Clinical Trial Report - Synopsis

Title of the clinical trial:	**CHANCE: C**OVID-19 – Reducing symptoms and **H**ospitalization rates by use of **A**zelastine **N**asal spray in patients suffering from **C**OVID-19 in **E**arly stages
Investigational medicinal product(s):	Azelastine 0.1% (1mg/mL) Nasal spray
Indication:	COVID-19 related symptoms
Design of the clinical trial:	Prospective, randomized, double-blind, placebo-controlled trial including up to 600 eligible participants with a positive SARS-CoV-2 test result
Sponsor:	Ursapharm Arzneimittel GmbH Industriestraße 35 66129 Saarbrücken
EU trial number:	2021-006485-20
Protocol number:	CHANCE
Trial phase:	Phase III
First participant enrolled:	20-Oct-2022
Last visit of the last trial participant:	13-Dec-2023

This trial was performed in compliance with the protocol, with the Clinical Trials Regulation (EU) No 536/2014, with the principles of good clinical practice (GCP), and with the World Health Organization's Declaration of Helsinki in its most recent version, including the archiving of essential documents.

Date of Clinical Trial Report: 30-Oct-2024

2 SYNOPSIS

Name of Sponsor:
Ursapharm Arzneimittel GmbH

Name of Finished Product:
Azelastine 1mg/mL Nasal Spray

Name of Active Ingredient:
Azelastine hydrochloride

Title of the clinical trial:
CHANCE: COVID-19 – Reducing symptoms and **H**ospitalization rates by use of **A**zelastine **N**asal spray in patients suffering from **C**OVID-19 in **E**arly stages

EU trial number: 2021-006485-20

Protocol number: CHANCE

Trial phase: Phase III

Number of trial site(s) and countries: 11 trial sites in 3 EU countries

Publications (reference, if any): None

Clinical trial periods:
First trial participant enrolled: 20-Oct-2022
Last visit of the last trial participant: 13-Dec-2023

Primary and Secondary Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To evaluate the treatment effect of azelastine 0.1% on the proportion of sustained clinical recovery from COVID-19 related symptoms	• Time to sustained clinical recovery, defined as (a) all symptoms from the FDA COVID-19 symptom list scored with "2" or "3" at baseline are subsequently reduced to "0" or "1" AND (b) all symptoms from the FDA COVID-19 symptom list scored with "0" or "1" at baseline are subsequently scored with "0" AND no worsening up to Day 29.
Secondary	
• To evaluate the efficacy of azelastine 0.1% treatment to prevent hospitalization or death in COVID-19 infected participants	• Rate of COVID-19 related hospitalizations or all-cause mortality up to V6 and V7

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• To evaluate the efficacy of azelastine 0.1% treatment on the development of COVID-19 symptoms	• Time to sustained clinical recovery, defined as (a) all symptoms from the FDA COVID-19 symptom list scored with "2" or "3" at baseline are subsequently reduced to "0" or "1" AND (b) all symptoms from the FDA COVID-19 symptom list scored with "0" or "1" at baseline are subsequently scored with "0" AND no worsening up to Day 15. • Change in symptom severity for individual symptoms between baseline and V4, V5 and V6 • Persistence of COVID-19 related symptoms at V7
• To assess the treatment effect of azelastine 0.1% on virus load of SARS-CoV-2	• Change in Ct-value (measured semi-quantitatively) between baseline and V4
• To evaluate the treatment effect of azelastine 0.1% on participant status	• Change of peripheral blood oxygen saturation (SpO2) between baseline and V6 and V7 • Change in WHO status between baseline and V6 and V7
Safety	
• To evaluate the safety characteristics of azelastine 0.1% in participants with COVID-19	• Frequency, severity and relationship of adverse events to treatment
Exploratory	
• To evaluate the overall tolerability and efficacy of azelastine 0.1%	• Participants' and Investigators' subjective assessment on a 4-point NRS

Estimands:

Power and sample size calculations were based on the expected reduction of the time to sustained clinical recovery in the group treated with azelastine 0.1% nasal spray. Assuming

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a time to sustained clinical recovery of 8.06 days in the placebo group and a 30% decrease in the azelastine therapy group (to 5.7 days), a two-sided Tarone-Ware test on a significance level of α=0.05 and a power of 90%, a sample size of 261 patients per treatment group was calculated. Expecting a dropout rate of approximately 13%, 300 patients per group and 600 patients in total were planned to be randomized 1:1.
Methodology: This trial was designed to test the null hypothesis that the median time to sustained clinical recovery as primary endpoint in subjects treated with azelastine is equal to the subjects treated with placebo. This analysis was conducted in an adaptive group-sequential design, including a first interim analysis after 200 participants have been included, and a second interim analysis after additional 200 participants. In Germany, trial visits V1 and V4 were performed on-site (at participants' home, or alternatively, at the clinical site), visits V2, V3, V5, V6 and V7 were held remotely as video consultations (or alternatively, at the clinical site). In Bulgaria and Romania, trial visits V1, V4, V5 and V6 were performed at the clinical site; visits V2, V3, and V7 could be held remotely as phone calls if site visit was not possible (or alternatively, at the clinical site).
Number of trial participants (planned and analysed): This trial was designed as prospective, randomized, double-blind, placebo-controlled trial including up to 600 eligible participants with a positive SARS-CoV-2 test result. 300 participants per group were planned to be included in the trial to obtain 261 evaluable participants per group. A dropout rate of approximately 13% was assumed. Eventually, the trial was stopped after the results of the first interim analysis. At this point in time, 275 participants were included, of which 272 were randomized and received trial medication.
Diagnosis and main criteria for inclusion and exclusion: The following criteria were used to assess the eligibility of participants: <u>Inclusion criteria:</u> • Legally competent participants who are personally capable of giving informed consent and to sign and date the Consent Form prior to any trial related activity, • Participants that exhibit COVID-19-related symptoms, of which - at least two are scored at baseline with "2" or "3" OR - at least six are scored at baseline at "1" or higher, but which have not yet lasted longer than 2 days.

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- Participants aged from 18 to 80 years, whether vaccinated to SARS-CoV-2 or not. Unvaccinated participants can be included only if they do not fulfil the following risk factors for a severe course of SARS-CoV-2 infection:
  Diabetes, obesity (BMI > 25), chronic lung disease (including asthma), chronic kidney disorder, current smoking, immunosuppressive disease or immunosuppressive therapy, heart disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medical technological dependence, or age 60 years or older, regardless of comorbidities.
  The participant's family physician had to take the decision on the inclusion of unvaccinated participants, considering the participant's anamnesis and concomitant medication.
- Having the diagnosis of SARS-CoV-2 infection documented by a positive Rapid Antigen Test or positive PCR testing. Positive Rapid Antigen Test results must be confirmed through another Rapid Antigen test performed in presence of the investigator during the inclusion visit.
  Participants were included in the trial based on eligibility criteria and after signing the informed consent. The participant underwent all trial related procedures on the same day (baseline RT-PCR test using nasal swabs, physical examination, vital signs, concomitant medications etc) including trial drug administration.
  The decision of continuing the participant further in the trial was based on the results of RT-PCR (participants exhibiting baseline Ct-values ≤ 25 were continued, participants exhibiting baseline Ct-values > 25 were discontinued from the trial). In case of baseline Ct-values > 25, the drug was immediately withdrawn, and participants discontinued from the trial.

<u>Exclusion criteria:</u>

- Patients requiring hospitalization at the time of enrolment
- Simultaneous participation in other clinical trials or previous participation within 30 days before inclusion
- Being in any relationship or dependence with the Sponsor, CRO and/or Investigator
- Inability to understand instructions/trial documents
- Inability to administer the nasal spray
- Specific vulnerable patients: subjects who are detained or committed to institutions by law court or by legal authorities, such as psychiatric wards, prisons or other state institutions

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- Any additional anti-histamine therapy from Day 1 of the trial to Day 16 (locally or systemically applied), any antihistamine therapy 7 days prior to enrolment
- Any concurrent nasalia including nasal lavage fluids
- Any concurrent anti-COVID therapy (including off-label-use) such as (inhalative) corticosteroids or anti-viral and immune-modulatory active substances, for example sotrovimab, molnupiravir, paxlovid (nirmatrelvir und ritonavir)
- Unvaccinated patients who are eligible for therapy with already approved COVID-19 medicinal products
- Females who are pregnant, lactating, or of child-bearing potential* and not using an adequate contraceptive method** until D60. Females in post-menopausal state*** may be included.
- Having any contraindication for the use of azelastine nasal spray (incl. hypersensitivity to the active substance or other ingredients).

* Definition of woman of childbearing potential:
A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal*** unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

** Birth control methods which are considered as highly effective (adequate contraception)
1. Oral, intravaginal or transdermal hormonal medical drugs or -devices containing estrogen and progesterone;
2. Oral, injectable or implantable hormonal medical drugs or -devices containing progesterone-only;
3. Intrauterine device (IUD);
4. Intrauterine hormone-releasing system (IUS)
5. bilateral tubal occlusion
6. vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
7. sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments).

*** A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Trial interventions, dose, mode of administration, and batch number(s):

Investigational medicinal product: Azelastine hydrochloride 0.1%

Dose: 1 puff (=0.14mL) contains 0.14mg azelastine hydrochloride

Mode of administration: Nasal spray (clear colourless solution)

Batch number: 302926 / 302928

Control: Placebo nasal spray (10mL of aqueous solution)

Dose: 1 puff (0.14mL) contains disodium edetate, hypromellose, disodium phosphate dodecahydrate, citir acid sodium chloride, water

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Mode of administration: Nasal spray

Batch number: 233054

Duration of treatment:

Individual participants were observed in the trial during a total period of 60 days, including 4 observation time points during an 11-day treatment with azelastine or placebo nasal spray. Additionally, safety follow-ups of the treatment and with regard to the participant status were performed on days 16, 30 and 60.

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint:

To evaluate the treatment effect of azelastine (0.1%) on the proportion of sustained clinical recovery from COVID-19-related symptoms:

- Time to sustained clinical recovery, defined as
  (a) all symptoms from the FDA COVID-19 symptom list scored with „2“ or „3“ at baseline are subsequently scored with „0“ or „1“, AND
  (b) all symptoms from the FDA COVID-19 symptom list scored with „0“ or „1“ at baseline are subsequently scored as „0“, with no subsequent worsening up to Day 29.

Secondary efficacy endpoints:

To evaluate the efficacy of azelastine (0.1%) treatment preventing hospitalization or death in COVID-19 infected participants.

- Rate of COVID-19 related hospitalizations or all-cause mortality up to V6 (composite endpoint).
- Rate of COVID-19 related hospitalizations or all-cause mortality up to V7 (composite endpoint)

To evaluate the treatment effect of azelastine (0.1%) on the development of COVID-19 symptoms:

- Time to sustained clinical recovery, defined as
  (a) all symptoms from the FDA COVID-19 symptom list scored with „2“ or „3“ at baseline are subsequently scored with „0“ or „1“, AND
  (b) all symptoms from the FDA COVID-19 symptom list scored with „0“ or „1“ at

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baseline are subsequently scored as „0“, with no subsequent worsening up to Day 15

- Time to sustained clinical recovery, defined as
  (a) all symptoms from the FDA COVID-19 symptom list excluding „low energy and tiredness” scored with „2“ or „3“ at baseline are subsequently scored with „0“ or „1“, AND
  (b) all symptoms from the FDA COVID-19 symptom list excluding “low energy and tiredness” scored with „0“ or „1“ at baseline are subsequently scored as „0“, with no subsequent worsening up to Day 15.
- Time to sustained clinical recovery, defined as
  (a) all symptoms from the FDA COVID-19 symptom list excluding “low energy and tiredness” scored with „2“ or „3“ at baseline are subsequently scored with „0“ or „1“, AND
  (b) all symptoms from the FDA COVID-19 symptom list excluding “low energy and tiredness” scored with „0“ or „1“ at baseline are subsequently scored as „0“, with no subsequent worsening up to Day 29.
- Change in symptom severity for individual symptoms between baseline, V4, V5 and V6.
- Persistence of COVID-19 related symptoms at V7.

To assess the treatment effect on virus load of SARS-CoV-2:

- Change in Ct-value (measured with semi-quantitative methods) between baseline and V4.

To evaluate the treatment effect on participant status:

- Change of blood oxygen saturation from baseline up to V6 and on V7.
- Change in WHO status from baseline up to V6 and on V7.

Safety:

To evaluate safety of azelastine in subjects in COVID-19 infected participants

- Frequency, severity, and relationship of AEs to treatment up to V7.
- Changes to vital signs over time

Exploratory:

To evaluate the overall tolerability and efficacy of azelastine 0.1%

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- Participants' and investigators' subjective assessment of tolerability and efficacy of azelastine treatment at V4.

Statistical considerations:

Methodology:

Two interim analyses were planned: first after 200 patients have been included, then after additional 200 patients, who have completed the trial until V7. Blinding was broken by an external biometrician and the statistical analysis has comprised all data available to this date.

Comparison of categorial variables between groups were performed by Chi square or Fisher's exact tests, as appropriate. Continuous variables were compared with Student's t or Mann-Whitney-U tests in accordance with normality analyses. These evaluations are presented just as descriptive statistics for not normally distributed variables.

Continuous data are described by statistical estimates (mean, standard deviation, median, Q1, Q3, minimum, and maximum values). Categorical data are described by absolute frequencies and percentage of valid cases. If appropriate, descriptive p-values and 95%-confidence intervals are presented.

Primary endpoint:

The analysis aimed to compare the time to sustained clinical recovery of COVID-19 related symptoms by day 29 between the two treatment groups. The primary endpoint was analysed with the Tarone-Ware test at an overall 2-sided significance level of α=0.05 (adjusted for 2 interim analyses).

Secondary endpoints:

The secondary trial endpoints are presented by descriptive statistics, and their changes from baseline are displayed.

RESULTS

EFFICACY RESULTS:

The final analysis on the primary efficacy endpoint was performed on the 222 participants included in the ITT population and revealed that a statistically significant benefit of azelastine on the mean (+/- SD) time to sustained clinical recovery up to day 29 versus placebo could not confirmed (azelastine: 11.35; +/-0.78 days versus placebo: 11.34; +/-0.76 days; p=0.951; Tarone-Ware test). This result was also observed in all sensitivity analyses and subgroup analyses of the primary endpoint.

Two subgroups were identified which potentially indicate a sub-population with benefit of azelastine treatment:

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1. In the subgroup of participants with a Ct-score of 20 to 25 the overall mean (+/- SD) time to sustained clinical recovery was not significantly different between the azelastine (9.96; +/- 0.88 days) and placebo group (12.95; +/- 1.39; p=0.175). However, the day-by-day comparison separates from day 16 onwards statistically significantly and the participants in the active group recovered more quickly from COVID-19-specific symptoms.
2. A remarkable trend towards a shorter time to sustained clinical recovery of the azelastine group was also present in the subgroup of low S-antibody levels (1st Quartile). Among participants with the 25% lowest S-antibodies, the mean (+/- SD) time to sustained clinical recovery was 7.72; +/- 0.8 days in the azelastine group and 11.28; +/- 1.51 days in the placebo group (p=0.086).

Since the trial was not designed nor powered for these subgroups, no firm conclusions on these subgroups can be drawn. However, these findings may well indicate a treatment effect of azelastine in selected patient populations.

SAFETY RESULTS:

Treatment-emergent adverse events (TEAEs) were reported for approximately 50% of participants exposed to trial medication. The overall number of reported TEAEs was slightly higher than expectable (910 TEAEs); however attributable to the implementation of a rather conservative interpretation of the concept to assess worsening of pre-existing clinical symptoms as adverse events. This has resulted in the identification of 874 (of the overall 910) TEAEs, which have been extracted from fluctuations of the COVID-19 symptom scores. In essence, these 874 events are rather reflective of the natural clinical course of the COVID-19 disease than adverse events.

Besides these 874 events, there were only 36 additional TEAEs, which may be indicative of adverse changes. Of these however, only 1 event (MedDRA PT “rhinorrhoea”) was reported as related to azelastine treatment.

More than 90% of all adverse events (834 of 910; 91.6%) were reported with mild (n=709) and moderate (n=125) severity, no TEAE fulfilled any of the seriousness criteria or resulted in withdrawal from treatment. As expectable, there were no relevant changes to vital signs, either.

The safety data collected in this trial therefore confirmed the good tolerability of the trial medication and are in line with the known safety profile of azelastine.

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CONCLUSION
The trial could not confirm any beneficial effects of azelastine in the treatment of COVID-19 in the general population. However, the trial data indicate sub-populations which may well benefit from azelastine treatment. These observations need confirmation with adequately designed clinical trials. The safety profile of azelastine in COVID-19 patients is comparable to that described for the authorized indications and does not preclude any further exploration in COVID-19 populations.
Date of Clinical Trial Report: 30-Oct-2024