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Innovation for patient care

Protocol Title: A phase III, open-label, multicentre, single arm study to assess the efficacy and safety of the triptorelin 6-month formulation in Chinese paediatric participants with central precocious puberty

Protocol Number: D-CN-52014-244

Compound: Triptorelin pamoate (embonate) salt (IPN52014)

Short Title: A study to assess the efficacy and safety of the triptorelin 6-month formulation in paediatric participants with central precocious puberty.

Study Phase: Phase III

Sponsor Name: Ipsen Pharma

Legal Registered Address: 65, Quai Georges Gorse, 92100 Boulogne Billancourt, France

Regulatory Authority Identifier Numbers
Not applicable

Date: 29 April 2022

Version number: 2.0

Approved

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Sponsor Signatory:

PPD

PPD

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Principal Investigator Signature Page

I have read and agree to Protocol D-CN-52014-244, entitled 'A phase III, open-label, multicentre, single arm study to assess the efficacy and safety of the triptorelin 6-month formulation in Chinese paediatric participants with central precocious puberty'. 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: [ ]
[ ]
[ ]
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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	29 April 2022 (Version 2.0)
Original Protocol	21 January 2021 (Version 1.0)

Amendment 1 (29 April 2022, Version 2.0)

Summary of 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 1.0, 21 January 2021)	IS (Version 2.0, 29 April 2022)	Rationale
Sponsor Signatory	PPD	PPD	Update the information of the sponsor representative.
1.3 Schedule of Activities (Table 2)		Add **X[W]**" to row "Clinical laboratory tests [p]", column "Day 1". w. **If the screening tests performed within 1 week prior to Day 1, clinical laboratory assessment will not be repeated on Day 1.**	Clarify the time of clinical laboratory examination.
1.3 Schedule of Activities (Table 2)		Add "**X**" to row "Body weight [m]", column "Day 1"and "Month 9". Add footnote "**[v]**" to row "Auxological parameters [j]", column "Month 9". v. **BMI will not be collected at Month 9.**	Clarify BMI measurement time.
1.3 Schedule of Activities (Table 2 footnote)	d **Head MRI** for all subjects to confirm CPP and check for tumours at screening, unless they have available ~~brain~~ MRI scans within 6 months for site to verify. p **Clinical laboratory tests** including chemistry, haematology and urinalysis. In case of abnormal blood glucose as per investigator's judgement, repetition of these tests will be performed before the injection and fasting status might be required. ~~If the intervention injection is performed within 1 week of Screening tests, clinical laboratory assessment will not be repeated.~~	d **Head (Pituitary) MRI** for all subjects to confirm CPP and check for tumours at screening, unless they have available-MRI scans within 6 months for site to verify. p **Clinical laboratory tests** including chemistry, haematology and urinalysis. In case of abnormal blood glucose as per investigator's judgement, repetition of these tests will be performed before the injection and fasting status might be required.	Update according to the actual situation.

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Section	WAS (Version 1.0, 21 January 2021)	IS (Version 2.0, 29 April 2022)	Rationale
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.	Detailed information about the known and expected benefits and risks and reasonably expected AEs of triptorelin may be found in the IB **and development safety update report.**	As per new template version.
4.2 Scientific Rationale for Study Design	The total blood volume (~~116~~ mL) to be collected during this study is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard reported in Ni [Ni 2017].	The total blood volume (**114** mL) to be collected during this study is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard reported in Ni [Ni 20 7].	Update the total blood volume according to the actual situation.
5.1 Inclusion Criteria	-Girls with Tanner staging ≥2 for breast development and who have enlarged uterine length and/or ovarian volume and ~~several~~ follicles with diameter >4 mm in the ovary observed by pelvic type B ultrasound at the Screening visit; boys who have testicular volume ≥4 mL observed by testicular orchidometer at the Screening visit.	-Girls with T nner staging ≥2 for breast d velopment and who have enlarged uterine length and/or ovarian volume and **at least 2** follicles with diameter >4 mm in the ovary observed by pelvic type B ultrasound at the Screening visit; boys who have testicular volume ≥4 mL observed by testicular orchidometer at the Screening visit.	Clarify the minimum number of follicles larger than 4 mm in diameter.
8 STUDY ASSESSMENTS AND PROCEDURES	• The maximum amount of blood collected from each participant over the dur tion of the study, including any extra assessments that may e required, will not exceed ~~1~~ 6 mL. (see [Ni 2017])	• 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 **114** mL. (see [Ni 2017])	Update the total blood volume according to the actual situation.
8.4 Pharmacokinetics	• Approximately 4 mL of blood samples will be collected for measurement of triptorelin 6-month formulation plasma concentrations of as specified in the SoA (Section 1.3) to be analysed at a bionalytics Service Provider (~~Covance~~). ~~These blood samples will also be used~~ to derive serum for bioanalytical cross-validation purposes.	• Approximately **2** mL of blood samples will be collected for measurement of triptorelin 6-month formulation plasma concentrations of as specified in the SoA (Section 1.3) to be analysed at a bionalytics Service Provider (**Labcorp**). • **Approximately 2 mL of blood samples will be collected** to derive serum for bioanalytical cross-validation purposes.	Update according to the actual situation.

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Section	WAS (Version 1.0, 21 January 2021)	IS (Version 2.0, 29 April 2022)	Rationale
9.4.3.1 Pharmacokinetic Analyses	Individual listings of triptorelin concentrations and descriptive summary statistics (n, mean, standard error of mean (SEM), SD, coefficient of variance (%CV), geomean, geomean SD, geomean %CV, median, min, max, ~~90~~% CI) will be presented by timepoint/visit following each administration. If required and warranted by the data, an attempt to build a model to characterize the PK in the population will be made. This will be described in a separate analysis plan and the outcomes summarised in a standalone report.	Individual listings of triptorelin concentrations and descriptive summary statistics (n, mean, standard error of mean (SEM), SD, coefficient of variance (%CV), geomean, geomean SD, geomean %CV, median, min, max, **95**% CI) will be presented by timepoint/visit following each administration. If required and warranted by the data, an attempt to build a model to characterize the PK in the population will be made. **An analysis to look at the relationship between concentrations versus efficacy and/ safety may be performed if warranted by the data.** This will be described in a separate analysis plan and the outcomes summarised in a standalone report.	Typo corrected and relevant description added.
10.2 Appendix 2: Clinical Laboratory Tests (Table 6)	a If the ~~intervention injection is~~ performed within 1 week ~~of Screening tests~~, clinical laboratory assessments (~~uri lysis, biochemistry and haematology~~) will not be repeated on Day 1.	Add "**[a]**" to row "Haematology" and "Routine Urinalysis". Add "**X**" to row "Alkaline Phosphatase", column "Screening". a If the **screening tests** performed within 1 week **prior to Day 1**, clinical laboratory assessments (**haematology, clinical chemistry and urinalysis**) will not be repeated on Day 1	Update according to the actual situation.
10.3.2 Definition of Serious Adverse Events	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 **seriousness assessed based on the reported seriousness criteria.** If no seriousness criteria **is reported by the investigator, the COVID-19 infection will be collected and recorded as "non serious"**.	Update to conform to new protocol template.

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Section	WAS (Version 1.0, 21 January 2021)	IS (Version 2.0, 29 April 2022)	Rationale
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~~	**SAE Reporting to sponsor via paper** • **All SAEs regardless of treatment group or suspected relationship to triptorelin, must be reported immediately (within 24 hours of the Investigator s knowledge of the event) using the SAE report form via the email address or the fax number specified t the beginning of this prot col as well as recording them in the eCRF.** • Contacts for SAE reporting can be found on the SAE form and the cover sheet.	Update to conform to new protocol template.

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Section	WAS (Version 1.0, 21 January 2021)	IS (Version 2.0, 29 April 2022)	Rationale
	~~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.		

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LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
AE(s)	Adverse Event(s)
BA	Bone Age
BMI	Body Mass Index
CA	Chronological Age
CI	Confidence Interval
CIOMS	Council for International Organisations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CPP	Central Precocious Puberty
CTFG	Clinical Trial Facilitation Group
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
%CV	Coefficient of variance
EU	European Union
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Pr ctice
GLP	Good Lab ratory Practice
GnRH	Gonadotropin-releasing Hormone
GnRHa(s)	GnRH Agonist(s)
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor 1
i.m.	Intramuscular
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intention-to-treat
i.v.	Intravenous
IWRS	Interactive Web Response System
LAM	Lactational amenorrhoea method

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ABBREVIATION	Wording Definition
LH	Luteinising hormone
LHRH	Luteinising Hormone-releasing Hormone
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PASS	Power Analysis and Sample Size
PK	Pharmacokinetic
PP	Per protocol
PR	Prolonged Release
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD(s)	Standard Deviation(s)
SEM	Standard error of the mean
SoA	Schedule of activities
SOC	System Organ Class
SUSAR	Suspect d unexpected serious adverse reaction
TEAE(s)	Treatment-emergent Adverse Event(s)
ULN	Upper Limit of Normal
USA	United States of America
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Woman of childbearing potential

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase III, open-label, multicentre, single arm study to assess the efficacy and safety of the triptorelin 6-month formulation in Chinese paediatric participants with central precocious puberty.

Short Title: A study to assess the efficacy and safety of the triptorelin 6-month formulation in paediatric participants with central precocious puberty.

Rationale:

Currently marketed in China there is a triptorelin 1-month formulation indicated for the treatment of children with central precocious puberty (CPP).

A global pivotal study, DEBIO 8206CPP301, demonstrat d the efficacy and safety of the 6-month formulation over a period of 12 months and led to registration in the European Union (EU) and United States of America (USA).

This current study is intended to document the efficacy, safety and pharmacokinetics (PK) of triptorelin 6-month formulation in Chinese children with CPP over a period of 12 months. Henceforth in this protocol, triptorelin pamoate 22.5 mg 6-month formulation will be referred to as 'triptorelin 6-month formulation'.

Objectives and Endpoints:

Objectives and endpoints are summarised in Table 1.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of the triptorelin 6-month PR formulation in suppressing LH levels to prepubertal levels (def ned as a peak LH ≤5 IU/L) after i.v. GnRH stimulation at Month 6 (Day 169) in Chinese children with CPP	• Proportion of children with LH suppression defined as stimulated peak LH ≤5 IU/L after GnRH stimulation at Month 6.
Secondary	
• To assess the efficacy in suppressed LH response to GnRH test at Months 3 and 12	• Proportion of children with LH response to GnRH test at Months 3 and 12
• To assess change of basal serum LH and FSH levels at Months 3, 6, 9 and 12	• Change in basal serum LH and FSH levels at Months 3, 6, 9 and 12 compared to baseline
• To assess change of peak serum LH and FSH levels after the GnRH stimulation test at Months 3, 6 and 12	• Change in peak serum LH and FSH level after the GnRH stimulation test at Months 3, 6 and 12 compared to baseline
• To assess sex hormone serum concentrations (oestradiol for girls and testosterone for boys) at Months 3, 6, 9 and 12	• Proportion of children with pre-pubertal levels of sex steroids (defined as oestradiol ≤20 pg/mL in girls or testosterone ≤30 ng/dL in boys) at Months 3, 6, 9 and 12

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Objectives	Endpoints
• To assess height (Z-score [height for age] and percentile for height for age) growth velocity and BA (Greulich and Pyle method) at Months 6 and 12	• Change in height (Z-score [height for age] and percentile for height for age) and growth velocity at Months 6 and 12 compared to baseline • Proportion of children in whom the BA/CA ratio did not rise at Month 6 and 12 relative to baseline (X ray) • Change in the ratio BA/CA at Months 6 and 12 compared to baseline
• To assess sexual maturation at Months 6 and 12	• Proportion of children with stabilised pubertal (Tanner method) stage at Months 6 and 12.
• To assess uterine length in girls and testis volumes in boys at Months 6 and 12	• Proportion of girls with regression of uterine length at Months 6 and 12 (transabdominal ultrasound) • Proportion of boys with absence of progression of testis volumes at Months 6 and 12 (clinical assessment with orchidometer)
• To assess the change of body weight and BMI at Months 6 and 12	• Change in BMI and weight compared to baseline at Months 6 and 12
• To assess the safety profile • To evaluate local tolerability at the injection site immediately and 2 hours after triptorelin injection	• Incidence of TEAEs throughout the study, including local tolerability at the injection site immediately and 2 hours after triptorelin injection • Change in clinical safety laboratory (blood biochemistry, haematology and urinalysis) parameters at Month 3, 6, 9 and 12 compared to baseline. • Change in physical examination and vital signs (blood pressure and heart rate) measurements at each visit compared to baseline
• To assess the PK of plasma triptorelin	• Sparse plasma triptorelin concentrations at Day 1, Months 3, 6 and 12

BA=bone age; BMI=body mass index; CA=chronological age; CPP=central precocious puberty; FSH=follicle-stimulant hormone; GnRH=gonadotropin-releasing hormone; i.v.=intravenous; IU=international unit; LH=luteinising hormone; PK=pharmacokinetics; PR=prolonged release; TEAEs=treatment-emergent adverse events

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Overall Design:

- This is an open-label, multicentre, single arm interventional study to evaluate the efficacy and safety of triptorelin 6-month formulation in Chinese paediatric participants with CPP over a period of 12 months.
- This study aims to demonstrate that triptorelin 6-month formulation is efficacious in suppressing luteinizing hormone (LH) to prepuberal levels in children with CPP (defined as a peak LH ≤5 IU/L after intravenous (i.v.) gonadotropin-releasing hormone (GnRH) stimulation) at Month 6.
- This study will enrol Chinese participants with CPP in girls less than 9 years old and boys less than 10 years old at initiation of triptorelin treatment.
- Approximately a total of 66 participants (including at least three boys) will be enrolled to be administered intramuscular (i.m.) injections of triptorelin on Day 1 and Month 6 of the study. The triptorelin injection dose will not be adapted based on body weight.

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- The study consists of a Screening period (the Screening visit will take place up to 28 days before enrolment), during which participants with CPP will be screened for eligibility. Participants will receive triptorelin injections on Day 1 and Month 6 of the study. Participants will have study visits at Screening, Day 1 and at Months 3, 6, 9 and 12 (Figure 1).
- Each participant is expected to be enrolled in this study for a minimum of 12 months and up to 13 months (including Screening period).
- Participants who complete the study will perform final procedures and assessments at the final visit (Month 12). Participants who withdraw from the study before the completion of the evaluation period will be invited to attend an Early Withdrawal visit to perform early discontinuation procedures and assessments.

Condition/Disease: Central precocious puberty

Study Hypothesis: Triptorelin 6-month formulation is safe and efficacious in children with CPP as confirmed by a suppressed peak-stimulated LH a Month 6 (defined as peak of LH≤5 IU/L after i.v. GnRH stimulation).

Intervention Groups and Duration:

- The study will consist of a Screening period (the Screening visit will take place up to 28 days before enrolment), during which participants with CPP will be screened for eligibility before receiving the triptorelin injection (Day 1 of the study) and will visit the study centre at Month 3, 6, 9 and 12 (See Section 1.3). Participants will receive two injections during the study period before they attend the End of Study (EOS) visit at Month 12.
- Participants who complete the study will perform final procedures and assessments at the final visit (Month 12). Parti ipants who withdraw from the study before the completion of the evaluation pe iod will be invited to attend an Early Withdrawal visit to perform early discontinuation procedures and assessments.

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Study Participant Duration: approximately 13 months; i.e. screening and two injections of the study intervention.

Intervention Duration: approximately 12 months; i.e. two injections of the study intervention.

Number of Participants: Approximately 66 participants will be enrolled in the study, including at least three boys.

Statistical Methods:

Sample Size determination

The sample size of this study is estimated based on following assumptions according to global pivotal study DEBIO 8206-CPP-301 [Klein 2016].

- Expected outcome for the proportion of children with a suppressed LH response to the GnRH stimulation test (stimulated peak serum LH ≤5 IU/L) at Month 6 is 93%;
- Null proportion is 80%;
- An exact binomial test of a proportion with a one-sided nominal significance level of 0.025 and power =85%;

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- Expected common dropout rate =5%.

Under these assumptions, approximately 66 participants (Power Analysis and Sample Size (PASS) software) are planned to be enrolled into the study to ensure there are 62 treated participants to confirm the efficacy of the triptorelin 6-month formulation by the proportion of children with a suppressed LH response to the GnRH stimulation test at Month 6.

Primary Analysis

For the primary efficacy endpoint, the summary statistics of number and percentage of participants and the exact two-sided 95% confidence interval (CI) for a binomial proportion will be computed by Statistical Analysis System® (SAS®) using the exact binomial distributions on the intention-to-treat (ITT) population (primary population of analysis), modified (m)ITT and per protocol (PP) sets.

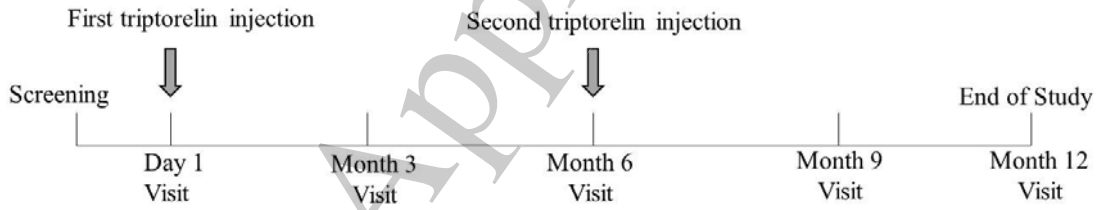
Secondary Analyses

For secondary efficacy endpoints related to a change at Months 3, 6, 9 and 12 compared to baseline, the descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) will be calculated on the ITT population. In addition, secondary efficacy endpoints will be performed on the PP set. Exact two sided 95% CIs will also be constructed for all secondary endpoints expressed as percentages

1.2 Schema

The study design is shown in Figure 1.

Figure 1 Study Design



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1.3 Schedule of Activities

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.

Table 2 Schedule of Activities

Procedures [a]	Screening Visit		M nth 3	Month 6	Month 9	Month 12
	Day -28 to Day -1 Prior to Treatment	Day 1	Day 85	Day 169	Day 253	Day 337 (EOS/Early Withdrawal) [u]
Visit window (days)			±3 days	±3 days	±3 days	+7 days
Informed consent /assent [b]	X					
Inclusion and exclusion criteria [c, d]	X	X				
Demography	X					
Medical and surgical history	X					
PK samples[e]		X	X	X		X
Basal LH and FSH [f]	X		X	X	X	X
GnRH test with LH and FSH [g]	X		X	X		X
Oestradiol or testosterone [h]	X		X	X	X	X
Pubertal Stage (Tanner method) [i]	X			X		X
Auxological parameters [j]	X		X	X	X[v]	X
Bone age [k] and chronological age	X			X		X
Gonad development [l]	X			X		X
Body weight [m]	X	X	X	X	X	X
Adverse events [n]	X	X	X	X	X	X
Pregnancy test [o]		X				X
Clinical laboratory tests [p]	X	X [w]	X	X	X	X
Physical examination and vital signs [q]	X	X	X	X	X	X

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Procedures [a]	Screening Visit		Month 3	Month 6	Month 9	Month 12
Prior and concomitant medications [r]	X	X	X	X	X	X
Study drug administration [s]		X		X		
Local tolerability [t]		X		X		

BMI=body mass index; CPP=central precocious puberty, eCRF=electronic case report form, EOS=End of Study; FSH=follicle-stimulating hormone; GnRH=gonadotropin-releasing hormone; IEC=Independent Ethics Committee; IRB=Institutional Review Board; LH=luteinising hormone; MRI=magnetic resonance imaging, PK=pharmacokinetic.

Footnotes to Schedule of Assessments

a **Study procedures** to be done before dosing except local tolerability and post-dose PK. Note that in the case that Sc eening is more than 1 week prior to first intervention, clinical laboratory tests (chemistry, haematology and urinalysis) will need to be reassessed.
b **Informed consent/assent** to be performed by parent/legal guardian and by children if determined by local IRB/IEC requirements.
c **Eligibility check** of inclusion and exclusion criteria to occur at Screening and prior to dosing on Day 1.
d **Head (Pituitary) MRI** for all subjects to confirm CPP and check for tumours at screening, unles they have ailable MRI scans within 6 months for site to verify.
e **PK Samples** on Day 1 to be taken predose and at 4 hours postinjection (±2-hour window); PK sample at Month 3 visit, Month 6 (predose of second injection, and 4 hours postinjection (±2 hour window)), and Month 12 EOS/early withdrawal visits to be taken preGnRH agonist stimulation.
f **Basal LH and FSH** samples to be drawn before GnRH test. Blood sampling should be tak n at approximately the same time of day during each visit.
g **GnRH test** samples for LH and FSH concentrations will be collected at 30, 60 and 9 minutes after the GnRH test.
h **Oestradiol and Testosterone** samples for girls and boys, respectively. Blood sampling should be taken at approximately the same time of day during each visit.
i **Tanner pubertal stage** as defined in Appendix 6.
j **Auxological parameters** including height, growth velocity, BMI will be assess d
k **Bone Age** by Greulich and Pyle method.
l **Gonad development** uterine length in girls assessed by Type B ultraso nd or testicular volume in boys assessed by orchidometer.
m **Body weight** is required for administration of gonadorelin in the GnRH te t
n **Adverse events** will be collected up to and including the Month 12 visit (i.e. Day 337+7 days).
o **Pregnancy test** for female participants only. Girls who have entered menarche must have a negative pregnancy test prior to the start of study treatment and should not be at risk of pregnancy throughout the study period. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC before drug treatment for all female participants of childbearing potential and if clinically indicated thereafter. First pregnancy test to be performed within 24 hours prior to first injection.
p **Clinical laboratory** tests including chemistry, haematology and urinalysis. In case of abnormal blood glucose as per investigator's judgement, repetition of these tests will be performed before the injection and fasting status might be required.
q **Physical examination and vital signs** blood pressure and heart rate.
r **Prior and concomitant medications** assessed at every visit
s **Study drug administration** following all other assessments, apart from PK samples on Day 1 and Month 6
t **Local tolerability** Measured by tenderness, redness, bruising, erythema, swelling, rash, pain, itching, induration, haematoma, ulceration or necrosis, immediately and 2 hours after triptorelin injection.
u **EOS/Early Withdrawal** For participants who do not have a final visit within 6 months after their last triptorelin dose, efficacy evaluations (including PK sampling) will not be performed. Data from any efficacy evaluations performed after this time will not be collected on the eCRF.
v **BMI** will not be collected at Month 9.
w If the screening tests performed within 1 week prior to Day 1, clinical laboratory assessment will not be repeated on Day 1.

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1.4 Brief Summary

The purpose of this study is to assess the safety and efficacy of the triptorelin 6-month formulation in Chinese children with CPP. Efficacy will be defined by peak (LH levels ≤5 IU/L) after i.v. GnRH stimulation at Month 6.

Study Participant Duration: approximately 13 months; i.e. screening and two injections of the study intervention.

Intervention Duration: approximately 12 months; i.e. two injections of the study intervention.

Visit Frequency: Screening, Day 1, Months 3, 6, 9 and 12.

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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 CPP, prostate cancer, endometriosis, uterine fibromyomas, in vitro fertilisation and breast cancer.

2.1 Study Rationale

Currently marketed in China there is a triptorelin 1-month formulation indicated for the treatment of children with CPP.

A global pivotal study, DEBIO 8206-CPP-301, demonstrated the efficacy and safety of the 6-month formulation over a period of 12 months and led to registration in the EU and USA.

This current study is intended to document the efficacy, safety and PK of triptorelin 6-month formulation in Chinese children with CPP over a period of 12 months.

Henceforth in this protocol, triptorelin pamoate 22.5 mg 6-month formulation will be referred to as 'triptorelin 6-month formulation'.

2.2 Background

Precocious puberty is a condition that causes early sexual development in girls and boys. While the chronological age (CA) limit for the onset of puberty is 8 years in girls and 9 years in boys for children in North America and Western European countries [Carel 2008], children with precocious puberty exhibit precocious pubertal development that can be 2.5 to 3 SDs earlier than the current estimated average. The prevalence of precocious puberty is 10 times higher in girls than in boys [Carel 2008].

In a minority of children, precocio s puberty can occur due to an organic lesion (cerebral tumour); in most children, this condition is caused by the early release of GnRH (also known as luteinising hormone-releasing hormone (LHRH)) by the hypothalamus. In healthy children, GnRH stimulates the release of pitui ary gonadotropins follicle-stimulating hormone (FSH) and LH, which is then followed by pr longed suppression of these hormones, contributing to normal pubertal development. The form of precocious puberty caused by early GnRH stimulation is termed CPP. In children with CPP, early GnRH release leads to the precocious secretion of LH and FSH which, in turn, activate the early secretion of gonadal hormones by the ovaries or testes.

Signs of puberty include pubic and axillary hair growth and changes in the child's body shape and behaviour. Boys develop facial hair and their penis lengthens and girls develop breasts and may have menstrual periods. In children with CPP, these signs prematurely appear before the age of 8 years in girls and 9 years in boys, respectively. Furthermore, growth velocity accelerates, initially inducing a rapid height increase, which stops at an early age. Accelerated bone maturation leads to premature epiphyseal closure and a final height below the target height that was otherwise expected for the child's age. These premature changes may also lead to psychological disorders in children with CPP.

There is currently no nationwide epidemiology study of CPP data in China. Only two studies have been published about the incidence of precocious puberty in two cities: Jiu Jiang (study with 3,312 children investigated and an incidence of 0.68%, 1.25% in girls and 0.11% in boys) [Hu 2012] and Zhengzhou (study with 8,750 children investigated and an incidence of 0.74%, 1.37% in girls and 0.26% in boys) [Wei 2010]. In coastal areas of China, precocious puberty has an incidence rate of 0.38%; the incidence in girls is higher at 0.67%. The prevalence of

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precocious puberty in Shanghai is 100/10,000 [Lin 2004]. These data refer to precocious puberty without GnRH-dependent stimulation, which is not specific for CPP and are probably lower than numbers described above.

As reported by Carel and Léger [Carel 2008], the assessment of gonadotropin levels (based on ultrasensitive assays) is central to the diagnosis of CPP. The gold standard for evaluation is the measurement of gonadotropin levels after stimulation with GnRH or a GnRH agonist (GnRHa). Peak LH levels of 5 to 8 IU/L suggest progressive CPP but there is an overlap between prepubertal and early pubertal values [Carel 2008, Resende 2007]. Caution should be taken when interpreting gonadotropin levels in children younger than 2 to 3 years old as gonadotropin levels are normally high in this age group [Carel 2008].

In CPP (i.e. with no other identified cause such as a cerebral tumour), there is no surgical therapy available and no effective alternative therapeutic option other than taking a prolonged release (PR) formulation of synthetic GnRH. In severe cases, untreated CPP causes physical and psychological problems for the child.

Treatment with GnRH analogues, which act by downregulating pituitary GnRH receptors [Carel 2009, Comite 1981 Crowley 1981, Bertelloni 2013] represent the standard of care for the treatment of CPP [Carel 2009]. Their efficacy to stop precocious development has been demonstrated and their use involves only minor adverse events (AEs). A review of CPP treatment by Krishna et al confirmed that treatment with PR formulations of GnRHas is safe, with relatively minor side effects, and supported that the outcome in terms of final height is favourable in most patients [Krishna 2019].

Diphereline® (international non-proprietary name (INN): triptorelin) is a synthetic GnRH analogue that is mainly characterised by th replacement of the L-glycine in the 6th position by a D-tryptophan. This structural modification increases both the resistance to enzymatic degradation and the affinity to the pituitary receptor, thus prolonging the plasma half-life ($t_{1/2}$) and increasing the potency of the drug

In China, Diphereline® is availabl as a 1-month formulation, which is approved for use in patients with CPP, prostate c ncer end metriosis, fibromyomas and female infertility.

Study DEBIO 8206-CPP-301 was the first 6-month triptorelin clinical trial in the treatment of CPP sponsored by Debiopharm International SA [Klein 2016]. This was an international, multicentre, nonrandomised, open-label, noncomparative phase III study of two i.m. injections of triptorelin 6-month formulation administered twice over 12 months in a group of 44 children with CPP comprising 39 girls and 5 boys. The 6-month formulation was safe and effective in suppressing the pituitary-gonadal axis in children with CPP. The extended injection interval may improve compliance and increase comfort in the management of CPP.

The worldwide marketing status of all triptorelin formulations of which Ipsen and Debiopharm are the marketing authorisation holders (marketed by Ipsen under Debiopharm/Ipsen agreement) can be found in the Investigator's Brochure (IB). Further details/additional information regarding risks and benefits to participants may also be found in the IB.

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 and development safety update report.

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2.3.1 *Risk Assessment*

A risk assessment for triptorelin can be found in Table 3.

Table 3 Triptorelin Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Triptorelin		
There is no major known nonclinical risk associated with the study intervention Clinical risks associated with the study intervention may include: • vaginal bleeding of mild or moderate intensity in girls • decreased bone mineral density • risk of abortion or foetal abnormality[a] See Section 8.3.	See IB Section 6.2.3	**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 participant safety including local tolerability (see Section 8.2.5). **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 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; SAEs=serious adverse events

a Pregnancy is highly unlikely in this study population, but reproductive risks are listed for completeness.

2.3.2 *Benefit Assessment*

Based on the nonclinical and clinical data generated up to the writing of this protocol, treatment with triptorelin 6-month formulation may prevent the paediatric participant's progression of precocious puberty while safeguarding the regular development of the child.

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 participants with CPP.

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3 OBJECTIVES AND ENDPOINTS

Table 4 displays the objectives and corresponding endpoints. Other attributes are described in further sections: Population in Section 5, study intervention in Section 6, prohibited medications in Section 6.8, analysis sets are defined in Section 9.3 and endpoints are described in further detail in Section 9.4.

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of the triptorelin 6-month PR formulation in suppressing LH levels to prepubertal levels (defined as a peak LH ≤5 IU/L) after i.v. GnRH stimulation at Month 6 (Day 169) in Chinese children with CPP	• Proportion of children with LH suppression defined as stimulated peak LH ≤5 IU/L after GnRH stimulation at Month 6.
Secondary	
• To assess the efficacy in suppressed LH response to GnRH test at Months 3 and 12	• Proportio of children with LH response to GnRH test at Months 3 and 12
• To assess change of basal serum LH and FSH levels at Months 3, 6, 9 and 12	• Change in basal serum LH and FSH levels at Months 3, 6, 9 and 12 compared to baseline
• To assess change of peak serum LH and FSH levels after the GnRH stimulation test t Months 3, 6 and 12	• Change in peak serum LH and FSH level after the GnRH stimulation test at Months 3, 6 and 12 compared to baseline
• To assess sex hormone serum concentr tions (oestradiol for girls and testosterone f r boys) at Months 3, 6, 9 and 12	• Proportion of children with pre-pubertal levels of sex steroids (defined as oestradiol ≤20 pg/mL in girls or testosterone ≤30 ng/dL in boys) at Months 3, 6, 9 and 12
• To assess height (Z-score [height fo age] and percentile for height for age) g wth velo ity and BA (Greulich and Pyle method) at Months 6 and 12	• Change in height (Z-score [height for age] and percentile for height for age) and growth velocity at Months 6 and 12 compared to baseline • Proportion of children in whom the BA/CA ratio did not rise at Month 6 and 12 relative to baseline (X ray) • Change in the ratio BA/CA at Months 6 and 12 compared to baseline
• To assess sexual maturation at Months 6 and 12	• Proportion of children with stabilised pubertal (Tanner method) stage at Months 6 and 12.
• To assess uterine length in girls and testis volumes in boys at Months 6 and 12	• Proportion of girls with regression of uterine length at Months 6 and 12 (transabdominal ultrasound) • Proportion of boys with absence of progression of testis volumes at Months 6 and 12 (clinical assessment with orchidometer)
• To assess the change of body weight and BMI at Months 6 and 12	• Change in BMI and weight compared to baseline at Months 6 and 12

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Objectives	Endpoints
• To assess the safety profile • To evaluate local tolerability at the injection site immediately and 2 hours after triptorelin injection	• Incidence of TEAEs throughout the study, including local tolerability at the injection site immediately and 2 hours after triptorelin injection • Change in clinical safety laboratory (blood biochemistry, haematology and urinalysis) parameters at Month 3, 6, 9 and 12 compared to baseline. • Change in physical examination and vital signs (blood pressure and heart rate) measurements at each visit compared to baseline
• To assess the PK of plasma triptorelin	• Sparse plasma triptorelin concentrations at Day 1, Months 3, 6 and 12

BA=bone age; BMI=body mass index; CA=chronological age; CPP=central precocious puberty; FSH=follicle-stimulant hormone; GnRH=gonadotropin-releasing hormone; i.v.=intravenous; IU=international unit; LH=luteinising hormone; PK=pharmacokinetics; PR=prolonged release; TEAEs=treatment-emergent adverse events

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4 STUDY DESIGN

4.1 Overall Design

- This is an open-label, multicentre, single arm interventional study to evaluate the efficacy and safety of triptorelin 6-month formulation in Chinese paediatric participants with CPP over a period of 12 months.
- This study aims to demonstrate that triptorelin 6-month formulation is efficacious suppressing LH to prepuberal levels in children with CPP (defined as a peak LH ≤5 IU/L after i.v. GnRH stimulation) at Month 6.
- This study will enrol Chinese participants with CPP in girls less than 9 years old and in boys less than 10 years old at initiation of triptorelin treatment.
- Approximately a total 66 participants (including at least three boys) will be enrolled to be administered i.m. injections of triptorelin on Day 1 and Month 6 of the study. The triptorelin injection does not have to be adapted based on body weight.
- The study consists of a Screening period (the Screening visit will take place up to 28 days before enrolment), during which participants with CPP will be screened for eligibility. Participants will receive triptorelin injections on Day 1 and Month 6 of the study. Participants will have study visits at Screening Day 1 and Months 3, 6, 9 and 12 (Figure 1).
- Each participant is expected to be enrolled in this study for a minimum of 12 months and up to 13 months (including Screening period).
- Participants who complete the study will perform final procedures and assessments at the final visit (Month 12). Participants who withdraw from the study before the completion of the evaluation period will be invited to attend an Early Withdrawal visit to perform early discontinuation procedures and assessments.

The study design is illustrated in Figure 1.

4.2 Scientific Rationale for Study Design

This uncontrolled phase III study will investigate the efficacy, safety and PK of triptorelin 6-month formulation in children with CPP over 12 months.

For CPP, a non-comparative, open clinical trial design is acceptable as the efficacy of triptorelin will be assessed by the percentage of children achieving LH suppression to pre-pubertal levels, defined as LH ≤5 IU/L, after GnRH stimulation at Month 6 (primary endpoint).

As the efficacy of the drug is based on the suppression of the pituitary receptors responsible for LH (and FSH) production, no studies in this field with any GnRHa have had a comparative design. The recent approved leuprolide 3 months formulation in China is one of the examples of single arm, non-comparative design.

The LH response after the GnRH stimulation test, associated with clinical data and within a context of CPP, constitutes a reliable and feasible resource and can assist in monitoring the effectiveness of treatment.

The primary objective of the study is to assess the percentage of children with LH level suppression to prepubertal levels (serum LH ≤5 IU/L after GnRH stimulation) at Month 6. Participants would receive two injections of triptorelin (Day 1 and Month 6) and be followed for a total of 12 months. The objective of this study is to exclude any ethnicity factor that may lead to a different response. The serum LH ≤5 IU/L cut-off for primary endpoint definition of prepubertal levels is consistent with the global pivotal DEBIO 8206-CPP-301 study.

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Measures to safeguard the development and maturation of the child including assessment of physical growth, neuropsychiatric development, sexual maturation will be implemented and subject to close monitoring.

The total blood volume (114 mL) to be collected during this study is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard reported in Ni [Ni 2017].

This study will evaluate the PK profile of triptorelin 6-month formulation given to paediatric participants with CPP. The blood sample collection scheme was designed to collect the minimum number of blood samples to help provide useful information on the PK of the triptorelin 6-month formulation in paediatric Chinese population.

As with all clinical and PK studies, there are risks associated with venipuncture and multiple blood sample collection. To avoid multiple venipunctures, which cause additional discomfort and other potentially toxic effects, the use of i.v. indwelling catheters is permitted in this study. This minimises the number of venipunctures and the total volume of blood collected from each participant during the study.

4.3 Justification for Dose

For this intervention, the term "dose" refers to the i.m. injection of a triptorelin 22.5 mg created to guarantee the release of a monthly dose of 3.75 mg over a 169-day period. For more information see Section 6.5. This formulation has been made available in different countries (such as USA, Europe, South-East Asia) for th treatment of CPP since 2009 and has been tested in the phase III Study DEBIO 8206-CPP-301 (see Section 2.2).

4.4 End of Study Definition

The EOS is defined as the date of the last visit of the last participant in the study as shown in the schedule of activities (SoA) (Table 2)

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 di ontinuation 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.

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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:

Age

(1) Participant is less than 9 years old for girls and less than 10 years old for boys at initiation of triptorelin treatment or at the time of signing the informed consent.

Type of Participant and Disease Characteristics

(2) Participant must present evidence of CPP documented by:

- Onset of development of secondary sex characteristics (breast development in girls or testicular enlargement in boys according to the Tanner method: Stage II) before the age of 8 years in girls and 9 years in boys
- Pubertal response of LH to GnRH stimulation test (stimulated peak LH ≥6 IU/L) in both sexes.
- Difference between bone age (BA) and CA >1 year.
- Girls with Tanner staging ≥2 for breast development and who have enlarged uterine length and/or ovarian volume and at least 2 follicles with diameter >4 mm in the ovary observed by pelvic type B ultrasound at the Screening visit; boys who have testicular volume ≥4 mL observed by testicular orchidometer at the Screening visit.

Sex and Contraception/Barrier Requirements

(3) Girls who have already had menophania/menarche must have a negative highly sensitive (urine) pregnancy test as required by local regulations within 24 hours before the first dose of study intervention (see Section 8.2.6) and should not be at risk of pregnancy throughout the study period.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.6.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female participant with an early undetected pregnancy.

Informed Consent and Assent

(4) The investigator, or a person designated by the investigator, will obtain written informed consent from each participant's legal guardian (as defined in Appendix 10.1.3) and the participant's assent, in case determined by local requirements before any study-specific activity is performed. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand.

5.2 Exclusion Criteria

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

Medical Conditions

(1) Major medical or psychiatric illness that could interfere with study visits.

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(2) Gonadotropin-independent (peripheral) precocious puberty: extrapituitary secretion of gonadotropins or gonadotropin-independent gonadal or adrenal sex steroid secretion.

(3) Non-progressing isolated premature thelarche.

(4) Presence of an unstable intracranial tumour or an intracranial tumour requiring neurosurgery or cerebral irradiation. Participants with hamartomas not requiring surgery are eligible.

(5) Any other condition or chronic illness or treatment possibly interfering with growth or other study endpoints (e.g. chronic steroid use except topical steroids, renal failure, diabetes, moderate to severe scoliosis).

Prior/Concomitant Therapy

(6) Prior or current therapy with a GnRHa, medroxyprogesterone acetate, growth hormone or insulin-like growth factor 1 (IGF-1).

(7) Use of anticoagulants (heparin and coumarin derivatives) within the 2 weeks prior to the Screening visit.

Prior/Concurrent Clinical Study Experience

Not applicable

Diagnostic Assessments

(8) Evidence of renal (creatinine >1.5 x upper limit of normal (ULN)) or hepatic impairment (bilirubin >1.5 x ULN or alanine aminotransferase or aspartate transaminase >3 x ULN)

Other Exclusions

(9) Diagnosis of short stature, i.e. >2.25 SD below the mean height for age

(10) Known hypersensitivity to any of the test materials or related compounds.

5.3 Lifestyle Considerati ns

5.3.1 Meals and Dieta y Restrictions

Participants will refrain from poppy seed consumption from 48 hours prior to Day 1 and until the EOS visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are 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.

5.5 Criteria for Temporarily Delaying

Not applicable. For information about temporarily delaying during the COVID-19 pandemic, please see the Appendix 7 in Section 10.6.

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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

Arm Name	Triptorelin 6-month
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 monthly dose of 3.75 mg over a 169-day period)
Dosage Level(s)	Single dose delivered on Day 1 and Month 6
Route of Administration	i m. injection
Use	Experimental
IMP and AMP/NIMP	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; PR=prolonged release

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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 triptorelin reconstitution and administration.

The suspension for injection must be reconstituted using an aseptic technique and using the ampoule of solvent supplied 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 (20G, without safety device) and transferred to the vial containing the powder. The suspension should be reconstituted by swirling the vial in a gentle circular motion 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 (20G) 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 sedimentation.

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The excipients used in the paediatric formulation are safe for administration in the paediatric population participating in the study.

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

- The investigator or 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 reco ds).
- 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.
- The excipients used in the formulation are safe for administration in the paediatric population participating in the st dy.

At each treatment dispensation (Day 1 and Month 6), a treatment number will be assigned by the Interactive Web Response System (IWRS). The IWRS will also manage all logistical aspects of the study treatment (e.g. replacement, drug supplies and expiry dates) and the recording of drug accountability/destruction. This service provides the investigator, investigational site coordinato s nd project team members with a service that is available 24 hours a day, 7 days a week. Additional details may be found in the IWRS reference manual provided to each investigational site. In case of technical or dispensation queries, a 24-hour helpline is available. If a participant discontinues the study before any intake of study treatment, his/her assigned treatment number will not be reused.

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

6.3 Measures to Minimize Bias: Randomisation and Blinding

6.3.1 Randomisation

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

6.3.2 Maintenance of blinding

This is an open-label study therefore no procedures for blinding are applicable.

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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 trials (for more information see the summary of package characteristics). If overdose occurs, this should be managed symptomatically.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities (at least up to the Month 12 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 or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant receives within 2 months before triptorelin administration or during triptorelin administration must be recorded on the eCRF along with:

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

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

The following concomitant medications are not permitted during this study:

- Any treatment or procedure with an effect on the metabolism or secretion of gonadotropins (LH or FSH) or sex steroids (oestradiol and/or testosterone) will be considered as a protocol violation
- All drugs mentioned as prohibited in the non-inclusion criteria remain prohibited during the study period: GnRH analogues (other than triptorelin 6-month formulation), medroxyprogesterone acetate, growth hormone or IGF-1, systemic or inhaled steroids (mild topical steroids are permitted) or anticoagulants.

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- Drugs which raise prolactin levels should not be prescribed concomitantly as they reduce the level of GnRH receptors in the pituitary. When triptorelin is co-administered with drugs affecting pituitary secretion of gonadotropins, caution should be taken, and it is recommended that the participant's hormonal status be supervised.

6.8.1 Rescue Medicine

Not applicable

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7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of the Study Intervention

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

7.1.1 Pregnancy

See Section 8.3.5.

7.1.2 Temporary Discontinuation

In case of suspected or confirmed COVID-19 (SARS-CoV-2) infection, the intervention administration may be temporarily discontinued depending on the participant clinical presentation. In some cases, the investigator may request a participant be retested before the intervention administration is resumed.

7.2 Participant Discontinuation/Withdrawal from the Study

The legal guardian and the paediatric participant have the right to withdraw permission (consent or assent, respectively) at any time during the study. If the study staff identify any reluctance in the legal guardian or paediatric participant (e.g signs of verbal or physical dissent) about continued participation in the study, the pa di tric participant's continuation in the study should be re-evaluated. The same principles that govern permission/assent/consent also govern its withdrawal.

A participant may be withdrawn from the study for any of the following reasons:

- Withdrawal of consent or assent if applicable (a paediatric participant's dissent should be respected.)
- Drug-related AE
- Non-drug related AE
- Non-drug related reason, e.g. participant relocates
- Lack of efficacy.

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, it should be explained in detail in the medical records by the investigator as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up. This information must be entered in the CRF.

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.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if they 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:

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- 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 or not 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.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 10.1.

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8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (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 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 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 114 mL. (see [Ni 2017])
- Repeat or unscheduled samples may be taken for safety reasons or in case of technical issues with the samples.

8.1 Efficacy Assessments

Efficacy and PK measurements will be performed centrally. The timing of efficacy assessments is summarised in the SoA (Table 2). Procedures for recording efficacy data are discussed in this section and methods of analyses are discussed in Section 9.4.

8.1.1 Luteinising Hormone and Follicle-stimulating Hormone Serum Concentrations

These parameters will be analysed centrally. The preparation and storage of samples are described separately in the Laboratory Manual.

8.1.2 Gonadotropin-Releasing Hormone Stimulation Test

Gonadorelin, a synthetic GnRH (manufacturer to be defined), will be used for gonadotrophin stimulation. Clinical sites will be supplied with gonadorelin to use in the GnRH stimulation test.

Blood samples will be collected prior to gonadorelin injection (timepoint T0) and at 30 minutes (T30), 60 minutes (T60) and 90 minutes (T90) after a single i.v. injection of gonadorelin with 2.5 µg/kg (maximum 100 µg).

A suppressed LH response to GnRH stimulation test is defined as peak serum LH ≤5 IU/L among the four timepoints (T0, T30, T60 and T90).

The FSH response to GnRH stimulation will be the peak serum FSH level among the four timepoints (T0, T30, T60 and T90).

8.1.3 Sex Steroids (Oestradiol and Testosterone Serum Concentrations)

These parameters will be analysed centrally. The preparation and storage of samples are described separately in the Laboratory Manual.

8.1.4 Pubertal Stage Using the Tanner Method

See Pubertal Stages According to the Tanner Method (Appendix 10.5) for details.

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8.1.5 Auxological Parameters, Bone Age and Chronological Age Measurements and Gonad Development

Target height and percentile height-for-age will be obtained from Tanner tables [Tanner 1966].

Bone age determination (in years and months) will be performed by X-rays of the hand and wrist and estimated by the Greulich and Pyle method [Greulich 1959].

Gonad development (uterine length or testis volume) will be determined by type B ultrasound or orchidometer respectively.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 2).

8.2.1 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, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any clinically significant physical examina ion 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 reaching a clinically stable endpoint.

8.2.2 Vital Signs

Blood pressure and heart rate wil be assessed with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded in sitting position after 5 minutes of rest (seated). Absolute values and change from baseline will be analysed. Blood pressure will be measured using an appropriate cuff size.

8.2.3 Electrocardiograms

Not applicable

8.2.4 Clinical Safety Laboratory Assessments

- Clinical safety laboratory tests (haematology and serum chemistry) and urinalysis will be performed by the study site or local laboratory as outlined in the SoA (Table 2).
- See Appendix 10.2 for the list of clinical laboratory tests to be performed and 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

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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.

8.2.5 Local Tolerability

Assessment of local tolerability will be conducted as described in this section.

After each triptorelin injection, the injection site will be examined by a physician or medical staff (e.g. paediatric nurse) 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.

Any reaction deemed clinically significant by the investigator meets the definition of a TEAE, thus it needs to be reported in the eCRF as such as indicated in Appendix 10.3.3.

8.2.6 Pregnancy Testing

- Pregnancy tests for female participants of childbearing potential will be performed as outlined in the SoA (Table 2).
- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine) will be repeated at the end of the study (see SoA Table 2).
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3 Adverse Events, Serious Adverse Events and Other Safety Reporting.

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

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, or that caused the participant to discontinue the study intervention or the study (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.

8.3.1 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 visit at the time points specified in the SoA (Section 1.3).

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

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.

8.3.2 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.

Clinical Presentation of Adverse Events

Study-site staff should instruct the legal guardians and caregivers on how to report signs and symptoms (e.g. crying and pain) as well as viral signs of infections (eg nasopharyngitis, sinusitis, influenza) in the individual paediatric participant. They will be instructed to report both specific and nonspecific symptoms (including vomiting, diarrhoea, sleepiness, variation in the intensity and pattern of crying, etc). These nonspecific symptoms may be the only manifestations of some adverse reactions observed in childr n. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

Moreover, symptoms that are dependent on participant communication ability (e.g. nausea, pain, mood alterations) in younger or mentally disabled children could potentially be at risk for under- or misreporting.

These events may or may not have been noted in the participant diary.

8.3.3 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, stabilisation, the event is otherwise explained, 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.

8.3.4 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, IRBs and IECs 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

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- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

The occurrence of pregnancy is very unlikely in this study population. In case a participant becomes pregnant, this information will be shared with the participant's legal guardian as required by local regulations.

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate forms (SAE form in the eCRF and Drug Exposure Form – paper form) and submit it to the sponsor within 24 hours
- If pregnancy occurs during the study, the outcome of the pregnancy will be collected following completion of the study. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Drug Exposure for Pregnancy Form.
- The investigator must instruct all female participants who have already had menophania/menarche to inform them immediately should they become pregnant during the study. The Investigator should counsel the participant, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the participant should continue until conclusion of the pregnancy, which may involve follow-up after the participant's involvement in the study has ended.
- Pregnancies with a conception date within 6 months after the participant's last dose of study medication must also be reported to the investigator for onward reporting to the sponsor.
- If the Investigator becomes aware of a pregnancy occurring in the partner of a participant participating in the study, this should be reported to the sponsor as described above. Pregnancies in the partner with a conception date until 6 months after participant's last dose of study medication should be reported after the partner has given written consent and the partner should be counselled and followed as described above. Monitoring of the partner should continue until conclusion of the pregnancy.

Any participant becoming pregnant during the study will be withdrawn.

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

Not applicable.

8.3.7 Adverse Events of Special Interest

Not applicable

8.3.8 Reporting of Study Intervention Errors Including Misuse/Abuse

- Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a study intervention (medicinal product) while under the control of a healthcare professional, participant or consumer (European Medicines Agency definition).
- 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.

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- 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.
- Misuse or abuse will be collected and reported in the safety database, whether associated or not with an AE/SAE, within 24 hours of investigator's awareness.

8.4 Pharmacokinetics

- Approximately 2 mL of blood samples will be collected for measurement of triptorelin 6-month formulation plasma concentrations of as specified in the SoA (Section 1.3) to be analysed at a bionalytics Service Provider (Labcorp).
- Approximately 2 mL of blood samples will be collected to derive serum for bioanalytical cross-validation purposes.
- Instructions for the collection, handling, shipment methodology and reference ranges will be provided in the 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 (both for triptorelin level determination: a primary and a back-up aliquot). 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.
- On predetermined dates, plasma samples will be shipped to the bioanalytical Service Provider under frozen conditions. For security reasons, aliquots of each sample will be shipped separately. The batch containing the second aliquot will not be shipped until the first one has arrived. Upon receipt at the bioanalytical Service Provider, samples will be checked and stored until analysis.
- The concentration of triptorelin will be analysed using a validated specific and sensitive method, and in accord nce with Good Laboratory Practice (GLP).
- Serum samples will be used for the bioanalytical method cross-validation (two aliquots – a primary and a backup).
- On predetermined dates, serum samples will be shipped to the bioanalytical Service Provider in charge of the cross-validation under frozen conditions. For security reasons, aliquots of each sample will be shipped separately. The batch containing the second aliquot will not be shipped until the first one has arrived. Upon receipt, samples will be checked and stored until analysis.
- Residual plasma/serum samples remaining from the analyses may also be retained by the sponsor for additional investigations. This could include using leftover plasma/serum samples for long-term stability, reproducibility, or other bioanalytical assessments.

8.5 Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.6 Biomarkers

Biomarkers are not evaluated in this study.

Note that a description of primary and secondary efficacy biomarkers can be found in Section 8.1.

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8.7 Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.8 Health Economics OR Medical Resource Utilization and Health Economics

This section is not applicable for this study.

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9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The null hypothesis H0: P≤80% versus the alternative hypothesis H1: P>80%, where P is the proportion of children with LH suppression defined as stimulated peak LH ≤5 IU/L after GnRH stimulation at Month 6.

9.2 Sample Size Determination

The sample size of this study is estimated based on following assumptions according to global pivotal study DEBIO 8206-CPP-301 [Klein 2016].

- Expected outcome for the proportion of children with a suppressed LH response to the GnRH stimulation test (stimulated peak serum LH ≤5 IU/L) at Month 6 is 93%;
- Null proportion is 80%;
- An exact binomial test of a proportion with a one-sided nominal significance level of 0.025 and power =85%;
- Expected common dropout rate =5%.

Under these assumptions, approximately 66 participants (including at least three boys) (PASS software) are planned to be enrolled into the study to ensure there are 62 treated participants to confirm the efficacy of the triptorelin 6-month formulation by the proportion of children with a suppressed LH response to the GnRH stimulation test at Month 6.

9.3 Analysis Sets

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

Participant Analysis Set	Description
Screened population	All participants screened (i.e. who signed the ICF)
Safety population	All participants who received at least one dose of study intervention and have at least one postb seline safety assessment;
ITT/mITT population	The ITT population will include all participants who received at least one dose of study intervention; The modified intention-to-treat (mITT) population will contain all treated participants having a Month 6 post-baseline assessment of the primary efficacy endpoint
PP population	The PP population will contain all participants in the mITT after exclusion of the participants who had major protocol deviations that could potentially affect the primary efficacy endpoint outcome for the participants
PK population	All participants who received at least one dose of study intervention and have at least one valid triptorelin concentration

ICF=informed consent form; ITT=intention-to-treat; mITT=modified ITT; PK=pharmacokinetics; PP=per protocol.

The primary efficacy analysis will be performed on the ITT population. Supportive analysis of the primary efficacy endpoint will be based on the modified intention-to-treat (mITT) and the PP populations.

The secondary efficacy analyses will be based on the ITT population. Supportive analysis of the secondary analyses may be performed on the PP population.

The analyses of safety data will be performed based on the Safety population.

The analyses of PK data will be performed based on the PK population.

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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 the 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 protocol deviations which may impact the analysis of each population.

9.4.1.2 Significance Testing and Estimations

For the primary efficacy endpoint, the summary statistics of number and percentage of participants and the exact two-sided 95% CI for a binomial proportion will be computed by SAS® using the exact binomial distributions on the ITT population (primary population of analysis), mITT and PP sets.

For secondary efficacy endpoints related to a change at Months 3, 6, 9 and 12 compared to baseline, the descriptive summary statistics (n, mean, SD, median, minimum, maximum) will be calculated on the ITT population. In addition, secondary efficacy endpoints may be performed on the PP set. Exact two-sided 95% CIs will also be constructed for all secondary endpoints expressed as percentages.

9.4.1.3 Statistical/Analytical Methods

Statistical analyses will be performed by an external Service Provider, managed by the Sponsor's Biometry department.

Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, SD, median, minimum, maximum) and frequency counts of demographic and baseline data (medical history, concomitant disease, predosing AEs and ongoing medical history, prior and concomitant medications and therapies) will be presented for the ITT, mITT and PP sets, as well as the Safety population.

Participant Disposition and Withdrawals

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

Adjustment for Country/Centre Effect

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

9.4.2 Analysis of Primary Endpoint

The primary endpoint in this study is the proportion of children with LH suppression defined as stimulated peak LH ≤5 IU/L after GnRH stimulation at Month 6. The number and percentage

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of participants with LH suppression (stimulated peak LH ≤5 IU/L after GnRH stimulation) will be presented and its two-sided 95% CI using Clopper-Pearson method will be presented and calculated. A test to the null hypothesis (P≤80%) will be performed with a (one-sided) type I error as 2.5%.

9.4.3 Analysis of Secondary Endpoints

- Proportion of children with LH suppression defined as stimulated peak LH ≤5 IU/L after GnRH stimulation at Months 3 and 12:

  The number and percentage of participants with LH suppression (stimulated peak LH ≤5 IU/L after GnRH stimulation) will be presented at Months 3 and 12 and its two-sided 95% CI will be presented and calculated using the same method as primary efficacy endpoint.

- Change in basal serum LH and FSH levels at Months 3, 6, 9 and 12 compared to baseline:

  A summary table for the basal serum LH and FSH levels will be provided with descriptive statistics (n, mean, SD, median, minimum and maximum) at Baseline, Months 3, 6, 9 and 12 and for absolute changes from Baseline.

- Change in peak serum LH and FSH level after the GnRH stimulation test at Months 3, 6 and 12 compared to baseline:

  A summary table for the peak LH and FSH levels after the GnRH stimulation test will be provided with descriptive statistics (n mean, SD, median, minimum and maximum) at Baseline, Months 3, 6 and 12 and for absolute changes from Baseline.

- Proportion of children with pre-pubertal levels of sex steroids (defined as oestradiol ≤20 pg/mL [<73 pmol/L] in girls or testosterone ≤30 ng/dL [<0.8 nmol/L] in boys) at Months 3, 6, 9 and 12:

  The number and percentage of participants with pre-pubertal levels of sex steroids (defined as oestradiol ≤ 20 pg/mL in girls or testosterone ≤ 30 ng/dL in boys) will be presented at Months 3, 6, 9 and 12. The two-sided 95% CIs will be presented and calculated using the same method as primary efficacy endpoint.

- Change in height (Z-score [height for age] and percentile for height for age) and growth velocity at Months 6 and 12 compared to baseline:

  A summary table for the change in height (Z-score [height for age] and percentile for height for age) and growth velocity will be provided with descriptive statistics (n, mean, SD, median, minimum and maximum) at Months 6 and 12. In addition to the study endpoint on the change in height (Z-score and percentile) at Months 6 and 12, a summary table for the height absolute Z-scores and percentiles will be provided with descriptive statistics (n, mean, SD, median, minimum and maximum) at Baseline, Month 3, 6, 9 and 12.

- Proportion of children in whom the BA (Greulich and Pyle method):CA ratio did not rise at Months 6 and 12 relative to baseline (X-ray):

  The number and percentage of participants without increase of bone age (Greulich and Pyle method)/chronological age ratio from Baseline to Months 6 and 12 will be presented and its two-sided 95% CI will be presented and calculated using the same method as primary efficacy endpoint.

- Change in difference between BA and CA and ratio BA:CA at Months 6 and 12 compared to baseline:

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A summary table for the difference between BA and CA and ratio BA:CA will be provided with descriptive statistics (n, mean, SD, median, minimum and maximum) at Baseline, Month 6 and Month 12 and for absolute changes from Baseline.

- Proportion of children who achieve stabilisation of sexual maturation compared to baseline stage using Tanner method at Months 6 and 12:

  The number and percentage of participants with no increase in Tanner puberty staging from Baseline to Months 6 and 12 will be presented and its two-sided 95% CI will be presented and calculated using the same method as primary efficacy endpoint.
- Proportion of girls with regression of uterine length at Months 6 and 12 (transabdominal ultrasound):

  The number and percentage of girls with regression of uterine length at Months 6 and 12 will be presented and its two-sided 95% CI will be presented and calculated using the same method as primary efficacy endpoint.
- Proportion of boys with absence of progression of testis volumes at Month 6 and 12 (clinical assessment with orchidometer):

  The number and percentage of boys with absence of progression of testis volumes at Months 6 and 12 will be presented and its two-sided 95% CI will be presented and calculated using the same method as primary efficacy endpoint.
- Change in body weight and BMI at Month 6 and 12:

  A summary table for the body weight and BMI will be provided with descriptive statistics (n, mean, SD, median, minimum and maximum) at Baseline and Months 6 and 12 and for absolute changes from Baseline.

9.4.3.1 Pharmacokinetic Analyses

Individual listings of triptorelin co cent ations and descriptive summary statistics (n, mean, standard error of mean (SEM), SD, coefficient of variance (%CV), geomean, geomean SD, geomean %CV, median, min, max, 95% CI) will be presented by timepoint/visit following each administration. If required and w rranted by the data, an attempt to build a model to characterize the PK in the population will be made. An analysis to look at the relationship between concentrations versus efficacy and/or safety may be performed if warranted by the data. This will be described in a separate analysis plan and the outcomes summarised in a standalone report.

9.4.4 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 on the Safety population.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version (version in use before database lock) and will be classified by MedDRA preferred term (PT) and system organ class (SOC).

The incidence of all reported TEAEs, TEAEs associated with early withdrawal 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 if:

- It was not present prior to receiving the dose of triptorelin, or

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- It was present prior to receiving the dose of triptorelin but the grade increased or became serious during the active phase of the study, or
- It was present prior to receiving the dose of triptorelin, the grade/seriousness is the same, but the causality changed to "related" during the active phase of the study.

All TEAEs will be flagged in the AE listings.

Summary incidence tables will be provided, classified by SOC, PT and associated National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) worst grade. In the event of multiple occurrences of the same AEs being reported for the same participant, the maximum intensity (Grade 5 >Grade 4 >Grade 3 >Grade 2 >Grade 1 >missing >not applicable) will be chosen. All AEs will be collected up to the EOS visit (see Table 2 for SoA).

Concomitant medication will be coded by using World Health Organization Drug Dictionary (WHO-DD) version (version in use before database lock) and will be summarised with the number and percentage of participants receiving concomitant medication by drug class and preferred drug name.

Haematological and biochemical toxicities will be record d and graded according to the NCI-CTCAE criteria, where available. The NCI-CTCAE Grades 3 and 4 haematology and biochemistry variables will be listed by participant and by visit.

Actual values and changes from baseline in clinic l laboratory tests, physical examinations and vital signs will be summarised using descriptive statistics at each visit. For laboratory data, abnormal values will be flagged in the da a 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.

9.4.5 Subgroups Analyses

No subgroup analysis will be performed.

9.4.6 Other Analyses

Not applicable

9.5 Interim Analyses

No interim analysis will be performed. If an unplanned interim analysis is deemed necessary, the appropriate sponsor medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

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10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, 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 responsibl 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.
- The investigator will be responsible for reporting cases of suspected child abuse and/or neglect according to local regulations including local medical association (e.g., American Academy of Pediatrics, EU Academy of Pediatrics) or Health Department guidelines.

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 Legal Guardian Consent and Paediatric Participant Assent Processes:

- The informed consent/assent and any participant recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements,

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including applicable privacy laws. They must be approved before use, as described in Appendix 10.1.1.

- The investigator, or his/her authorised representative, will provide the legal guardian with the written ICF and the participant with the assent form, if applicable. They must be informed that participation is voluntary. The legal guardian will be required to sign written consent, and the participant, if applicable, will be required to sign written assent after the nature of the study has been fully explained and before performance of any study-related activity.
- Assent requirements for paediatric participants may vary across regions and countries; local regulations should be followed as appropriate.
- The medical record must include a statement that written informed consent from the legal guardian and assent from the paediatric participant (if deemed appropriate by local ethics review or local regulations) were obtained before the participant was enrolled in the study and the date the written consent and assent were obtained. The medical record should describe how the investigator determined that the person signing the ICF was the participant's legal guardian. The authorised person obtaining the informed consent must also sign the ICF and assent form attesting that the paediatric participant did not show signs of dissent particularly in those studies including toddlers and small children; it should be written in language appropriate to the child's developmental and functional status.
- Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their legal guardian still wants them to participate.
- A copy of the informed consent and assent forms must be provided to the participant and the participant's legal guardian.
- As appropriate, participants may be given the opportunity to meet privately with a member of the study site staff to ask confidential questions and to decline assent for confidential reasons which at their request, would not be shared with their legal guardian, unless required by local law.
- If an ICF amendment is not applicable to all participants, this will be communicated to the IEC/IRB with a rationale. A participant and the legal guardian must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study if the change has an impact on this participant.

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.

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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 in the US Clinical Trials Registry (ClinicalTrials.gov) and the EU/EEA on the EU Clinical Trials Register (www.clinicaltrialsregister.eu) if required. The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation; in the case of this protocol the China Clinical Trials Registry (www.chinadrugtrials.org.cn/index.html).
- A clinical study report will be prepared if at least one participant has signed informed consent and received intervention, regardless of whether the study is completed or prematurely terminated. The clinical study report may be disclosed according to regulatory requirements.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the sponsor or designee electronically (e g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the eCRF.
- Guidance on completion of the eCRF will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections, make ll documents available for audit and inspection and provide direct access to source data documents.
- Monitoring details describing strategy (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. Service Providers).
- Records and documents, including signed ICFs, pertaining to the conduct of this study should be retained by the investigator according to the ICH-GCP guidelines, to local regulations, or as specified in the study agreement, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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- The investigator must maintain accurate documentation that supports the information entered in the eCRF. Source data must be attributable, legible, contemporaneous, original, accurate and complete.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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.

Study/Site Termination

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

The investigator may initiate study-site closure t 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 t 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 Service Providers 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.

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- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed either locally or centrally: safety clinical laboratory assessments will be done locally and only central assessment for hormone primary/secondary endpoints will be used in the analysis.
- Bioanalysis of PK samples will be done at a bioanalytical Service Provider.
- The preparation and storage of all samples are described separately in the laboratory manual.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-Required Safety Laboratory Tests

Parameters	Screening	Day 1	Month 3 (Day 85)	Month 6 (Day 169)	Month 9 (Day 253)	Month 12 (Day 337) EOS/ Discontinuation
Haematology [a]						
Complete blood count	X		X	X	X	X
Clinical Chemistry [a]						
Creatinine	X		X	X	X	X
Nonfasting Glucose [b]	X		X	X	X	X
Aspartate Aminotransferase (AST)	X		X	X	X	X
Alanine Aminotransferase (ALT)	X		X	X	X	X
Alkaline Phosphatase	X		X	X	X	X
Total and direct bilirubin	X		X	X	X	X
Calcium	X		X	X	X	X
Phosphorous	X		X	X	X	X
Routine Urinalysis [a]						
Specific gravity	X		X	X	X	X
pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick	X		X	X	X	X
Microscopic examination (if blood or protein is abnormal)	X		X	X	X	X
Pregnancy testing						
Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP)	X					X
Other Hormone Tests						
Basal serum LH and FSH	X		X	X	X	X
GnRH test with LH and FSH	X		X	X		X
Oestradiol or testosterone	X		X	X	X	X

EoS=end of study; FSH=follicle-stimulating hormone; LH=luteinising hormone; WOCBP=women of childbearing potential

Notes:

Clinical laboratory tests will be performed either locally or centrally: safety clinical laboratory assessments will be done locally. For hormone primary/secondary endpoints only central assessment will be used in the analysis.

a If the screening tests performed within 1 week prior to Day 1, clinical laboratory assessments (haematology, clinical chemistry and urinalysis) will not be repeated on Day 1.

b In case of abnormal blood glucose as per investigator's judgement, repetition of these tests will be performed before the injection and fasting status might be required.

Investigators must document their review of each laboratory safety report.

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10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of Adverse Events

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 which 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.

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- 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 Serious Adverse Events

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 even 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) which 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 seriousness assessed based on the reported seriousness criteria. If no seriousness criteria is

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reported by the investigator, the COVID-19 infection will be collected and recorded as "non serious".

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 according to CTCAE v5.0 grading system.

Where:

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instr mental activities of daily living.
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL.
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **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.
- 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.
- The investigator will use clinical judgment to determine the relationship.

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- 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 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 are professionals.
- New or updated information will be recorded in the eCRF.
- The investigator 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 sponsor via paper

- All SAEs regardless of treatment group or suspected relationship to triptorelin, must be reported immediately (within 24 hours of the Investigator s knowledge of the event) using the SAE report form via the email address or the fax number specified at the beginning of this protocol as well as recording them in the eCRF.
- Contacts for SAE reporting can be found on the SAE form and the cover sheet.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Note: Some of the definitions below are not applicable for this study population but are listed for completeness.

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

(1) Following menarche

(2) From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

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- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.
- If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Notes: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

10.4.2 Contraception Guidance

Note: Pregnancy is highly unlikely in this study population and the guidance is listed for completeness

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CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Intrauterine device (IUD)
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a to medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* *Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*
Highly Effective Methods [b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant)*

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of <1% per year when used consistently and orrectly. Typical use failure rates differ from those when used consistently and correctly.

c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelin , acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode f action.

Note: Periodic abstinence (calendar, symptoth rmal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrh ea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

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10.5 Appendix 6: Pubertal Stages According to Tanner Method

STAGES OF DEVELOPMENT OF SECONDARY SEXUAL CHARACTERISTICS

BOYS: Genital (penis) development

Stage 1. Prepubertal: testes, scrotum, and penis of about same size and proportion as in early childhood.

Stage 2. Enlargement of scrotum and testes. Skin of scrotum reddens and changes in texture.

Stage 3. Enlargement of penis, at first mainly in length. Further growth of testes and scrotum.

Stage 4. Increased size of penis with growth in breadth and development of glans. Testes and scrotum larger; scrotal skin darkened.

Stage 5. Genitalia adult in size and shape.

GIRLS: Breast development

Stage 1. Prepubertal: elevation of papilla only.

Stage 2. Breast bud stage: elevation of breast and papilla as small mound. Enlargement of areola diameter.

Stage 3. Further enlargement and elevation of breast and areola, with no separation of their contours.

Stage 4. Projection of areola and papilla to form a secondary mound above level of breast.

Stage 5. Mature stage: projection of papilla only, related to recession of areola to general contour of breast.

BOTH SEXES: Pubic hair

Stage 1. Prepubertal: vellus over pubes is not further developed than over abdominal wall.

Stage 2. Sparse growth of l ng sligh ly pigmented, downy hair, straight or slightly curled, chiefly at base of penis or along labia.

Stage 3. Considerably darker, coarser, and more curled hair. Hair spreads sparsely over junction of pubes.

Stage 4. Hair now adult in type but area covered is still considerably smaller than in adult. No spread to medial surface of thighs.

Stage 5. Adult in quantity and type with distribution of horizontal (or classically “feminine”) pattern.

Stage 6. Spread up linea alba (male-type pattern).

Modified from Tanner JM. Growth at Adolescence. 2nd ed. Oxford: Blackwell Scientific Publications, 1962.

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10.6 Appendix 7: Temporary Measures and Procedures Related to COVID-19 Pandemic

This appendix serves as notification of the temporary measures put in place for the conduct of the study during the COVID-19 pandemic and until such time as the situation resolves, at which point the protocol assessments will return to those specified in the current approved protocol effective at that time. The timing of when the pandemic is declared over may vary on a country by country basis as well as between sites in the same country, and as such the temporary measures may remain in place for differing periods of time per country/site. Investigators will determine the feasibility of starting or continuing study treatment on a patient by patient basis, depending on the ability to conduct safety monitoring and providing patients an adequate supply of study treatment, in accordance with local requirements.

Any temporary measure will be reported as a protocol deviation related to COVID-19.

Withdrawal from Study

Participants who are suspected or confirmed to have COVID-19 infection after enrolment will withdraw from the study (see also Section 7.1.2 for temporary withdrawal).

Telemedicine Visit

If the COVID-19 pandemic prevents participants from coming to the site for the Month 9 visit, the investigator will perform a telemedicine visit to collect all important medical information and safety event(s) occurring since the last visit. Besides the Month 9 visit, the participants may delay other visits no more than 2 weeks and preferably within 1 week or be withdrawn from the study as appropriate, as judged by the investigator and agreed with the sponsor.

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