



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 would have interfered with the clinical results werw prohibited from one months before Day 1 of the trial to Day 11:

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