 and the proportion of subjects who maintained the levels from Week 8 to end of Week 24~~ will be tabulated with two-sided 95% confidence interval (95% CI) using the ~~binomial distribution~~.	**Co-primary endpoints** will be tabulated with two-sided 95% confidence interval (95% CI) using the **Clopper-Pearson exact method**.	Removal of repetition in the synopsis and clarification of analysis

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
1.3 / Schedule of Activities	The schedule of activities during the study is summarised for all ~~subjects~~, except the PK/PD subset of ~~subjects in Table 1 and for the PK/PD subset of participants~~ in Table 2.	The schedule of activities during the study is summarised for all **participants in Table 1**, except the PK/PD subset of **12 participants which is summarised** in Table 2. **If the 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 will be provided to the investigator in a separate document. Such document will be filed in the trial master file. Independent ethics committees (IECs)/institutional review boards (IRBs) will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.**	Guidance for COVID-19 management during the study added per new template.
1.3 / Schedule of Assessments		The following assessments were added for screening in Table 1 and Table 2: **Demography** **MRI scan [g] for Table 1 [h] for Table 2** **Footnote "g" and "h":** **Scan for prostate gland or the whole body, only if necessary, based on investigator's judgement. An MRI scan is not required if performed within 1 month of screening.**	Clarification of procedures required at screening
1.3 / Schedule of Assessments (Table 1 and Table 2)	Medical history	Medical **and surgical** history	Clarification of information to be collected at screening

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
1.3 / Schedule of Assessments (Table 1 and Table 2)	Physical examination	Physical examination **[f]** for Table 1 and Physical examination **[g]** for Table 2 Corresponding footnote "f" and "g": **Participants, particularly those with M1b status, should be advised regarding clinical signs suggestive of spinal cord compression**.	Clarification of procedures for physical examination
1.3 / Schedule of Assessments (Table 1 and Table 2)	Disease history ~~and previous treatment~~ X	Disease-**specific medical** history X **Prior disease-specific treatment** **X**	Clarification of collection of prior treatments as screening for prostate cancer
1.3 / Schedule of Assessments (Table 1 and Table 2)	Blood sample for testosterone PD X X [e]	Blood sample for testosterone PD X X [**a,** e]	Clarification added to footnote "a" that sampling should occur pre-dose on Day 1
1.3 / Schedule of Assessments (Table 1)	Blood sample [c] for laboratory safety tests X X [e]	Blood sample [c] for laboratory safety tests X X [**a,** e]	Clarification of assessment timing on Day 1
1.3 / Schedule of Assessments (Table 2)	Blood sample [d] for laboratory safety tests X X [f]	Blood sample [c] for laboratory safety tests X X [**a,** f]	Clarification of assessment timing on Day 1
1.3 / Schedule of Assessments (Table 2)	Blood sample for triptorelin PK X X [c]	Blood sample for triptorelin PK X X [**a,** c]	Clarification of assessment timing on Day 1

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
1.3 / Schedule of Assessments (Table 1 and Table 2)	Blood samples for PSA |	Blood samples for PSA | **X**	PSA added at screening for consistency with eligibility requirements
1.3 / Schedule of Assessments (Table 1 and Table 2)	Previous and concomitant medication	Previous **(excluding disease-specific)** and concomitant medication	Clarification that other prior medication collection excludes disease-specific treatments
1.3 / Schedule of Assessments (Table 1 and Table 2)	Footnote "c" Haematology (WBC, Platelet count, Hb), Blood Chemistry (creatinine, glucose, ALT, AST, alkaline phosphatase, bilirubin). Glucose: ~~Non-~~fasting levels in all participants at Screening visit, fasting levels on Days 1 and 169. Fasting is not necessary for diabetic participants.	Footnote "c" Haematology (WBC, platelet count, Hb), Blood Chemistry (creatinine, glucose, ALT, AST, alkaline phosphatase, bilirubin (**total and conjugated**)). Glucose: Fasting levels in all participants at Screening visit, fasting levels on Days 1 and 169. Fasting is not necessary for diabetic participants.	Clarification of bilirubin and glucose collection
2.1 / Study Rationale	~~At the same time~~, triptorelin pharmacokinetics (PK) and testosterone pharmacodynamics (PD) will be assessed in ~~a subset of 12 Chinese subjects.~~	**In addition,** triptorelin pharmacokinetics (PK) and testosterone pharmacodynamics (PD) will be assessed in **the study population**.	Clarification of study procedures
2.2 / Background	~~Further details/additional information regarding risks and benefits to human subjects may be found in the Investigator's Brochure.~~		Removal of repetition with other sections in the protocol
2.3 / Benefit/Risk Assessment		**Detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of triptorelin may be found in the IB.**	Addition per new template

<table>
<tr>
<td>2.3.1 / Risk Assessment</td>
<td></td>
<td>
A risk assessment for this study is provided in Table 3.

Table 3 Study Risk Assessment
<table>
<tr><th>Potential Risk of Clinical Significance</th><th>Summary of Data/Rationale for Risk</th><th>Mitigation Strategy</th></tr>
<tr><td colspan="3">Study Intervention: Triptorelin</td></tr>
<tr>
<td>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 [b]
See Section 8.3</td>
<td>See IB Section 6.6.1</td>
<td>Participant selection: Participants with significant medical conditions and at high risk of presenting treatment related SAEs and high-grade toxicity will be excluded from the study. Participant monitoring: During the study, there will be close monitoring of the participants for safety including local tolerability</td>
</tr>
</table>
</td>
<td>Addition per new template</td>
</tr>
</table>

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)			Rationale
				(see Section 8.3.6) Withdrawal criteria: Participants who become at risk of unacceptable toxicity 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	
		IB=investigator's brochure; SAE=serious adverse event a Pregnancy is not relevant in this study population. However, reproductive risks are listed for completeness for female partners of participants who may become pregnant.			

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
2.3.2 / Benefit Assessment		**Based on the nonclinical and clinical data generated up to finalisation of the protocol, treatment with triptorelin 6-month formulation may maintain castrate levels of testosterone for a longer period i.e. 6 months (24 weeks), thereby reducing the need for frequent injections, in Chinese participants with locally advanced or metastatic prostate cancer to a similar extent as in a previous global phase III study.**	Addition per new template
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 triptorelin are justified by the anticipated benefits that may be afforded to Chinese participants with locally advanced or metastatic prostate cancer.**	Addition per new template
4.3 / Justification for Dose		**For this intervention, the term "dose" refers to the i.m. injection of triptorelin 22.5 mg created to guarantee the release of a monthly dose of 3.75 mg over a 169-day period. In addition, results from a phase III study have shown the 6-month triptorelin 22.5 mg formulation to induce and maintain castration in participants with locally advanced or metastatic prostate cancer, as well as demonstrate a good safety profile [Lundstrom 2009].**	Addition per new template
4.4 / End of Study Definition	This study will consist of a 4-week screening period, a single open-label administration of the IMP on Day 1 followed by an assessment period of 24 weeks. Subjects are expected to participate in this study for the entire 24 weeks. The subject's participation in the study will be considered to have ended at the time of the last visit. The overall duration of the study (from first subject in to last subject out) will be approximately 30 months. The study will be considered to have started when the first subject has provided signed informed consent.	**The end of the study (EoS) is defined as the date of the last visit of the last participant in the study as shown in the SoA (Table 1 and Table 2).** The overall duration of the study (from first participant in, to last participant out) will be approximately 30 months. The study will be considered to have ended after the last participant has completed the last **visit** (at Week 24) in the study. 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.**	Updated per new template

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
	The study will be considered to have ended after the last subject has completed the last follow up period (at Week 24) in the study.		
5.1 / Inclusion Criteria	1. Signed written informed consent **before entry into the study**. 3. A histologically or cytologically confirmed, locally advanced or metastatic prostate cancer, and should be staged T3-4NxM0 or TxN1M0 or TxNxM1 according to the TNM classification or participant should have rising PSA after failed local therapy and be a candidate for androgen deprivation therapy (ADT).	1. **Participant is capable of giving** signed informed consent **as described in Appendix 10.1 which included compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol**. 3. Has a histologically or cytologically confirmed **adenocarcinoma**, locally advanced or metastatic prostate cancer **which is** staged T_{3-4}NxM0 or TxN1M0 or TxNxM1 according to the TNM classification**. Or** participant **has** PSA **recurrence** after **curative treatment** and be a candidate for androgen deprivation therapy (ADT). **(Note: PSA recurrence after radical prostatectomy: PSA ≥0.2 ng/mL and rising, confirmed on a repeat test; PSA recurrence after radiation therapy: PSA increased 2 ng/mL than the lowest level.)** **8. Participant is male** **9. Male participants must agree that, if their partner is at risk of becoming pregnant, they will use an effective method of contraception. The participant must agree to use the contraception during the whole period of the study and for 9 months after the last dose of study intervention.**	Addition per new template
5.2 / Exclusion Criteria		**4. Metastatic hormone-sensitive prostate cancer with high tumour burden**	Clarification of participant eligibility
5.2 / Exclusion Criteria	19. Inability to give informed consent or to comply fully with the protocol.		Removal of duplication with inclusion #1

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
5.3 / Lifestyle Considerations		**Participants will be advised to avoid chronic alcohol use and smoking during the study.**	Addition per new template
5.4 / Screen Failures	Under no circumstances will subjects be screened more than once.	**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) will not be rescreened.**	Addition and clarification per new template
6.8 / Concomitant Therapy		**Any medication (excluding prior disease-specific medications) or vaccine (including over the counter prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant had received within 2 months before triptorelin administration or during triptorelin administration must be recorded on the eCRF along with**: […]	Addition per new template and clarification that prior medications exclude those for previous disease-specific treatment
6.8 / Concomitant Therapy	• Any treatment or procedure with an effect on androgenic hormones be administered concomitantly to the study drug (will be considered as a protocol violation).	[…] • Any treatment or procedure with a **specific or potential** effect on androgenic hormones be administered concomitantly to the study drug (will be considered as a protocol violation). **Per investigator's clinical judgement, suggest offering short-term administration of an older generation androgen receptor antagonist to M1 participants starting study intervention to reduce the risk of the 'flare-up' phenomenon.** **• Any medication which raises prolactin levels and those affecting pituitary secretion of gonadotropins**	Clarification of medications not permitted during the study

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
6.8 / Concomitant Therapy	[…] • Other medications: any treatment ~~including analgesics,~~ which is considered necessary for the participant's welfare, may be given at the discretion of the investigator	[…] **• 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.	Clarification of medication use that should be monitored during the study
7.1 / Discontinuation of Study Intervention		**In this study, there will only be one treatment cycle administered on Day 1 of the study, thus discontinuation of the study intervention is not applicable (i.e. no repeat cycles). In the event a participant is enrolled, but does not receive study intervention, the participant will not remain in the study and EoS/EW assessment will not be performed. Only the reason for discontinuation will be collected.** **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.**	Addition per new template
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 some cases, the investigator may request a participant be retested before the intervention administration.**	Guidance for COVID-19 management during the study added per new template.

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
7.3 / Lost to Follow-up		**A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.** **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, he/she 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 enrolled, 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.**	Addition per new template
8.1 / Demography		**Age, sex and, according to individual country regulations/requirements and if authorised in the country, ethnicity will be collected.**	Addition per new template

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
8.2 / Efficacy Assessments		**Approximately 26 mL of blood will be collected from all participants, and approximately 38 mL of blood from the PK/PD subset participants, for measurement of testosterone and PSA. Serum samples used to evaluate testosterone and 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.**	Clarification of efficacy assessments and blood collection
8.2.1 / Testosterone	Testosterone will be assessed by a third-party vendor, as described in the Laboratory Manual ~~according to the analytical procedure described above in Section 9.1.2~~.	Testosterone will be assessed by a third-party vendor, as described in the Laboratory Manual. **Serum will be analysed to determine concentrations of testosterone using a validated, specific and sensitive liquid chromatography tandem mass spectrometry (LC-MS/MS) methods.** **[…]** **Residual serum samples remining from the analysis may also be retained by the sponsor for additional investigations. This could include using leftover serum for long-term stability, reproducibility, or other bioanalytical assessments.** **Surplus serum samples may be used in China or shipped outside China as required. Surplus serum samples will be managed anonymously and will not be identifiable.**	Clarification of efficacy assessment method.
8.3.1 / Physical Examination		**In addition, participants, particularly those with M1b status, should be advised regarding clinical signs suggestive of spinal cord compression.**	Clarification of procedures for physical examination
8.3.2 / Vital Signs	Blood pressure and heart rate will be assessed ~~at timepoints described in Table 1~~ with an automated device so that measurements are independent of the observer.	Blood pressure, **temperature, respiratory rate** and heart rate will be assessed **as outlined in the SoA (Section 1.3)** with an automated device so that measurements are independent of the observer. **Any clinically significant vital signs will be recorded as AEs.**	Clarification of collection of vital sign data

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
8.3.3 / Electrocardiograms	~~Twelve~~ lead ECG~~s~~ will be recorded so that the different ECG intervals (RR, PR, QRS, QT, QTcF) can be measured automatically.	**A single 12-**lead ECG will be recorded so that the different ECG intervals (RR, PR, QRS, QT, QTcF) can be measured automatically.	Clarification of data collection
8.3.4 / Magnetic Resonance Imaging Scan		**8.3.4 Magnetic Resonance Imaging Scan** **A magnetic resonance imaging scan for prostate gland or whole body (only if necessary, based on investigator's judgement) will be performed as described in the SoA (Table 1 and Table 2) to confirm disease stage prior to study entry. An MRI scan is not required, if performed within 1 month of study screening.**	Additional procedures at screening
8.3.6 / Local Tolerance	Local tolerance will be assessed ~~at~~ 2 ~~and 4~~ hours after injection.	Local tolerance will be assessed 2 hours after injection.	Simplified to improve participant compliance with study procedures
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 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.**	Added per new template

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
9.1 / Statistical Hypothesis		**No statistical hypotheses are planned for this study.**	Addition per new template
9.4 / Statistical Analysis		**The statistical analysis plan (SAP) will be finalised before the first participant enters 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.** **Statistical evaluation will be performed using Statistical Analysis System (SAS®) Version 9.4 (or higher if available).**	Addition per new template
9.4.2 / Analysis of Primary Endpoints	The co-primary efficacy variables are • percentage of participants achieving castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) ~~4 weeks after the first injection~~ and • percentage of participants maintaining the castrate levels from Week 8 to Week 24 ~~in participants with locally advanced or metastatic prostate cancer~~.	The co-primary efficacy variables are • percentage of participants achieving castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) and • percentage of participants maintaining the castrate levels from Week 8 to Week 24.	Endpoint presentation made consistent with new protocol template guidance
9.4.3.1 / Prostate-specific Antigen	The secondary efficacy variable is the change in PSA from baseline (prior to injection) measured at Week 12 and Week 24. The efficacy analysis will be presented for the FAS and PP population. ~~The main analysis will be conducted in the FAS population.~~	The secondary efficacy variable is the **percent** change in PSA from baseline (prior to injection) measured at Week 12 and Week 24. **Percent change in PSA is defined as the absolute value of difference between the PSA values at Week 12 and Week 24 and the baseline value divided by the baseline value.** The efficacy analysis **for the primary and secondary efficacy endpoints** will be presented for the FAS and PP population. The analysis of the safety data will be performed based on the safety set and analysis of PK and PD in the relevant PK analysis set.	Endpoint presentation made consistent with new protocol template guidance

Section	Was (Version1.0, 31 July 2019)	Is (Version 2.0, 11 November 2021)	Rationale
9.4.3.2 / Pharmacokinetic and Pharmacodynamic Data Analysis		[…] **Individual and mean triptorelin and testosterone concentration time profiles, as well as spaghetti plots, will be generated.**	Clarification of planned analysis
9.4.3.2 / Pharmacokinetic and Pharmacodynamic Data Analysis	*Non-compartmental Analysis* The PK analysis of triptorelin plasma concentrations and testosterone serum concentrations of the rich sampling PK/PD ~~subgroup~~ will be performed by NCA approach using Phoenix WinNonlin PK program version ~~6~~.3 or higher.	*Non-compartmental Analysis* The PK analysis of triptorelin plasma concentrations and testosterone serum concentrations of the rich sampling PK/PD **subset** will be performed by NCA approach using Phoenix WinNonlin PK program version **8**.3 or higher.	Clarification of planned analysis
9.4.3.2 / Pharmacokinetic and Pharmacodynamic Data Analysis	*Population Pharmacokinetic Analysis* Population pharmacokinetics (PopPK) modelling will be performed ~~to characterise triptorelin PK parameters, such as (but not restricted to) clearance (apparent total clearance, CL/F) and volume of distribution (apparent volume of distribution, V/F), as well as their interindividual variability~~.	*Population Pharmacokinetic Analysis* Population pharmacokinetics (PopPK) modelling will be performed **using concentrations obtained from all participants in order to describe the pharmacokinetics of triptorelin 6-month formulation in the prostate cancer population (if warranted by the data). In addition, quantification of the inter-participant variability on PK will be performed and an attempt to identify participant characteristics explaining the variability on PK will be made. The PK model developed will be used to derive exposure metrics to perform an exploratory analysis with efficacy and safety endpoints (should any safety signal emerge). Should a trend be observed, PK/PD modelling will be performed to describe the relationship between exposure and efficacy and/or safety endpoints. Population PK/PD analysis will be described in a separate data analysis plan and presented in a stand-alone report.**	Clarification of planned analysis

10.6.2 Amendment 2: 07 April 2022

Overall Rationale for the Amendment:

Protocol was updated to clarify definition of primary endpoints and change safety laboratory testing from central to local during the study.

Summary change table from previous version of the protocol

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

Section	Was (Version 2.0, 11 November 2021)			Is (Version 3.0, 07 April 2022)			Rationale
1.3 / Schedule of Activities (Table 1)	Blood sample for testosterone PD	X	X [a, e]	Blood sample for testosterone PD **[h]**	X	X [a, e]	Clarification of laboratory testing location.
	Blood samples for PSA	X	X [a]	Blood samples for PSA **[h]**	X	X [a, **e**]	

<table>
<tr><th>Section</th><th>Was (Version 2.0, 11 November 2021)</th><th>Is (Version 3.0, 07 April 2022)</th><th>Rationale</th></tr>
<tr><td>1.3 / Schedule of Activities (Table 1 Footnotes)</td><td>c Haematology (WBC, platelet count, Hb), Blood Chemistry (creatinine, glucose, ALT, AST, alkaline phosphatase, bilirubin (total and conjugated)). Glucose: fasting levels in all participants at Screening visit, fasting levels on Days 1 and 169. Fasting is not necessary for diabetic participants.

d Injection site to be specifically checked 2 ~~and 4~~ hours after injection for local reactions on Day 1. After Day 1, any local reaction AE to be collected on the CRF in the same manner as other AEs.

e Measurement of testosterone and laboratory safety tests for analysis purposes only and not for eligibility ~~—~~the screening testosterone and safety laboratory test results will be used for eligibility.

f Participants, particularly those with M1b status, should be advised regarding clinical signs suggestive of spinal cord compression.</td><td>c Haematology (WBC, platelet count, Hb), Blood Chemistry (creatinine, glucose, ALT, AST, alkaline phosphatase, bilirubin (total and conjugated)) will be tested at the local laboratory. Glucose: fasting levels in all participants at Screening visit, fasting levels on Days 1 and 169. Fasting is not necessary for diabetic participants.

d Injection site to be specifically checked 2 hours after injection for local reactions on Day 1. After Day 1, any local reaction AE to be collected on the CRF in the same manner as other AEs.

e Measurement of testosterone, PSA and laboratory safety tests for analysis purposes only and not for eligibility. The screening testosterone, PSA and safety laboratory test results will be used for eligibility.

f Complete physical examination to be performed (or brief physical examination based on investigator judgement). Participants, particularly those with M1b status, should be advised regarding clinical signs suggestive of spinal cord compression.

h Testosterone and PSA testing will be performed at the central laboratory.</td><td>Clarification of laboratory testing location and study procedures.</td></tr>
<tr><td>1.3 / Schedule of Activities (Table 2)</td><td><table><tr><td>Blood sample for triptorelin PK</td><td></td><td>X [~~a,~~ c]</td></tr><tr><td>Blood sample for testosterone PD</td><td>X</td><td>X [a, f]</td></tr><tr><td>Blood sample for PSA</td><td>X</td><td>X [a]</td></tr></table></td><td><table><tr><td>Blood sample for triptorelin PK</td><td></td><td>X [c]</td></tr><tr><td>Blood sample for testosterone PD [i]</td><td>X</td><td>X [a, f]</td></tr><tr><td>Blood sample for PSA [i]</td><td>X</td><td>X [a, f]</td></tr></table></td><td>Removed reference to footnote “a” to avoid confusion with footnote “c”.

Clarification of laboratory testing location.</td></tr>
</table>

Section	Was (Version 2.0, 11 November 2021)	Is (Version 3.0, 07 April 2022)	Rationale
1.3 / Schedule of Activities (Table 2 Footnotes)	d Haematology (WBC, platelet count, Hb), Blood Chemistry (creatinine, glucose, ALT, AST, alkaline phosphatase, bilirubin (total and conjugated). Glucose: Fasting levels in all participants at Screening visit, fasting levels on Days 1 and 169. Fasting is not necessary for diabetic participants. e Injection site to be specifically checked 2 ~~and 4~~ hours after injection for local reactions on Day 1. After Day 1, any local reaction AE to be collected on the CRF in the same manner as other AEs. f Measurement of testosterone and laboratory safety tests for analysis purposes only and not for eligibility ~~—~~the screening testosterone and safety laboratory test results will be used for eligibility. g Participants, particularly those with M1b status, should be advised regarding clinical signs suggestive of spinal cord compression.	d Haematology (WBC, platelet count, Hb), Blood Chemistry (creatinine, glucose, ALT, AST, alkaline phosphatase, bilirubin (total and conjugated) **will be tested at the local laboratory**. Glucose: Fasting levels in all participants at Screening visit, fasting levels on Days 1 and 169. Fasting is not necessary for diabetic participants. e Injection site to be specifically checked 2 hours after injection for local reactions on Day 1. After Day 1, any local reaction AE to be collected on the CRF in the same manner as other AEs. f Measurement of testosterone**, PSA** and laboratory safety tests for analysis purposes only and not for eligibility**.** The screening testosterone**, PSA** and safety laboratory test results will be used for eligibility. g **Complete physical examination to be performed (or brief physical examination based on investigator judgement).** Participants, particularly those with M1b status, should be advised regarding clinical signs suggestive of spinal cord compression. **i Testosterone and PSA testing will be performed at the central laboratory.**	Clarification of laboratory testing location and study procedures.

Section	Was (Version 2.0, 11 November 2021)	Is (Version 3.0, 07 April 2022)	Rationale
7.2 / Participant Discontinuation/ Withdrawal from the Study	• A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or compliance reasons. ~~A participant may be withdrawn from the study for any of the following reasons including:~~ o ~~Drug-related AE~~ o ~~Non-drug-related AE~~ o ~~Participant lost to follow-up~~ o ~~Non-drug-related reason, e.g. the participant relocates~~ • 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 follow-up and for any further evaluations that need to be completed.	• A participant may withdraw from the study at any time at his/her 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, 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 follow-up and for any further evaluations that need to be completed.	Removed for conciseness as reasons for withdrawal will be presented in the electronic case report form.
8.1 / Demography	Age, sex and, according to individual country regulations/requirements and if authorised in the country, ethnicity will be collected.	Age, sex and, according to individual country regulations/requirements and if authorised in the country, **race**/ethnicity will be collected.	Clarification of demographic information to be collected.
8.2.1 / Testosterone	Residual serum samples remining from the analysis may also be retained by the sponsor for ~~additional investigations~~. This could include using leftover serum for long-term stability, reproducibility~~, or other bioanalytical~~ assessments. Surplus serum samples ~~may~~ be used in China ~~or shipped outside China as required~~. Surplus serum samples will be managed anonymously and will not be identifiable.	Residual serum samples remining from the analysis may also be retained by the sponsor for **up to 5 years after completion of the study**. This could include using leftover serum for long-term stability **or** reproducibility assessments. Surplus serum samples **can only** be used in China. Surplus serum samples will be managed anonymously and will not be identifiable.	Clarification of sample use.

Section	Was (Version 2.0, 11 November 2021)	Is (Version 3.0, 07 April 2022)	Rationale
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. Body weight will be measured in underwear and without shoes. A brief physical examination will include, at a minimum, assessments of the ~~skin,~~ lungs, cardiovascular system, abdomen (liver and spleen).	A complete physical examination will include, at a minimum, assessments of the **skin, and** cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded. Body weight will be measured in underwear and without shoes. A brief physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, abdomen (liver and spleen).	Clarification of study procedures.
8.3.5 / Clinical Safety Laboratory Assessments	•All clinical laboratory safety tests (haematology and blood biochemistry) will be assessed ~~at a central laboratory (as described in the Laboratory Manual). Local testing can be performed optionally as required~~.	•All clinical laboratory safety tests (haematology and blood biochemistry) will be assessed **locally**.	To reduce complexity of obtaining safety assessments during study.
8.5 / Pharmacokinetics	• Surplus plasma samples ~~may~~ be used in China ~~or~~ shipped outside China~~, if required, for the purposes of cross validating the bioanalytical method/s used in this study~~. Surplus plasma samples will be managed anonymously and will not be identifiable. • Residual plasma samples remaining from the analyses may also be retained by the sponsor for ~~additional investigations~~. This could include using leftover plasma for long-term stability~~,~~ reproducibility~~, or other bioanalytical~~ assessments.	• Surplus plasma samples **will** be used in China **and will not be** shipped outside China. Surplus plasma samples will be managed anonymously and will not be identifiable. • Residual plasma samples remaining from the analyses may also be retained by the sponsor for **up to 5 years after the completion of the study**. This could include using leftover plasma for long-term stability **or** reproducibility assessments.	Clarification of sample use.
9.4.2 / Analysis of the Primary Endpoints		**The percentage of participants achieving castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) on Day 29 will be obtained as the number of participants with castrate levels at the visit, divided by the total number of participants on Day 29 in the considered population.**	Clarification of definition for primary endpoints.

Section	Was (Version 2.0, 11 November 2021)	Is (Version 3.0, 07 April 2022)	Rationale
		Percentage of participants maintaining the castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) from Week 8 to Week 24 will be calculated as the number of participants with castrate levels at all visits from Week 8 to Week 24, divided by the total number of assessable participants. **To derive the percentage of participants maintaining castration levels of testosterone, missing data will be handled as follows:** **(a) In participants escaping castration at a certain visit, subsequent missing data is irrelevant.** **(b) Participants maintaining castration up to a certain visit with missing data afterwards (drop-out due to non-drug-related reasons) will be excluded from the analysis.** **(c) Participants maintaining castration up to a certain visit with missing data afterwards (drop-out due to drug-related reasons) will be treated as having escaped castration (failure).** **(d) Missing data between two visits where castration levels are maintained will be handled as missing for that particular visit, and the participant will be considered to have maintained castration.** **To derive the percentage of participants maintaining castrate levels of testosterone, assessable participants are defined as the total number of all participants having values at all visits and all participants having missing data according to the criteria a), c) and d) mentioned previously. Participants having missing data according to the criteria b) will be excluded from this calculation.**	

Section	Was (Version 2.0, 11 November 2021)	Is (Version 3.0, 07 April 2022)	Rationale
9.4.3.2 / Pharmacokinetic and Pharmacodynamic Data Analysis (Population Pharmacokinetic Analysis)		**Historical PK data from other studies may also be used to compare the PK profiles from this study against other populations.**	Clarification of potential pharmacokinetic analysis.
10.1.8 / Study and Site Start and Closure	The study start date is the date on which the clinical study will be open for recruitment of participants.	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 is enrolled**.	Statement made consistent with definition in 42 CFR 11.10(b) (16).
10.2 / Appendix: Clinical Laboratory Tests	• The tests detailed in Table 6 will be performed ~~by a central laboratory (local testing can be performed optionally as required)~~.	• The tests detailed in Table 6 will be performed **locally**.	To reduce complexity of obtaining safety assessments during study.
10.2 / Appendix: Clinical Laboratory Tests	Note: All parameters will be analysed ~~centrally~~. The preparation and storage of samples ~~are described separately in the Laboratory Manual. Local tests will be conducted as optional extra tests as required by local sites~~.	Note: All parameters will be analysed **locally**. The preparation and storage of samples **will be performed per each local laboratory practice**.	To reduce complexity of obtaining safety assessments during study.
10.3.2 / Definition of SAEs	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)~~.	A suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection **should** be reported as serious **if the event meets the defined seriousness criteria. If no seriousness criteria are reported by the investigator, the COVID-19 event will be collected and recorded as nonserious**.	Protocol template update.

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Document page count:	1
Number of supporting files:	0
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"dcn52014237v4.0 2024March08_SponsorSignature page" History

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