Clinical trial results:
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

Summary

EudraCT number	2022-003857-78
Trial protocol	Outside EU/EEA
Global end of trial date	13 February 2023

Results information

Result version number	v1 (current)
This version publication date	26 August 2023
First version publication date	26 August 2023

Trial information

Trial identification

Sponsor protocol code	D-CN-52014-244

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05029622
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma
Sponsor organisation address	65, quai Georges Gorse, Boulogne Billancourt, France, 92100
Public contact	Medical Director, Ipsen Pharma, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Pharma, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to assess the efficacy of the triptorelin 6-month prolonged release (PR) formulation in suppressing luteinising hormone (LH) levels to prepubertal levels [defined as a peak LH <=5 international units per liter (IU/L)] after intravenous (IV) GnRH stimulation at Month 6 (Day 169) in Chinese children with central precocious puberty (CPP).

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, in accordance with the Good Clinical Practice of China and in compliance with ethics committee and informed consent regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 66
Worldwide total number of subjects	66
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	66
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 3, open-label, single arm, study was conducted in children with CPP at 12 investigational sites in China.

Pre-assignment

Screening details:

This study consisted of screening period (up to 28 days) and study duration of minimum 12 months and up to 13 months including screening period.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	All Participants

Arm description:

Participants received triptorelin pamoate 22.5 milligrams (mg) intramuscular (IM) injection on Day 1 and Month 6 (Day 169).

Arm type	Experimental
Investigational medicinal product name	Triptorelin pamoate
Investigational medicinal product code	
Other name	Diphereline®
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Triptorelin pamoate was administered as an IM injection of 6 milliliter (mL), containing 22.5 mg dose with release of monthly dose of 3.75 mg over a 169-day period.

Number of subjects in period 1	All Participants
Started	66
Completed	65
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	All Participants
Reporting group description:	
Participants received triptorelin pamoate 22.5 milligrams (mg) intramuscular (IM) injection on Day 1 and Month 6 (Day 169).	

Reporting group values	All Participants	Total	
Number of subjects	66	66	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	7.5		
standard deviation	± 0.9	-	
Gender categorical Units: Subjects			
Female	62	62	
Male	4	4	
Race Units: Subjects			
Chinese	66	66	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	66	66	

End points

End points reporting groups

Reporting group title	All Participants

Reporting group description:

Participants received triptorelin pamoate 22.5 milligrams (mg) intramuscular (IM) injection on Day 1 and Month 6 (Day 169).

Primary: Percentage of Participants With LH Suppression

End point title	Percentage of Participants With LH Suppression[1]

End point description:

LH response was defined as a peak LH <=5 IU/L after IV GnRH stimulation. The GnRH stimulation test was performed by using an IV injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release and blood samples were collected after the gonadorelin injection for central assessment of serum LH levels. Percentage of response was calculated by number of participants in the specified category divided by number of participants in the analysis population multiplied by 100. The intention-to-treat (ITT) population consisted of all participants who received at least 1 dose of study intervention.

End point type	Primary

End point timeframe:

At Month 6

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was prespecified for this endpoint.

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentage of participants				
number (confidence interval 95%)	100 (94.6 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With LH Response to GnRH Test

End point title	Percentage of Participants With LH Response to GnRH Test

End point description:

LH response was defined as a peak LH <=5 IU/L after IV GnRH stimulation. The GnRH stimulation test was performed by using an IV injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release and blood samples were collected after the gonadorelin injection for central assessment of serum LH levels. Percentage of response was calculated by number of participants in the specified category divided by number of participants in the analysis population multiplied by 100. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

At Months 3 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentage of participants				
number (confidence interval 95%)				
Month 3 (n =64)	97.0 (89.5 to 99.6)			
Month 12 (n =65)	98.5 (91.8 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Basal Serum LH and Follicle-Stimulating Hormone (FSH) Levels

End point title	Change From Baseline in Basal Serum LH and Follicle-Stimulating Hormone (FSH) Levels

End point description:

Basal LH and FSH serum concentrations were analyzed centrally. Change from baseline was defined as the values for LH and FSH at indicated timepoints minus the value at baseline. Baseline was defined as the last non-missing measurement taken prior to the first study treatment administered. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

Baseline and at Months 3, 6, 9 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: IU/L				
arithmetic mean (standard deviation)				
LH, Month 3 (n = 64)	-1.6420 (± 2.4287)			
LH, Month 6 (n = 66)	-1.8015 (± 2.4109)			
LH, Month 9 (n = 57)	-1.6307 (± 2.3396)			
LH, Month 12 (n = 65)	-1.8504 (± 2.4524)			
FSH, Month 3 (n = 64)	-2.9938 (± 1.9450)			
FSH, Month 6 (n = 66)	-2.4871 (± 2.0414)			

FSH, Month 9 (n = 57)	-2.8586 (± 1.9310)			
FSH, Month 12 (n = 65)	-2.5348 (± 1.9162)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Peak Serum LH and FSH Level After the GnRH Stimulation Test

End point title	Change From Baseline in Peak Serum LH and FSH Level After the GnRH Stimulation Test

End point description:

Peak LH and FSH serum concentrations were analyzed centrally. Change from baseline was defined as the values for LH and FSH at indicated timepoints minus the value at baseline. Baseline was defined as the last non-missing measurement taken prior to the first study treatment administered. Blood samples were collected prior to gonadorelin injection (timepoint T0) and at 30 minutes (T30), 60 minutes (T60) and 90 minutes (T90) after a single IV injection of gonadorelin. A suppressed LH response to GnRH stimulation test was defined as peak serum LH <=5 IU/L among the four timepoints (T0, T30, T60 and T90). The FSH response to GnRH stimulation was the peak serum FSH level among the four timepoints (T0, T30, T60 and T90). The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

Baseline and at Months 3, 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: IU/L				
arithmetic mean (standard deviation)				
LH, Month 3 (n = 64)	-26.0075 (± 19.8863)			
LH, Month 6 (n = 66)	-26.2867 (± 20.3004)			
LH, Month 12 (n = 65)	-26.6065 (± 20.5680)			
FSH, Month 3 (n = 64)	-11.7297 (± 5.1787)			
FSH, Month 6 (n = 66)	-10.0656 (± 5.0160)			
FSH, Month 12 (n = 65)	-10.1645 (± 5.2442)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With LH Response (Peak LH <=5 IU/L) From Month 6 to Month 12

End point title	Percentage of Participants With LH Response (Peak LH <=5 IU/L) From Month 6 to Month 12

End point description:

Peak LH serum concentration was analyzed centrally. LH response was defined as a peak LH <=5 IU/L after IV GnRH stimulation. The GnRH stimulation test was performed by using an IV injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release and blood samples were collected after the gonadorelin injection for central assessment of peak LH levels. Percentage of response was calculated by number of participants in the specified category divided by number of participants in the analysis population multiplied by 100. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported.

End point type	Secondary

End point timeframe:

Month 6 to Month 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: percentage of participants				
number (confidence interval 95%)	98.5 (91.8 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Prepubertal Levels of Sex Steroids

End point title	Percentage of Participants With Prepubertal Levels of Sex Steroids

End point description:

Prepubertal sex steroids assessment included estradiol in female participants and testosterone in male participants. Prepubertal sex steroids levels were defined as: estradiol <=20 picogram (pg)/mL in female participants and testosterone <=30 nanogram (ng)/ deciliter (dL) in male participants. Percentage of response was calculated by number of participants in the specified category divided by number of participants in the analysis population multiplied by 100. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

At Months 3, 6, 9 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentage of participants				
number (confidence interval 95%)				
Month 3 (n = 64)	97.0 (89.5 to 99.6)			
Month 6 (n = 66)	100 (94.6 to 100.0)			
Month 9 (n = 57)	86.4 (75.7 to 93.6)			
Month 12 (n = 65)	98.5 (91.8 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Height for Age (Z-Score)

End point title	Change From Baseline in Mean Height for Age (Z-Score)

End point description:

Z-scores are calculated using Centers for Disease Control and Prevention (CDC) Growth Charts. Change from baseline was defined as the values for Z-score at indicated timepoints minus the value at baseline. Baseline was defined as the last non-missing measurement taken prior to study treatment administration. Negative Z-score indicates values lower than the mean while a positive Z-score indicates values higher than the mean. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

Baseline and at Months 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Z-score				
arithmetic mean (standard deviation)				
Month 6 (n = 66)	0.0734 (± 0.1433)			
Month 12 (n = 65)	0.0204 (± 0.1567)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percentile for Height for Age

End point title	Change From Baseline in Percentile for Height for Age

End point description:

Z-scores were calculated using CDC growth charts, that contained Box-Cox transformation (L), the median (M) and the generalized coefficient of variation (S). Percentile was obtained using the following equation M (1 + LSZ) ** (1/L), where ** indicated an exponent, such that m (1+LSZ)** (1/L) meant raising (1+LSZ) to the (1/L)th power and then multiplying the M. Z was the Z-score that corresponds to the percentile. Negative Z-score indicates values lower than the mean while a positive Z-score indicates values higher than the mean. Change from baseline was defined as the values for percentile of Z-score at indicated timepoints minus the value at baseline. Baseline was defined as the last non-missing measurement taken prior to the first study treatment administered. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

Baseline and at Months 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentiles of Z-score				
arithmetic mean (standard deviation)				
Month 6 (n = 66)	1.4675 (± 2.8638)			
Month 12 (n = 65)	0.2810 (± 3.2237)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Growth Velocity

End point title	Change From Baseline in Growth Velocity

End point description:

Growth velocity analysis was part of auxological parameter. Change from baseline was defined as the value for each auxological parameter at indicated timepoints minus the value at baseline. Baseline was defined as the last non-missing measurement taken prior to the first study treatment administered. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

Baseline and at Months 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: centimeter (cm)/year				
arithmetic mean (standard deviation)				
Month 6 (n = 65)	-3.938 (± 6.075)			
Month 12 (n = 63)	-4.798 (± 5.577)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Bone Age (BA)/Chronological Age (CA) Ratio not Risen

End point title	Percentage of Participants With Bone Age (BA)/Chronological Age (CA) Ratio not Risen

End point description:

BA was determined using X-rays of the hand and wrist by Greulich and Pyle method. CA was calculated as (visit date -birth date + 1)/365.25. Percentage of response was calculated as n/N*100, where n was number of participants in the specified category and N was number of participants in the analysis population. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

At Months 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentage of participants				
number (confidence interval 95%)				
Month 6 (n = 66)	95.5 (87.3 to 99.1)			
Month 12 (n = 65)	92.4 (83.2 to 97.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in BA:CA Ratio

End point title	Change From Baseline in BA:CA Ratio

End point description:

BA was determined using X-rays of the hand and wrist by Greulich and Pyle method. CA was calculated as (visit date -birth date + 1)/365.25. Change from baseline was defined as the values for BA:CA ratio at indicated timepoints minus the value at baseline. Baseline was defined as the last non-missing measurement taken prior to the first study treatment administered. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

Baseline, Months 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: ratio				
arithmetic mean (standard deviation)				
Month 6 (n = 66)	-0.04 (± 0.06)			
Month 12 (n = 65)	-0.06 (± 0.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Stabilized Pubertal Stage

End point title	Percentage of Participants With Stabilized Pubertal Stage

End point description:

Pubertal stage parameters were analyzed using Tanner method. Pubertal stage parameters included genital stage in male participants, breast stage in female participants and pubic hair stage in both sexes. Percentage of response was calculated by number of participants in the specified category divided by number of participants in the analysis population multiplied by 100. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point. Breast development stage (BDS), Genital development stage (GDS), Pubic hair development (PHD), Month 6 (M6), Month 12 (M12).

End point type	Secondary

End point timeframe:

At Months 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentage of participants				
number (confidence interval 95%)				
BDS for female participants, M6, (n = 62)	98.4 (91.3 to 100.0)			
GDS for male participants, M6, (n = 4)	100 (39.8 to 100.0)			

PHD for female participants, M6, (n = 62)	91.9 (82.2 to 97.3)			
PHD for male participants, M6, (n = 4)	100 (39.8 to 100.0)			
BDS for female participants, M12, (n = 61)	93.5 (84.3 to 98.2)			
GDS for male participants, M12, (n = 4)	100 (39.8 to 100.0)			
PHD for female participants, M12, (n = 61)	87.1 (76.1 to 94.3)			
PHD for male participants, M12, (n = 4)	75.0 (19.4 to 99.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Regression of Uterine Length

End point title	Percentage of Participants With Regression of Uterine Length

End point description:

Uterine length was determined by transabdominal ultrasound. Percentage of response was calculated by number of participants in the specified category divided by number of participants in the analysis population multiplied by 100. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the female participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

At Months 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: percentage of participants				
number (confidence interval 95%)				
Month 6 (n = 57)	64.5 (51.3 to 76.3)			
Month 12 (n = 54)	64.5 (51.3 to 76.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Absence of Progression of Testis Volumes

End point title	Percentage of Participants With Absence of Progression of Testis Volumes

End point description:

Testis volume was a clinical assessment with orchidometer. Percentage of response was calculated by number of participants in the specified category divided by number of participants in the analysis population multiplied by 100. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the male participants analyzed were reported.

End point type	Secondary

End point timeframe:

At Months 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percentage of participants				
number (confidence interval 95%)				
Month 6	75.0 (19.4 to 99.4)			
Month 12	75.0 (19.4 to 99.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Mass Index (BMI)

End point title	Change From Baseline in Body Mass Index (BMI)

End point description:

BMI analysis was part of auxological parameter assessment. Change from baseline was defined as the value for each auxological parameter at indicated timepoints minus the value at baseline. Baseline was defined as the last non-missing measurement taken prior to the first study treatment administered. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

Baseline and at Months 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: kilogram (kg)/meter square				
arithmetic mean (standard deviation)				
Month 6 (n = 66)	0.282 (± 0.882)			
Month 12 (n = 65)	1.195 (± 1.196)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weight

End point title	Change From Baseline in Weight

End point description:

Weight analysis was part of auxological parameter assessment. Change from baseline was defined as the value for each auxological parameter at indicated timepoints minus the value at baseline. Baseline was defined as the last non-missing measurement taken prior to the first study treatment administered. The ITT population consisted of all participants who received at least 1 dose of study intervention. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

Baseline and at Months 6 and 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: kg				
arithmetic mean (standard deviation)				
Month 6 (n = 66)	2.020 (± 1.927)			
Month 12 (n = 65)	5.146 (± 2.816)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Triptorelin

End point title	Plasma Concentrations of Triptorelin

End point description:

Blood samples were collected at specified timepoints. The pharmacokinetic (PK) set consisted of all participants who received at 1 dose of study treatment and had at least 1 valid triptorelin concentration. Only data from the participants analyzed were reported. Here, 'n' = number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:

Day 1, 4 hours post-injection; Month 3; Month 6, predose; Month 6, 4 hours post-injection; and Month 12

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1, 4 hours post-injection (n = 66)	41.8 (± 56.9)			
Month 3 (n = 63)	0.0434 (± 76.8)			
Month 6, predose (n = 46)	0.0251 (± 648.7)			
Month 6, 4 hours post-injection (n = 61)	24.7 (± 66.0)			
Month 12 (n = 50)	0.0223 (± 110.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were reported from the first dose of study treatment (Day 1) up to a maximum of approximately 344 days.

Adverse event reporting additional description:

Safety population consisted of all participants who received at least 1 dose of study treatment and have at least 1 post-baseline safety assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	All Participants

Reporting group description:

Participants received triptorelin pamoate 22.5 mg IM injection on Day 1 and Month 6 (Day 169).

Serious adverse events	All Participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 66 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All Participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 66 (89.39%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 66 (13.64%)		
occurrences (all)	9		
Influenza like illness			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Vaginal haemorrhage			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Nocturnal emission			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 66 (10.61%)		
occurrences (all)	7		
Rhinitis allergic			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Allergic cough			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Psychiatric disorders			
Listless			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Investigations			
Weight increased			
subjects affected / exposed	9 / 66 (13.64%)		
occurrences (all)	9		
Urinary occult blood positive			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	2		
Eosinophil count increased			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Liver function test abnormal			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Myoglobin blood increased			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Scratch			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Leukocytosis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Eye disorders			
Asthenopia			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Refraction disorder			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Xerophthalmia			

subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	3		
Mouth ulceration			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Anal fissure			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			

Urticaria subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Rash subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Dermatitis subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Eczema subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	31 / 66 (46.97%) 45		
COVID-19 subjects affected / exposed occurrences (all)	10 / 66 (15.15%) 10		
Suspected COVID-19 subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4		
Bronchitis subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4		
Tonsillitis subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3		
Rhinitis subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3		
Respiratory tract infection			

subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	3		
Sinusitis			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Acarodermatitis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Helicobacter infection			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Acute sinusitis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Overweight			
subjects affected / exposed	7 / 66 (10.61%)		
occurrences (all)	7		
Obesity			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	3		

Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2022	Schedule of activities updated according to the actual situation and clarified the time of clinical laboratory examination and BMI measurement time. A new text was added to benefit/risk assessment as per new template version. Adjustment of blood collection volume was updated according to the actual situation in scientific rationale for study design and section 8. Clarified the inclusion criteria minimum number of follicles larger than 4 millimeter in diameter. The amount of blood to be collected was updated according to the actual situation and typo corrected and relevant description added in PK section. In Appendix 2 section adjusted table superscript and adjusted description of note. Adjusted the description of "report of suspected or confirmed coronavirus disease 2019 infection and updated serious adverse events report requirement as per new protocol template.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported