



Clinical trial results:

Double-blind placebo-controlled proof-of-concept trial to demonstrate the anti-viral efficacy of different doses of azelastine in COVID-19 positive patients.

Summary

EudraCT number	2020-005544-34
Trial protocol	DE
Global end of trial date	26 June 2021

Results information

Result version number	v1 (current)
This version publication date	13 July 2022
First version publication date	13 July 2022

Trial information

Trial identification

Sponsor protocol code	CARVIN
-----------------------	--------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ursapharm Arzneimittel GmbH
Sponsor organisation address	Industriestraße 35, Saarbrücken, Germany, 66129
Public contact	Dr. Peter Meiser, Leitung Med.-Wiss., Ursapharm Arzneimittel GmbH, peter.meiser@ursapharm.de
Scientific contact	Dr. Peter Meiser, Leitung Med.-Wiss., Ursapharm Arzneimittel GmbH, peter.meiser@ursapharm.de

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	01 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2021
Global end of trial reached?	Yes
Global end of trial date	26 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the first data on efficacy of azelastine nasal spray in SARS-CoV-2 infected patients with regards to virus load in nasopharyngeal swabs.

Protection of trial subjects:

Symptomatic treatments for COVID-19 (e.g., analgesic drugs) have been allowed, but the following concomitant medications and procedures that might have interfered with the clinical results were prohibited from one month before Day 1 of the trial to Day 11:

- Any nasal irrigation including nasal lavage fluids
- Any concurrent antihistamine therapies

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 March 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	Germany: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	90
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from March 2021 until May 2021 using newspaper advertisements and information flyers in COVID testing centres.

Pre-assignment

Screening details:

Main Inclusion criteria

Patients aged from 18 - 60 years, having the diagnosis of SARS-CoV-2 infection documented by a positive PCR test (patients do not need to suffer from COVID-19 symptoms)

Main Exclusion criteria

Patients requiring hospitalization, No enrolment permitted if COVID-19 testing was performed more than 48 hours ago

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Active 1

Arm description: -

Arm type	Experimental
Investigational medicinal product name	0.1 % Azelastine nasal spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

1 puff per nostril, three times daily

Arm title	Active 2
------------------	----------

Arm description: -

Arm type	Experimental
Investigational medicinal product name	0.02% Azelastine nasal spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

1 puff per nostril, three times daily

Arm title	Placebo
------------------	---------

Arm description: -

Arm type	Placebo
----------	---------

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

1 puff per nostril, three times daily

Number of subjects in period 1	Active 1	Active 2	Placebo
Started	29	31	30
Completed	29	31	30

Baseline characteristics

Reporting groups

Reporting group title	Active 1
Reporting group description: -	
Reporting group title	Active 2
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Active 1	Active 2	Placebo
Number of subjects	29	31	30
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Patients were aged 18 - 60 years			
Units: years			
arithmetic mean	37.66	33.81	35.67
standard deviation	± 12.96	± 12.90	± 13.12
Gender categorical			
Male or female patients were enrolled in this trial.			
Units: Subjects			
Female	15	16	15
Male	14	15	15

Reporting group values	Total		
Number of subjects	90		
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			
Patients were aged 18 - 60 years			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Male or female patients were enrolled in this trial.			
Units: Subjects			
Female	46		
Male	44		

Subject analysis sets

Subject analysis set title	safety population
Subject analysis set type	Full analysis
Subject analysis set description: safety population (baseline characteristics, adverse events)	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT population: all randomized patients who met key eligibility and evaluability criteria. This dataset was defined by the existence of evaluable viral load measurements at Day 1 (baseline) and at Day 11 or at the early termination visit, respectively.	

Reporting group values	safety population	ITT population	
Number of subjects	90	81	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Patients were aged 18 - 60 years			
Units: years			
arithmetic mean	35.67	35.67	
standard deviation	± 12.94	± 12.94	
Gender categorical			
Male or female patients were enrolled in this trial.			
Units: Subjects			
Female	46	46	
Male	44	44	

End points

End points reporting groups

Reporting group title	Active 1
Reporting group description: -	
Reporting group title	Active 2
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	safety population
Subject analysis set type	Full analysis
Subject analysis set description:	
safety population (baseline characteristics, adverse events)	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT population: all randomized patients who met key eligibility and evaluability criteria. This dataset was defined by the existence of evaluable viral load measurements at Day 1 (baseline) and at Day 11 or at the early termination visit, respectively.	

Primary: Efficacy of the treatment with azelastine (PCR E gene)

End point title	Efficacy of the treatment with azelastine (PCR E gene)
End point description:	
Primary endpoint of the efficacy of azelastine nasal spray in COVID-positive patients is the baseline adjusted course of the median of virus load in nasopharyngeal swabs of the three treatment groups at any of the six timepoints after baseline (PCR performed on E gene).	
End point type	Primary
End point timeframe:	
day 1 to day 11	

End point values	Active 1	Active 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	28	26	
Units: quantitative viral load cp/ml				
median (standard deviation)	-5.48 (± 2.29)	-5.81 (± 2.29)	-5.18 (± 2.00)	

Statistical analyses

Statistical analysis title	Decrease quantitative viral load (E gene)
Comparison groups	Active 1 v Active 2 v Placebo

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 ^[1]
Method	t-test, 1-sided

Notes:

[1] - overall statistical tests: Kruskal Wallis test

Pairwise comparisons were performed by Mann Whitney U test. Due to Bonferroni correction statistically significance level was $p < 0.0167$.

Primary: Efficacy of the treatment with azelastine (PCR ORF gene)

End point title	Efficacy of the treatment with azelastine (PCR ORF gene)
-----------------	--

End point description:

Primary endpoint of the efficacy of azelastine nasal spray in COVID-positive patients is the baseline adjusted course of the median of virus load in nasopharyngeal swabs of the three treatment groups at any of the six timepoints after baseline (PCR performed on ORF gene).

End point type	Primary
----------------	---------

End point timeframe:

day 1 to day 11

End point values	Active 1	Active 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	28	26	
Units: quantitative viral load cp/ml				
median (standard deviation)	-4.45 (± 2.26)	-4.02 (± 2.01)	-3.79 (± 1.61)	

Statistical analyses

Statistical analysis title	Decrease quantitative viral load (ORF gene)
Comparison groups	Active 1 v Active 2 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 ^[2]
Method	t-test, 1-sided

Notes:

[2] - overall statistical test: Kruskal Wallis test

Pairwise comparison performed by Mann Whitney U test. Due to Bonferroni correction statistically significance level was $p < 0.0167$.

Secondary: 10-fold decrease in virus load

End point title	10-fold decrease in virus load
-----------------	--------------------------------

End point description:

Proportion of patients who show a 10-fold decrease in virus load of SARS-CoV-2 within 3 days of treatment

End point type	Secondary
----------------	-----------

End point timeframe:

day 1 to day 4

End point values	Active 1	Active 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	28	26	
Units: Percentage				
10-fold decrease in viral load	70	59	62	

Statistical analyses

No statistical analyses for this end point

Secondary: change in sum symptom score

End point title	change in sum symptom score
End point description: The change in symptom severity (anosmia, ageusia, fever, cough, sore throat, shortness of breath, coryza, general weakness, headache, aching limbs, loss of appetite, pneumonia, nausea, abdominal pain, vomiting, diarrhoea, conjunctivitis, rash, lymph node swelling, apathy, somnolence) from baseline presented as total symptom score.	
End point type	Secondary
End point timeframe: day 1 to day 11	

End point values	Active 1	Active 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	28	26	
Units: sum score				
geometric mean (standard deviation)				
sum symptom score	-12.74 (\pm 10.74)	-8.38 (\pm 9.42)	-11.12 (\pm 9.45)	

Statistical analyses

No statistical analyses for this end point

Secondary: Patient state (WHO COVID-19 status)

End point title	Patient state (WHO COVID-19 status)
End point description: The change in patient state using a 11-category ordinal score as proposed by the WHO [A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020; 20:e192-97]. The investigator will assess the patient state as uninfected: no viral RNA detected (0); ambulatory mild	

disease: asymptomatic, viral RNA detected (1), OR symptomatic; independent (2); OR symptomatic; assistance needed (3); hospitalized moderate disease: hospitalized, no oxygen therapy* (4); OR hospitalized; oxygen by mask or nasal prongs (5); hospitalized severe disease: hospitalized; oxygen by NIV or high-flow (6), OR intubation and mechanical ventilation, pO₂/FiO₂ ≥ 150 or SpO₂/FiO₂ ≥ 200 (7) OR mechanical ventilation or vasopressors pO₂/FiO₂ < 150 (SpO₂/FiO₂ < 200 (8); OR mechanical ventilation pO₂/FiO₂ < 150 and vasopressors, dialysis, or ECMO (9); Dead: Dead (10). (*if hospitalised for isolation only, record status as for ambulatory patient.)

End point type	Secondary
End point timeframe:	
day 1 to day 60	

End point values	Active 1	Active 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	31	30	
Units: 11-category ordinal score				
patient status (WHO COVID-19 status)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: change in Quality of Life (SF-36)

End point title	change in Quality of Life (SF-36)
End point description:	
The change in quality of life as assessed by the SF-36 generic quality of life questionnaire.	
End point type	Secondary
End point timeframe:	
day 1 to day 11	

End point values	Active 1	Active 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	28	26	
Units: sum score				
median (standard deviation)				
SF-36 sum score (physical parameters)	5.73 (± 9.63)	-0.46 (± 10.58)	3.97 (± 8.20)	
SF-36 sum score (mental parameters)	0.16 (± 9.93)	-2.43 (± 9.21)	5.12 (± 10.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety
-----------------	--------

End point description:

Occurance of Adverse Events

End point type	Secondary
----------------	-----------

End point timeframe:

D1 - D60

End point values	Active 1	Active 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	31	30	
Units: AEs	16	13	12	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

D1 - D60 overall trial

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	24.0
--------------------	------

Reporting groups

Reporting group title	Active 1
-----------------------	----------

Reporting group description: -

Reporting group title	Active 2
-----------------------	----------

Reporting group description: -

Reporting group title	Placebo
-----------------------	---------

Reporting group description: -

Serious adverse events	Active 1	Active 2	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Active 1	Active 2	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 29 (55.17%)	13 / 31 (41.94%)	22 / 30 (73.33%)
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
loss of smell			
subjects affected / exposed	2 / 29 (6.90%)	3 / 31 (9.68%)	1 / 30 (3.33%)
occurrences (all)	2	3	1
loss of taste			

subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
sleepiness			
subjects affected / exposed	3 / 29 (10.34%)	5 / 31 (16.13%)	5 / 30 (16.67%)
occurrences (all)	3	5	5
taste bitter			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
nasal mucosa swelling			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
nasal sinus blockage			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
nose bleed			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
sinus pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
dry nasal mucosa			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

common cold			
subjects affected / exposed	4 / 29 (13.79%)	3 / 31 (9.68%)	5 / 30 (16.67%)
occurrences (all)	4	3	5
Conjunctivitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	4 / 30 (13.33%)
occurrences (all)	1	0	4
Rhinitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2021	Increase in the compensation for expenses of study subjects due to increased time spent on the reporting of patient-reported outcome
26 April 2021	Involvement of an additional trial site

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported