Clinical trial results:
ACcomplisH: A Phase 2, multicenter, double-blind, randomized, placebo-controlled, dose escalation trial evaluating safety, efficacy, and pharmacokinetics of subcutaneous doses of TransCon CNP administered once weekly for 52 weeks in prepubertal children with achondroplasia followed by an Open-Label Extension Period.

Summary

EudraCT number	2019-002754-22
Trial protocol	IE GB DE AT DK PT
Global end of trial date	

Results information

Result version number	v1
This version publication date	11 April 2023
First version publication date	11 April 2023

Trial information

Trial identification

Sponsor protocol code	TCC-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04085523
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ascendis Pharma Growth Disorders A/S
Sponsor organisation address	Tuborg Blvd 12, Hellerup, Denmark, DK 2900
Public contact	Clinical Trial Information Desk, Ascendis Pharma A/S, 0045 70222244, clinhelpdesk@ascendispharma.com
Scientific contact	Clinical Trial Information Desk, Ascendis Pharma A/S, 0045 70222244, clinhelpdesk@ascendispharma.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?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	20 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2022
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

In prepubertal children with achondroplasia (ACH) at 52 weeks
• To determine the safety of once weekly subcutaneous (SC) doses of TransCon CNP
• To evaluate the effect of once weekly SC doses of TransCon CNP on annualized height velocity (AHV)

Protection of trial subjects:

Written informed consent was obtained from all subjects prior to enrollment into the trial, as dictated by the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Ireland: 6
Worldwide total number of subjects	57
EEA total number of subjects	17

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	0

months)	
Children (2-11 years)	57
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:

Overall, 57 subjects were enrolled and dosed. Enrollment of subjects occurred in eight countries: Australia, Austria, Denmark, Germany, Ireland, Portugal, New Zealand, and the United States.

Pre-assignment

Screening details:

A total of 60 subjects were screened and 57 of these met eligibility criteria and were enrolled into the study.

Period 1

Period 1 title	52 Week Blinded Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	TransCon CNP (6 mcg/kg/wk)

Arm description:

Once weekly subcutaneous administration of TransCon CNP 6 mcg CNP/kg/week

Arm type	Experimental
Investigational medicinal product name	TransCon CNP
Investigational medicinal product code	ACP-015
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TransCon CNP 3.9 mg CNP-38/vial drug product is a lyophilized powder in a single-use glass vial. Prior to use, the lyophilizate is reconstituted with sterile Water for Injection from a prefilled syringe.

Arm title	TransCon CNP (20 mcg/kg/wk)

Arm description:

Once weekly subcutaneous administration of TransCon CNP 20 mcg CNP/kg/week

Arm type	Experimental
Investigational medicinal product name	TransCon CNP
Investigational medicinal product code	ACP-015
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TransCon CNP 3.9 mg CNP-38/vial drug product is a lyophilized powder in a single-use glass vial. Prior to use, the lyophilizate is reconstituted with sterile Water for Injection from a prefilled syringe.

Arm title	TransCon CNP (50 mcg/kg/wk)

Arm description:

Once weekly subcutaneous administration of TransCon CNP 50 mcg CNP/kg/week

Arm type	Experimental

Investigational medicinal product name	TransCon CNP
Investigational medicinal product code	ACP-015
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TransCon CNP 3.9 mg CNP-38/vial drug product is a lyophilized powder in a single-use glass vial. Prior to use, the lyophilizate is reconstituted with sterile Water for Injection from a prefilled syringe.

Arm title	TransCon CNP (100 mcg/kg/wk)

Arm description:

Once weekly subcutaneous administration of TransCon CNP 100 mcg CNP/kg/week

Arm type	Experimental
Investigational medicinal product name	TransCon CNP
Investigational medicinal product code	ACP-015
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TransCon CNP 3.9 mg CNP-38/vial drug product is a lyophilized powder in a single-use glass vial. Prior to use, the lyophilizate is reconstituted with sterile Water for Injection from a prefilled syringe.

Arm title	Pooled Placebo

Arm description:

Once weekly subcutaneous administration of placebo for TransCon CNP to mimick the dose (6, 20, 50, or 100 mcg/kg/week) of investigational product

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo for TransCon CNP is a lyophilized powder in a single-use glass vial. Prior to use, the lyophilizate is reconstituted with sterile Water for Injection from a prefilled syringe.

Number of subjects in period 1	TransCon CNP (6 mcg/kg/wk)	TransCon CNP (20 mcg/kg/wk)	TransCon CNP (50 mcg/kg/wk)
Started	10	11	10
Completed	10	11	10

Number of subjects in period 1	TransCon CNP (100 mcg/kg/wk)	Pooled Placebo
Started	11	15
Completed	11	15

Baseline characteristics

Reporting groups	
Reporting group title	TransCon CNP (6 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 6 mcg CNP/kg/week	
Reporting group title	TransCon CNP (20 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 20 mcg CNP/kg/week	
Reporting group title	TransCon CNP (50 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 50 mcg CNP/kg/week	
Reporting group title	TransCon CNP (100 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 100 mcg CNP/kg/week	
Reporting group title	Pooled Placebo
Reporting group description:	
Once weekly subcutaneous administration of placebo for TransCon CNP to mimick the dose (6, 20, 50, or 100 mcg/kg/week) of investigational product	

Reporting group values	TransCon CNP (6 mcg/kg/wk)	TransCon CNP (20 mcg/kg/wk)	TransCon CNP (50 mcg/kg/wk)
Number of subjects	10	11	10
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	6.52	6.29	5.20
standard deviation	± 2.593	± 2.896	± 2.991
Gender categorical Units: Subjects			
Female	7	3	3
Male	3	8	7
Race Units: Subjects			
American Indian or Alaskan Native	0	0	0
Asian	2	1	1
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	1
White	8	10	8
Other	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	2
Not Hispanic or Latino	9	11	6
Unknown/Not Reported	0	0	2
Region Units: Subjects			

North America	4	4	4
Europe	2	5	4
Oceania	4	2	2
Height			
Units: cm			
arithmetic mean	90.63	92.29	86.61
standard deviation	± 8.973	± 12.103	± 12.967
Height SDS			
Units: Standard deviation score (SDS)			
arithmetic mean	-5.45	-4.87	-4.85
standard deviation	± 1.046	± 0.673	± 0.801
Weight			
Units: kg			
arithmetic mean	17.49	19.67	15.67
standard deviation	± 3.677	± 6.602	± 4.399
Body Mass Index			
Units: kg^m2			
arithmetic mean	21.10	22.52	20.61
standard deviation	± 1.664	± 2.599	± 1.496
Baseline AHV			
Baseline annualized height velocity (AHV)			
Units: cm/year			
arithmetic mean	5.04	5.29	5.76
standard deviation	± 2.157	± 1.619	± 3.147

Reporting group values	TransCon CNP (100 mcg/kg/wk)	Pooled Placebo	Total
Number of subjects	11	15	57
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	5.79	5.89	
standard deviation	± 2.613	± 3.109	-
Gender categorical			
Units: Subjects			
Female	6	5	24
Male	5	10	33
Race			
Units: Subjects			
American Indian or Alaskan Native	0	0	0
Asian	0	2	6
Black or African American	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	1
White	10	12	48
Other	0	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	1	6
Not Hispanic or Latino	9	14	49

Unknown/Not Reported	0	0	2
Region Units: Subjects			
North America	8	9	29
Europe	3	3	17
Oceania	0	3	11
Height Units: cm			
arithmetic mean	89.23	90.85	
standard deviation	± 12.822	± 14.920	-
Height SDS Units: Standard deviation score (SDS)			
arithmetic mean	-4.92	-4.85	
standard deviation	± 0.829	± 0.958	-
Weight Units: kg			
arithmetic mean	17.03	17.99	
standard deviation	± 4.699	± 5.542	-
Body Mass Index Units: kg^m2			
arithmetic mean	21.11	21.39	
standard deviation	± 1.612	± 1.853	-
Baseline AHV			
Baseline annualized height velocity (AHV)			
Units: cm/year			
arithmetic mean	4.73	6.17	
standard deviation	± 1.133	± 1.394	-

End points

End points reporting groups

Reporting group title	TransCon CNP (6 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 6 mcg CNP/kg/week	
Reporting group title	TransCon CNP (20 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 20 mcg CNP/kg/week	
Reporting group title	TransCon CNP (50 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 50 mcg CNP/kg/week	
Reporting group title	TransCon CNP (100 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 100 mcg CNP/kg/week	
Reporting group title	Pooled Placebo
Reporting group description:	
Once weekly subcutaneous administration of placebo for TransCon CNP to mimick the dose (6, 20, 50, or 100 mcg/kg/week) of investigational product	

Primary: Annualized Height Velocity

End point title	Annualized Height Velocity
End point description:	
The primary efficacy analysis compared the difference in the primary efficacy endpoint between the TransCon CNP treatment group and the pooled placebo group using an ANCOVA model with the annualized height velocity (AHV) at Week 52 as the response variable, treatment (TransCon CNP dose groups and placebo) and sex as factors, baseline age and baseline height SDS as the covariates, and based on the Full Analysis Set.	
End point type	Primary
End point timeframe:	
52 weeks	

End point values	TransCon CNP (6 mcg/kg/wk)	TransCon CNP (20 mcg/kg/wk)	TransCon CNP (50 mcg/kg/wk)	TransCon CNP (100 mcg/kg/wk)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	10	11
Units: cm/year				
least squares mean (confidence interval 95%)	4.09 (3.34 to 4.84)	4.52 (3.82 to 5.22)	5.16 (4.43 to 5.90)	5.42 (4.74 to 6.11)

End point values	Pooled Placebo			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: cm/year				

least squares mean (confidence interval 95%)	4.35 (3.75 to 4.94)			

Statistical analyses

Statistical analysis title	Primary efficacy endpoint

Statistical analysis description:

ANCOVA model using treatment (dose groups and pooled placebo) and sex as fixed effects, and baseline age and baseline height SDS as the covariates.

Comparison groups	TransCon CNP (6 mcg/kg/wk) v Pooled Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6004
Method	ANCOVA

Statistical analysis title	Primary efficacy endpoint

Statistical analysis description:

ANCOVA model using treatment (dose groups and pooled placebo) and sex as fixed effects, and baseline age and baseline height SDS as the covariates.

Comparison groups	TransCon CNP (20 mcg/kg/wk) v Pooled Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7022
Method	ANCOVA

Statistical analysis title	Primary efficacy endpoint

Statistical analysis description:

ANCOVA model using treatment (dose groups and pooled placebo) and sex as fixed effects, and baseline age and baseline height SDS as the covariates.

Comparison groups	TransCon CNP (50 mcg/kg/wk) v Pooled Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0849
Method	ANCOVA

Statistical analysis title	Primary efficacy endpoint

Statistical analysis description:

ANCOVA model using treatment (dose groups and pooled placebo) and sex as fixed effects, and baseline age and baseline height SDS as the covariates.

Comparison groups	TransCon CNP (100 mcg/kg/wk) v Pooled Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0218
Method	ANCOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
52 Week Blinded Period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	TransCon CNP (6 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 6 mcg CNP/kg/week	
Reporting group title	TransCon CNP (20 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 20 mcg CNP/kg/week	
Reporting group title	TransCon CNP (50 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 50 mcg CNP/kg/week	
Reporting group title	TransCon CNP (100 mcg/kg/wk)
Reporting group description:	
Once weekly subcutaneous administration of TransCon CNP 100 mcg CNP/kg/week	
Reporting group title	Pooled Placebo
Reporting group description:	
Once weekly subcutaneous administration of placebo for TransCon CNP to mimick the dose (6, 20, 50, or 100 mcg/kg/week) of investigational product	

Serious adverse events	TransCon CNP (6 mcg/kg/wk)	TransCon CNP (20 mcg/kg/wk)	TransCon CNP (50 mcg/kg/wk)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Viral infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TransCon CNP (100 mcg/kg/wk)	Pooled Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Viral infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	TransCon CNP (6 mcg/kg/wk)	TransCon CNP (20 mcg/kg/wk)	TransCon CNP (50 mcg/kg/wk)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)	11 / 11 (100.00%)	10 / 10 (100.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	3 / 10 (30.00%)
occurrences (all)	0	1	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	4 / 11 (36.36%)	2 / 10 (20.00%)
occurrences (all)	2	7	2
Injection site reaction			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)	2 / 11 (18.18%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	2 / 11 (18.18%)	2 / 10 (20.00%)
occurrences (all)	1	4	3
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	3
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 10 (40.00%)	3 / 11 (27.27%)	4 / 10 (40.00%)
occurrences (all)	7	7	6
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	2 / 10 (20.00%)
occurrences (all)	0	2	4
Nasal congestion			
subjects affected / exposed	1 / 10 (10.00%)	3 / 11 (27.27%)	2 / 10 (20.00%)
occurrences (all)	1	4	3
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 11 (18.18%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Snoring			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	3 / 10 (30.00%)
occurrences (all)	1	1	7

Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	3 / 10 (30.00%)
occurrences (all)	1	0	4
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 10 (30.00%)	1 / 11 (9.09%)	5 / 10 (50.00%)
occurrences (all)	3	1	8
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	5 / 10 (50.00%)
occurrences (all)	2	0	6
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	3 / 10 (30.00%)
occurrences (all)	0	2	3
COVID-19			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Otitis media			
subjects affected / exposed	1 / 10 (10.00%)	2 / 11 (18.18%)	2 / 10 (20.00%)
occurrences (all)	1	2	2
Viral infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	1	2	4
Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	5
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	TransCon CNP (100 mcg/kg/wk)	Pooled Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 11 (90.91%)	14 / 15 (93.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 11 (18.18%)	2 / 15 (13.33%)	
occurrences (all)	2	8	

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 11 (18.18%)	5 / 15 (33.33%)	
occurrences (all)	4	8	
Injection site reaction			
subjects affected / exposed	1 / 11 (9.09%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 11 (27.27%)	3 / 15 (20.00%)	
occurrences (all)	3	5	
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Abdominal pain upper			
subjects affected / exposed	1 / 11 (9.09%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 11 (18.18%)	3 / 15 (20.00%)	
occurrences (all)	4	5	
Rhinorrhoea			
subjects affected / exposed	2 / 11 (18.18%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Nasal congestion			
subjects affected / exposed	0 / 11 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	5	
Epistaxis			

subjects affected / exposed	0 / 11 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 11 (9.09%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Snoring			
subjects affected / exposed	0 / 11 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	3 / 11 (27.27%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 15 (6.67%)	
occurrences (all)	1	18	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	2 / 11 (18.18%)	1 / 15 (6.67%)	
occurrences (all)	2	3	
Gastroenteritis			
subjects affected / exposed	1 / 11 (9.09%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
COVID-19			
subjects affected / exposed	3 / 11 (27.27%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Otitis media			
subjects affected / exposed	0 / 11 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	3	
Viral infection			
subjects affected / exposed	0 / 11 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	3	
Respiratory tract infection			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 15 (0.00%) 0	
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all)	 0 / 11 (0.00%) 0	 1 / 15 (6.67%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2020	Protocol Version 2.0 summary of changes: - increase enrollment to include approximately 14 participants in Cohorts 2-5 - add allowance for select visits to be conducted off-site - remove BMI as a secondary efficacy endpoint - modify the placebo comparator and dosing procedure for Cohort 1 - add availability of home health nurse to give weekly injections - update contact information for SAE reporting - update the definition of AE
08 January 2021	Protocol Version 3.0 added a 2 year Open-Label Extension period to assess long term safety and efficacy following the Randomized Period.
12 August 2021	Protocol Version 4.0 added implementation of unblinding per cohort after completion of the Randomized Treatment Period.
28 December 2022	Protocol Version 5.0 summary of changes: - Added information of a new separate long-term open-label extension study for participants completing treatment in the TCC-201 protocol - Updated SAE reporting

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported