Clinical trial results:
A double-blind, placebo-controlled, interventional parallel group study to evaluate the antiviral effect of a single nasal application of LTX-109 3% gel, in comparison to placebo gel, in subjects with COVID-19 infection

Summary

EudraCT number	2021-000455-39
Trial protocol	SE
Global end of trial date	22 August 2022

Results information

Result version number	v1 (current)
This version publication date	28 May 2023
First version publication date	28 May 2023

Trial information

Trial identification

Sponsor protocol code	C21-109-09

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pharma Holdings AS
Sponsor organisation address	Killengreensgt. 2-8, postbox 1288, Tromsø, Norway, NO-9263
Public contact	Johnny Ryvoll, VP Business Development, Pharma Holdings AS, ryvoll@pharmaholdings.no
Scientific contact	Johnny Ryvoll, VP Business Development, Pharma Holdings AS, ryvoll@pharmaholdings.no

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	Final
Date of interim/final analysis	22 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 August 2022
Global end of trial reached?	Yes
Global end of trial date	22 August 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of a single dose of LTX-109 3% nasal gel on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load, as measured by a standardised reverse transcription quantitative polymerase chain reaction (RT-qPCR) method on the sample material after virus cultivation to quantify the amount of live virus in the samples, from the deep nasal cavity in subjects with COVID-19 infection, as compared to placebo.

Protection of trial subjects:

The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are compliant with the International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) E6 (R2) guidance, the European Union (EU) Clinical Trials Directive 2001/20/EC, and applicable local regulatory requirements.
It was the responsibility of the Investigator or an authorised associate to give each potential study subject adequate verbal and written information before any study specific assessments were performed. The information included the objectives and the procedures of the study as well as any risks or inconvenience involved. It was emphasised that participation in the study was voluntary and that the subject could withdraw from participation at any time and for any reason, without any prejudice. All subjects were given the opportunity to ask questions about the study and were given sufficient time to consider participation before signing the Informed consent form (ICF). For subjects who performed the SARS-CoV-2 antigen test (only applicable in Sweden) during screening, a separate brief written information about the test was provided and consent was given for the antigen test only. If the test is positive and the subject was assessed as eligible full written and verbal information about the study was provided and the ICF was signed by the subject and by the Investigator.
Documentation of the discussion and the date of informed consent were recorded in the source documentation and in the electronic case report form (eCRF). The subject information sheet and the signed ICF were filed by the Investigator for possible future audits and/or inspections.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 May 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	Sweden: 11
Country: Number of subjects enrolled	India: 22
Worldwide total number of subjects	33
EEA total number of subjects	11

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	30
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Sweden: Recruitment via CTC's database of volunteers & from advertising in media/social media. India: Recruitment through PI's patient portfolios. The study was prematurely terminated due to recruitment challenges because of reduced spread of COVID-19 and high vaccination rates and coverage. Only 33 subjects (planned 60) were randomised.

Pre-assignment

Screening details:

A total of 34 subjects were screened and 33 were randomised and dosed in the study (11 in Sweden, 22 in India). 16 subjects were treated with a single dose of LTX-109 and 17 subjects received a single dose of placebo. All 33 dosed subjects completed all 3 study visits.

Period 1

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

Blinding implementation details:

This was a double-blind study, and the allocation of treatments was not disclosed until clean file had been declared and the database had been locked. The LTX-109 and placebo were identical in appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	LTX-109 3% w/w Gel

Arm description:

Subjects were randomised in a 1:1 ratio to receive 1 single dose of either active treatment (LTX-109 3% hydrogel; planned number: 30) or matching placebo (planned number: 30). This arm represents the active treatment group receiving LTX-109.

Arm type	Experimental
Investigational medicinal product name	LTX-109
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

A single dose of LTX-109 3% gel was administered to the nasal passages on Day 1. Prior to application, the subjects were to blow their nose to try to remove as much mucus secretions as possible. The IMP was administered while the subject lied in a supine position. A large drop was applied in the anterior parts of the nose, in each nostril, so that it covered the anterior and posterior parts of the nasal cavity. It was important that the volume was large enough to cover the whole inner area of the nose. After application of the IMP to both nostrils, the nostrils were gently squeezed together and massaged. The subject had to remain in the supine position for 15 minutes after application. Subjects were not allowed to blow their nose within 30 min after application. The IMP could not be removed until 2 hours after application. Each tube of IMP was used for 1 single subject only.

Arm title	LTX-109 Placebo Gel

Arm description:

Subjects were randomised in a 1:1 ratio to receive 1 single dose of either active treatment (LTX-109 3% hydrogel; planned number: 30) or matching placebo (planned number: 30). This arm represents the group receiving placebo.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

Placebo gel was identical in composition and appearance to the LTX-109 formulation but contained no drug substance. A single dose placebo gel was administered to the nasal passages on Day 1. Prior to application, the subjects were to blow their nose to try to remove as much mucus secretions as possible. The IMP was administered while the subject lied in a supine position. A large drop was applied in the anterior parts of the nose, in each nostril, so that it covered the anterior and posterior parts of the nasal cavity. It was important that the volume was large enough to cover the whole inner area of the nose. After application of the IMP to both nostrils, the nostrils were gently squeezed together and massaged. The subject had to remain in the supine position for 15 minutes after application. Subjects were not allowed to blow their nose within 30 min after application. The IMP could not be removed until 2 hours after application. Each tube of IMP was used for 1 single subject only.

Number of subjects in period 1	LTX-109 3% w/w Gel	LTX-109 Placebo Gel
Started	16	17
Completed	16	17

Baseline characteristics

Reporting groups	
Reporting group title	LTX-109 3% w/w Gel
Reporting group description:	
Subjects were randomised in a 1:1 ratio to receive 1 single dose of either active treatment (LTX-109 3% hydrogel; planned number: 30) or matching placebo (planned number: 30). This arm represents the active treatment group receiving LTX-109.	
Reporting group title	LTX-109 Placebo Gel
Reporting group description:	
Subjects were randomised in a 1:1 ratio to receive 1 single dose of either active treatment (LTX-109 3% hydrogel; planned number: 30) or matching placebo (planned number: 30). This arm represents the group receiving placebo.	

Reporting group values	LTX-109 3% w/w Gel	LTX-109 Placebo Gel	Total
Number of subjects	16	17	33
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	36.56	41.29	
standard deviation	± 15.95	± 16.17	-
Gender categorical Units: Subjects			
Female	5	7	12
Male	11	10	21

End points

End points reporting groups

Reporting group title	LTX-109 3% w/w Gel

Reporting group description:

Subjects were randomised in a 1:1 ratio to receive 1 single dose of either active treatment (LTX-109 3% hydrogel; planned number: 30) or matching placebo (planned number: 30). This arm represents the active treatment group receiving LTX-109.

Reporting group title	LTX-109 Placebo Gel

Reporting group description:

Subjects were randomised in a 1:1 ratio to receive 1 single dose of either active treatment (LTX-109 3% hydrogel; planned number: 30) or matching placebo (planned number: 30). This arm represents the group receiving placebo.

Primary: Reduction in SARS-CoV-2 viral load, based on the deep nasal swab sample, from baseline (pre-dose) to 2 hours post-dose, as measured by a standardised RT-qPCR method after virus cultivation (Full analysis set)

End point title	Reduction in SARS-CoV-2 viral load, based on the deep nasal swab sample, from baseline (pre-dose) to 2 hours post-dose, as measured by a standardised RT-qPCR method after virus cultivation (Full analysis set)

End point description:

Nasal swab sampling for analysis of SARS-CoV-2 viral load was performed by qualified personnel, blinded to the treatment allocation, in a standardised manner at the pre-specified timepoints. At each sampling timepoint, a swab sample was collected using a sterile swab; 1 standard deep nose swab (one nostril). The swab was placed back into the sterile container and stored frozen (-80°C) until shipment. Analysis was performed by Viroclinics, Rotterdam, the Netherlands by a standardised RT-qPCR method on the sample material after virus cultivation. Details on the nasal swab sampling procedure, sample shipment and analyses were specified in separate manuals.

End point type	Primary

End point timeframe:

Nasal swab sampling was performed Pre-dose (baseline) and 2 hours post-dose.

End point values	LTX-109 3% w/w Gel	LTX-109 Placebo Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: RNA copies/mL				
arithmetic mean (standard deviation)				
Treatment, Day 1, PREDOSE	36070000 (± 105800000)	50250000 (± 94080000)		
Treatment, Day 1, 2 H	15900000 (± 46140000)	19260000 (± 49100000)		
Absolute change from baseline	-20170000 (± 59720000)	-30990000 (± 63310000)		

Statistical analyses

Statistical analysis title	Differences between active and placebo

Statistical analysis description:

The aim of the primary analysis was to show that the proportion of subjects with reduced viral load in the deep nasal cavity from baseline (pre-dose) to 2 hours post-dose was higher in the active treatment group than in the placebo group. A subject was classified as a success if the reduction in viral load was greater than 75%, otherwise the subject was classified as a failure. The primary endpoint was analysed using a Fisher's exact test without without continuity correction.

Comparison groups	LTX-109 3% w/w Gel v LTX-109 Placebo Gel
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0894 [1]
Method	Fisher exact

Notes:

[1] - Fisher's exact test two-sided p-value. p-value <0.05 shows a significant difference between the groups.

Primary: Reduction in SARS-CoV-2 viral load, based on the deep nasal swab sample, from baseline (pre-dose) to 2 hours post-dose, as measured by a standardised RT-qPCR method after virus cultivation (Full analysis set) - Relative change from baseline

End point title	Reduction in SARS-CoV-2 viral load, based on the deep nasal swab sample, from baseline (pre-dose) to 2 hours post-dose, as measured by a standardised RT-qPCR method after virus cultivation (Full analysis set) - Relative change from baseline[2]

End point description:

Nasal swab sampling for analysis of SARS-CoV-2 viral load was performed by qualified personnel, blinded to the treatment allocation, in a standardised manner at the pre-specified timepoints. At each sampling timepoint, a swab sample was collected using a sterile swab; 1 standard deep nose swab (one nostril). The swab was placed back into the sterile container and stored frozen (-80°C) until shipment. Analysis was performed by Viroclinics, Rotterdam, the Netherlands by a standardised RT-qPCR method on the sample material after virus cultivation. Details on the nasal swab sampling procedure, sample shipment and analyses were specified in separate manuals.

End point type	Primary

End point timeframe:

Nasal swab sampling was performed Pre-dose (baseline) and 2 hours post-dose.

Notes:

[2] - 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: See Primary: Reduction in SARS-CoV-2 viral load, based on the deep nasal swab sample, from baseline (pre-dose) to 2 hours post-dose, as measured by a standardised RTqPCR method after virus cultivation.

End point values	LTX-109 3% w/w Gel	LTX-109 Placebo Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: percent				
arithmetic mean (standard deviation)	233.1 (± 893.6)	218.1 (± 584.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in SARS-CoV-2 viral load, based on the anterior nasal swab sample, from baseline (pre-dose) to 2 hours post-dose, as measured by a standardised RT-qPCR method after virus cultivation (Full analysis set)

End point title	Reduction in SARS-CoV-2 viral load, based on the anterior nasal swab sample, from baseline (pre-dose) to 2 hours post-dose, as measured by a standardised RT-qPCR method after virus cultivation (Full analysis set)

End point description:

Nasal swab sampling for analysis of SARS-CoV-2 viral load was performed by qualified personnel, blinded to the treatment allocation, in a standardised manner at the pre-specified timepoints. At each sampling timepoint, a swab sample was collected using a sterile swab; 1 standard deep nose swab (one nostril). The swab was placed back into the sterile container and stored frozen (-80°C) until shipment. Analysis was performed by Viroclinics, Rotterdam, the Netherlands by a standardised RT-qPCR method on the sample material after virus cultivation. Details on the nasal swab sampling procedure, sample shipment and analyses were specified in separate manuals.

End point type	Secondary

End point timeframe:

Nasal swab sampling was performed Pre-dose (baseline) and 2 hours post-dose.

End point values	LTX-109 3% w/w Gel	LTX-109 Placebo Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: RNA copies/mL				
arithmetic mean (standard deviation)				
Treatment, Day 1, PREDOSE	9969000 (± 25280000)	49050000 (± 96370000)		
Treatment, Day 1, 2 H	12620000 (± 39560000)	18100000 (± 51940000)		
Absolute change from baseline	2648000 (± 15060000)	-30960000 (± 66610000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in SARS-CoV-2 viral load, based on the anterior nasal swab sample, from baseline (pre-dose) to 2 hours post-dose, as measured by a standardised RT-qPCR method after virus cultivation (Full analysis set) - Relative change from baseline

End point title	Reduction in SARS-CoV-2 viral load, based on the anterior nasal swab sample, from baseline (pre-dose) to 2 hours post-dose, as measured by a standardised RT-qPCR method after virus cultivation (Full analysis set) - Relative change from baseline

End point description:

Nasal swab sampling for analysis of SARS-CoV-2 viral load was performed by qualified personnel, blinded to the treatment allocation, in a standardised manner at the pre-specified timepoints. At each sampling timepoint, a swab sample was collected using a sterile swab; 1 standard deep nose swab (one nostril). The swab was placed back into the sterile container and stored frozen (-80°C) until shipment. Analysis was performed by Viroclinics, Rotterdam, the Netherlands by a standardised RT-qPCR method on the sample material after virus cultivation. Details on the nasal swab sampling procedure, sample shipment and analyses were specified in separate manuals.

End point type	Secondary

End point timeframe:

Nasal swab sampling was performed Pre-dose (baseline) and 2 hours post-dose.

End point values	LTX-109 3% w/w Gel	LTX-109 Placebo Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: percent				
arithmetic mean (standard deviation)	96.19 (± 452.8)	185.9 (± 491.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency, intensity and seriousness of AEs (Safety analysis set)

End point title	Frequency, intensity and seriousness of AEs (Safety analysis set)

End point description:

Symptoms of COVID-19 not recorded at baseline, or worsening after IMP administration, were recorded as AEs. The grading of the severity/intensity (grade 1 to grade 5) of AEs followed the common terminology criteria for AEs (CTCAE) v5.0 [12]. AEs were assessed as unlikely, possibly or probably related to the IMP.

End point type	Secondary

End point timeframe:

AEs (including serious AEs [SAEs]) were collected from the start of IMP administration until the end-of-study visit of each part.

End point values	LTX-109 3% w/w Gel	LTX-109 Placebo Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: Number of subjects				
Any AE	10	10		
Any SAE	0	0		
Any AE leading to withdrawal from study	0	0		
Any AE leading to death	0	0		
Causality to IMP - Possibly Related	4	1		
Causality to IMP - Probably Related	1	1		
Causality to IMP - Unlikely Related	9	10		
Severity - Mild	8	5		
Severity - Moderate	6	7		
Severity - Severe	0	0		
Severity - Life-Threatening	0	0		
Severity - Death	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs (including serious AEs [SAEs]) were collected from the start of IMP administration until the end-of-study visit of each part.

Adverse event reporting additional description:

Symptoms of COVID-19 not recorded at baseline, or worsening after IMP administration, were recorded as AEs. The grading of the severity/intensity (grade 1 to grade 5) of AEs followed the common terminology criteria for AEs (CTCAE) v5.0. AEs were assessed as unlikely, possibly or probably related to the IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	LTX-109 3% w/w Gel

Reporting group description:

Subjects were randomised in a 1:1 ratio to receive 1 single dose of either active treatment (LTX-109 3% hydrogel; planned number: 30) or matching placebo (planned number: 30). This arm represents the active treatment group receiving LTX-109.

Reporting group title	LTX-109 Placebo Gel

Reporting group description:

Subjects were randomised in a 1:1 ratio to receive 1 single dose of either active treatment (LTX-109 3% hydrogel; planned number: 30) or matching placebo (planned number: 30). This arm represents the group receiving placebo.

Serious adverse events	LTX-109 3% w/w Gel	LTX-109 Placebo Gel	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	LTX-109 3% w/w Gel	LTX-109 Placebo Gel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 16 (62.50%)	10 / 17 (58.82%)	
Nervous system disorders			
Ageusia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	
occurrences (all)	2	1	

Anosmia			
subjects affected / exposed	2 / 16 (12.50%)	2 / 17 (11.76%)	
occurrences (all)	2	2	
Headache			
subjects affected / exposed	3 / 16 (18.75%)	2 / 17 (11.76%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 16 (18.75%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 16 (18.75%)	4 / 17 (23.53%)	
occurrences (all)	3	4	
Dyspnoea			
subjects affected / exposed	3 / 16 (18.75%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Nasal discomfort			
subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Rhinalgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	2 / 16 (12.50%)	3 / 17 (17.65%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	1 / 17 (5.88%) 1	
Infections and infestations Sinusitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 17 (5.88%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2021	Revision of exclusion criteria No's 2 and 5 to facilitate recruitment.
07 July 2021	Temporary halt in Sweden due stability issues with batch 7579/001.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 July 2021	Temporary halt in Sweden due stability issues with batch 7579/001.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Inter-individual variation was too large and sample size was too small to conclude if single dose of LTX-109 3% nasal gel administered to subjects with COVID-19 infection reduces the viral load in the deep nasal cavity and/or the anterior nose.

Notes: