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# Azelastine Nasal Spray for Prevention of SARS-CoV-2 Infections
## A Phase 2 Randomized Clinical Trial

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**IMPORTANCE** Limited pharmaceutical options exist for preexposure prophylaxis of COVID-19 beyond vaccination. Azelastine, an antihistamine nasal spray used for decades to treat allergic rhinitis, has in vitro antiviral activity against respiratory viruses, including SARS-CoV-2.

**OBJECTIVE** To determine the efficacy and safety of azelastine nasal spray for prevention of SARS-CoV-2 infections in healthy adults.

**DESIGN, SETTING, AND PARTICIPANTS** A phase 2, double-blind, placebo-controlled, single-center trial was conducted from March 2023 to July 2024. Healthy adults from the general population were enrolled at the Saarland University Hospital in Germany.

**INTERVENTIONS** Participants were randomly assigned 1:1 to receive azelastine, 0.1%, nasal spray or placebo 3 times daily for 56 days. SARS-CoV-2 rapid antigen testing (RAT) was conducted twice weekly, with positive results confirmed by polymerase chain reaction (PCR). Symptomatic participants with negative RAT results underwent multiplex PCR testing for respiratory viruses.

**MAIN OUTCOME** The primary end point was the number of PCR-confirmed SARS-CoV-2 infections during the study.

**RESULTS** A total of 450 participants were randomized, with 227 assigned to azelastine and 223 to placebo; 299 (66.4%) were female, 151 (33.6%) male, with a mean (SD) age of 33.0 (13.3) years. Most were White (417 [92.7%]), with 4 (0.9%) African, 22 (4.9%) Asian, and 7 (1.6%) of other ethnicity. In the intention-to-treat (ITT) population, the incidence of PCR-confirmed SARS-CoV-2 infection was significantly lower in the azelastine group (n = 5 [2.2%]) compared with the placebo group (n = 15 [6.7%]) (OR, 0.31; 95% CI, 0.11-0.87). As secondary end points, azelastine demonstrated an increase in mean (SD) time to SARS-CoV-2 infection among infected participants (31.2 [9.3] vs 19.5 [14.8] days), a reduction of the overall number of PCR-confirmed symptomatic infections (21 of 227 participants vs 49 of 223 participants), and a lower incidence of PCR-confirmed rhinovirus infections (1.8% vs 6.3%). Adverse events were comparable between the groups.

**CONCLUSIONS AND RELEVANCE** In this single-center trial, azelastine nasal spray was associated with reduced risk of SARS-CoV-2 respiratory infections. These findings support the potential of azelastine as a safe prophylactic approach warranting confirmation in larger, multicentric trials.

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Invited Commentary
Multimedia
Supplemental content

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The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to significant morbidity and mortality worldwide.[1] Although vaccination and established population immunity have substantially mitigated the severity of acute SARS-CoV-2 infections, infection rates and postacute morbidity continue to pose a considerable public health burden,[2] highlighting the critical need for effective preexposure prophylaxis for the general population, particularly for high-risk groups.

Azelastine is a second-generation histamine H1-receptor antagonist and widely used as over-the-counter nasal spray for treatment of allergies.[3] Beyond its established antiallergic and anti-inflammatory properties, recent research has revealed antiviral activity against a range of respiratory viruses, including SARS-CoV-2, respiratory syncytial virus (RSV), and influenza A (H1N1).[4-6] These effects are thought to involve multiple mechanisms such as interactions with angiotensin converting enzyme 2 (ACE2), inhibition of the SARS-CoV-2 protease Mpro, modulation of the σ-1 receptor, and suppression of ICAM-1 upregulation.[7-9]

Randomized clinical trials have demonstrated that azelastine nasal spray reduces viral load in patients with laboratory-confirmed SARS-CoV-2 infection, suggesting therapeutic efficacy in the acute treatment of COVID-19.[10,11] These findings, coupled with the proposed mechanisms of action and simulation studies,[12] provide a strong rationale for investigating azelastine as a prophylactic intervention. This study aimed to evaluate the efficacy of azelastine as a preexposure prophylaxis against SARS-CoV-2 and other respiratory pathogens.

### Key Points

**Question** Is regular application of azelastine nasal spray associated with reduced risk of SARS-CoV-2 infections?

**Findings** In this randomized placebo-controlled clinical trial that included 450 participants, the incidence of laboratory-confirmed SARS-CoV-2 infections was significantly lower with application of azelastine nasal spray compared with placebo treatment.

**Meaning** The use of azelastine nasal spray may help to reduce the risk of SARS-CoV-2 infections.

## Methods

### Trial Design and Oversight

The CONTAIN study was a double-blind, placebo-controlled phase 2 clinical trial including 450 healthy volunteers that was conducted at the Department of Internal Medicine V, University Hospital of Saarland. The trial protocol (Supplement 1) was approved by the ethics committee of the Landesärztekammer des Saarlandes (256/22) and the German Federal Institute for Drugs and Medical Devices (BfArM). Prior to enrollment of participants, the trial was registered in the German Clinical Trials Register (DRKS-ID: DRKS00031059; registration date: January 12, 2023) and performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki (Version Fortaleza 2013). For reporting the data of this trial, we followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. The statistical analysis plan is available in Supplement 2.

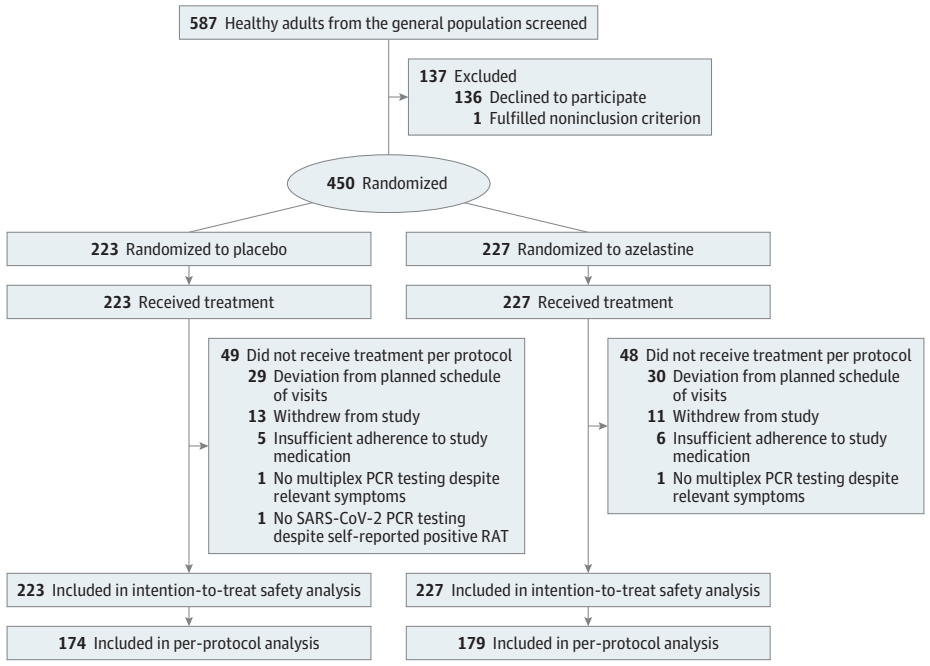
### Participant Selection and Randomization

Healthy volunteers aged from 18 to 65 years with no signs of an acute infection were eligible for inclusion if a SARS-CoV-2 rapid antigen test (RAT) showed negative results. Important noninclusion and exclusion criteria included the prohibition of any additional antihistamine therapy during the treatment period and within 7 days prior to enrollment, and the concomitant use of other nasal products during the treatment period. Participants with a known contraindication to the use of azelastine nasal spray as well as female individuals who were pregnant, breastfeeding, or of child-bearing potential without using adequate contraceptive methods were excluded from study participation. A complete list of the inclusion and noninclusion/exclusion criteria is provided in eTable 1 in Supplement 3. Recruitment was open to the general public. The study was advertised by sending invitations to employees of the hospital, students of the local medical school, through posters at the university campus, and local pharmacies, through a study website and social media. Assignment of the treatment with azelastine, 0.1%, nasal spray vs placebo nasal spray to each treatment number was performed in a centrally conducted, computer-generated 1:1 randomization procedure using permuted blocks, with block sizes of 50. The randomization list was created by the study statistician (D.S.), who was not involved in trial conduct. Allocation was implemented via a secure system and remained concealed from investigators, the sponsor, and site personnel throughout the study. All participants provided written informed consent prior to any trial-related activity. Racial and ethnic data were determined via self-report.

### Trial Interventions and Measurements

Treatment kits were manufactured by URSAPHARM Arzneimittel GmbH, Saarbruecken, Germany, according to the randomization list. Participants were assigned a treatment number in ascending mode according to their chronological order of inclusion. The investigators and trial participants were blinded to the treatment; the investigational medicinal products were identical in appearance. Both nasal sprays were composed of hypromellose, disodium edetate, citric acid, disodium phosphate dodecahydrate, sodium chloride, and purified water. In addition, azelastine, 0.1%, nasal spray was formulated by adding 1 mg/mL azelastine hydrochloride (identical to the commercial antiallergic product Pollival). One puff (0.14 mL) of the respective nasal spray was applied per nostril 3 times per day (morning, midday, and evening) for a mean (SD) of 56 (5) days. This duration was selected to encompass multiple incubation periods of circulating SARS-CoV-2 variants and to enable the detection of infections occurring under clinical conditions.[13] In case of acute respiratory symptoms, confirmed SARS-CoV-2 infection, or knowledge/suspicion of close contact with a SARS-CoV-2-infected person, 1 puff of the nasal spray per nostril was applied 5 times daily over a period of 3 days.

Figure 1. Screening and Randomization




One participant of the placebo group self-reported a positive rapid antigen testing (RAT) result, but this finding could not be confirmed by reverse-transcriptase polymerase chain reaction (PCR) due to home quarantine of this participant. Thus, this participant was considered negative in the intention to treat group and excluded from per-protocol evaluation.

At inclusion, participants were asked about previous infections and their SARS-CoV-2 vaccination status and underwent a first SARS-CoV-2 RAT (Flowflex; ACON Laboratories, Inc). Testing for baseline SARS-CoV-2 serostatus (antibodies directed against nucleocapsid proteins or spike receptor binding domain) using SARS-CoV-2 IgG or SARS-CoV-2 IgG II Quant assays (Abbott) according to the manufacturer's protocols was offered to all participants but was not mandatory for study participation.

Participants were tested twice per week by nasopharyngeal SARS-CoV-2 RAT by trained study personnel until mean (SD) day 56 (5), followed by a final visit. Positive RAT results were confirmed by subsequent SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) testing (cobas SARS-CoV-2; Roche) according to the manufacturer's protocol. In case of a confirmed SARS-CoV-2 infection, participants continued with treatment and daily RAT testing until the test was negative, which concluded their participation in the study. Participants daily documented the use of the investigational product and, if applicable, the occurrence of respiratory symptoms or adverse effects. Participants with symptoms of a respiratory infection classified as clinically relevant and negative SARS-CoV-2 RAT were tested for potential infection with SARS-CoV-2 by RT-PCR and via multiplex-PCRs for human coronaviruses 229E, NL63, HKU1, and OC43, influenza A virus, influenza A (H1N1) virus, influenza B virus, human parainfluenza viruses types 1, 2, 3, and 4, human respiratory syncytial virus (RSV), human metapneumovirus (HMPV), human adenovirus, human bocavirus, human rhinovirus, human enterovirus, human parechovirus, and the bacterial respiratory pathogen *Mycoplasma pneumoniae* (FTD Respiratory pathogens 21, Fast Track DIAGNOSTICS; Siemens Healthineers, after nucleic acid extraction with EMAG; bioMérieux) according to the manufacturer's protocols.

## Trial End Points

The primary end point was the development of SARS-CoV-2 infection through day 56. Secondary outcomes were the development of a symptomatic SARS-CoV-2 infection through day 56, time to SARS-CoV-2 infection, the duration of positivity as documented by a positive RAT, development of symptomatic upper respiratory tract infections through day 56, development of symptomatic infections with the pathogens tested via multiplex PCR through day 56, the frequency, severity, and relationship of adverse events (AEs) to treatment. Several subgroup and exploratory analyses were predefined in the protocol and the statistical analysis plan (eTable 7 in Supplement 3).

## Power Analysis

For the sample size calculation, a mean SARS-CoV-2 attack rate, based on the February to March 2022 data from the study region (7-day incidence of 991 per 100 000), was assumed, with a 200% underreporting adjustment. A 40% reduction in SARS-CoV-2 infections under treatment with azelastine nasal spray was assumed for the analysis. This effect size was considered clinically meaningful and biologically plausible based on multiple sources: a pharmacometric pharmacokinetic/pharmacodynamic modeling study predicted approximately 37% viral load reduction under azelastine treatment, and a large analysis of electronic health records found a 59% lower risk of SARS-CoV-2 positivity in older adults with prior azelastine use.[7,12] The sample size calculation used a significance level of $\alpha = .05$ (1-tailed), with at least 80% statistical power, an as-

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline

| Characteristic | No (%) | |
|---|---|---|
| | Azelastine (n = 227) | Placebo (n = 223) |
| Age, y | | |
| Mean (SD) | 33.0 (13.0) | 34.0 (13.6) |
| Median (range) | 28.0 (18.0-65.0) | 28.0 (19.0-65.0) |
| Sex | | |
| Female | 156 (68.7) | 143 (64.1) |
| Male | 71 (31.3) | 80 (35.9) |
| Race and ethnicity | | |
| African | 2 (0.9) | 2 (0.9) |
| Asian | 7 (3.1) | 15 (6.7) |
| White | 215 (94.7) | 202 (90.6) |
| Other[a] | 3 (1.3) | 4 (1.8) |
| Height, cm | | |
| Mean (SD) | 171 (9.08) | 172 (9.04) |
| Median (range) | 170 (152-194) | 171 (154-197) |
| Weight, kg | | |
| Mean (SD) | 71.9 (15.0) | 72.3 (14.8) |
| Median (range) | 70.0 (41.0-120.0) | 70.0 (46.0-125.0) |
| BMI[b] | | |
| Mean (SD) | 24.4 (4.29) | 24.3 (4.07) |
| Median (range) | 23.5 (15.6-39.4) | 23.6 (17.0-42.0) |
| SARS-CoV-2 vaccinated[c] | | |
| No | 3 (1.3) | 1 (0.4) |
| Yes | 224 (98.7) | 222 (99.6) |
| SARS-CoV-2 vaccinations[d] | | |
| Mean (SD) | 2.97 (0.80) | 3.01 (0.93) |
| Median (range) | 3.00 (1.00-6.00) | 3.00 (1.00-6.00) |
| Last SARS-CoV-2 vaccination, d[e] | | |
| Mean (SD) | 631 (222) | 601 (234) |
| Median (range) | 708 (35.0-1140.0) | 666 (30.0-1230.0) |
| Last SARS-CoV-2 infection, d | | |
| Mean (SD) | 430 (250) | 459 (279) |
| Median (range) | 404 (43.0-1060.0) | 416 (40.0-1240.0) |

Abbreviation: BMI, body mass index.

[a] Other included participants who reported ethnicities not captured by the predefined categories or who did not provide specific classification.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Participants with at least 1 vaccination against SARS-CoV-2 before inclusion.

[d] For participants with at least 1 vaccination against SARS-CoV-2 before inclusion.

[e] Days before study inclusion for participants with at least 1 vaccination.

sumed dropout rate of 5%, and a 1:1 randomization ratio between the placebo and treatment groups. The assumed dropout rate was based on the short study duration. The calculated sample size required 450 participants in total, with 225 individuals per arm. Power calculations were initially based on a 1-sided test to detect a reduction in SARS-CoV-2 infections with azelastine nasal spray. All analyses were 2-sided to account for the outcomes in either direction.

### Statistical Analysis

The primary outcome was the incidence of confirmed SARS-CoV-2 infection, compared between the azelastine and placebo groups using a 2-proportions *z* test. (See Supplement 2 for the statistical analysis plan.) Missing infection outcomes were imputed as "not infected." The risk difference and its 95% CI were calculated. A 2-sided $P < .05$ was considered statistically significant. Scenario-based and tipping point sensitivity analyses were conducted to assess the effect of different assumptions regarding SARS-CoV-2 infection status among participants who discontinued the study (Sensitivity Analysis in Supplement 3). For odds ratio (OR) calculation, the Wald method was used to estimate the 95% CI. Logistic regression was performed to assess the association between PCR positivity and predictor variables (treatment arm, spike levels, and nucleocapsid positivity), using a binomial model with a logit link function. Time-to-event (TTE) analyses of SARS-CoV-2 infection used the Kaplan-Meier estimator and Cox proportional hazard models. For this, participants were censored at dropout or administrative study end. Secondary analyses were not adjusted for multiplicity. All statistical analyses and figure creation were performed using R statistical software (version 4.3.1, R Foundation) with the *epitools* (odds ratios), *survminer* (TTE data) and *ggplot2* packages. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 27.0, and categorized by system organ class and lowest level term.

## Results

### Participants

From March 9, 2023, a total of 587 potential participants were assessed for eligibility, of which 450 healthy volunteers were randomly assigned to a treatment group: 227 to azelastine, 0.1%, nasal spray and 223 to placebo nasal spray (**Figure 1**), with a mean (SD) age of 33.5 (13.3) years. Most were female individuals (299 [66.4%]) and most participants identified as White (417 [92.7%]). Nearly all participants were vaccinated at least once against COVID-19 (441 [99.1%]), with a median (range) of 3 (1-6) vaccinations. The median (range) time since the last vaccination was 672 (30-1230) days. Characteristics at baseline were comparable between both groups (**Table 1**; eTable 2 in Supplement 3). The last visit of the last participant was on July 11, 2024.

The intention-to-treat (ITT) and safety populations consisted of all randomized participants (n = 450), while the per-protocol (PP) population included participants without major protocol deviations (n = 353, Figure 1; eTable 6 in Supplement 3 for details on protocol deviations).

### Efficacy

In the ITT population, which constituted the primary analysis set, the incidence of PCR-confirmed SARS-CoV-2 infection rate (primary end point) was significantly lower in the azelastine group (5 of 227 participants [2.2%]) compared with the placebo group (15 of 223 participants [6.7%]) (risk difference [RD], −4.5 percentage points; 95% CI, −8.3 to −0.7; $P = .02$), translating to an OR of 0.31 (95% CI, 0.11-0.87) (**Table 2**). These

Table 2. Primary and Secondary Outcomes of Azelastine Therapy for Preexposure Prophylaxis

| Outcome | No. (%) | | |
|---|---|---|---|
| | Azelastine (n = 227) | Placebo (n = 223) | Difference/effect estimate (95% CI)[a] |
| **Primary end point** | | | |
| SARS-CoV-2 infections[b] | 5 (2.2) | 15 (6.7) | OR, 0.31 (0.11-0.87) |
| **Secondary end points: SARS-CoV-2** | | | |
| Symptomatic SARS-CoV-2 infections | 4 (1.8) | 14 (6.3) | RD, −4.5 (−8.1 to −0.9) |
| Time to SARS-CoV-2 infection among infected participants, mean (SD), d | 31.20 (9.26) | 19.47 (14.77) | MD, 11.73 (9.45 to 14.01) |
| Duration of RAT positivity, mean (SD), d | 3.40 (1.34) | 5.14 (2.98) | MD, −1.74 (−2.17 to −1.31) |
| **Secondary end points: overall infections** | | | |
| Laboratory-confirmed infections, No. | 21 | 49 | NA |
| Participants with ≥1 laboratory-confirmed infection | 19 (8.4) | 42 (18.8) | NA |
| Self-reported days of illness, mean (SD)/median (IQR) | 1.73 (3.88)/0 (2) | 2.75 (4.64)/0 (4) | NA |
| **Frequency of laboratory-confirmed non-SARS-CoV-2 respiratory pathogens** | | | |
| *Coronaviridae* | | | |
| Human coronavirus HKU1 | 3 (1.3) | 6 (2.7) | NA |
| Human coronavirus OC43 | 3 (1.3) | 5 (2.2) | NA |
| Human coronavirus NL63 | 0 | 1 (0.4) | NA |
| Human coronavirus 229E | 0 | 1 (0.4) | NA |
| *Picornaviridae* | | | |
| Human rhinovirus | 4 (1.8) | 14 (6.3) | NA |
| *Orthomyxoviridae* | | | |
| Influenza A (H1N1) virus | 1 (0.4) | 1 (0.4) | NA |
| Influenza B virus | 0 | 1 (0.4) | NA |
| *Paramyxoviridae* | | | |
| Human parainfluenza virus type 3 | 1 (0.4) | 0 | NA |
| Human respiratory syncytial virus | 0 | 1 (0.4) | NA |
| Human metapneumovirus | 1 (0.4) | 1 (0.4) | NA |
| *Adenoviridae* | | | |
| Human adenovirus | 1 (0.4) | 2 (0.9) | NA |
| *Parvoviridae* | | | |
| Human bocavirus | 1 (0.4) | 1 (0.4) | NA |
| *Mycoplasmataceae* | | | |
| *Mycoplasma pneumoniae* | 1 (0.4) | 0 | NA |

Abbreviations: MD, mean difference; NA not applicable; OR, odds ratio; RAT, rapid antigen testing; RD, risk difference.

[a] Secondary outcomes related to SARS-CoV-2 infections are presented with between-group differences and 95% CIs only; *P* values are omitted. Risk and mean differences are calculated as azelastine minus placebo. Other secondary end points and frequency of infections with other respiratory pathogens are reported descriptively without inferential statistics.

[b] *P* value = .02.

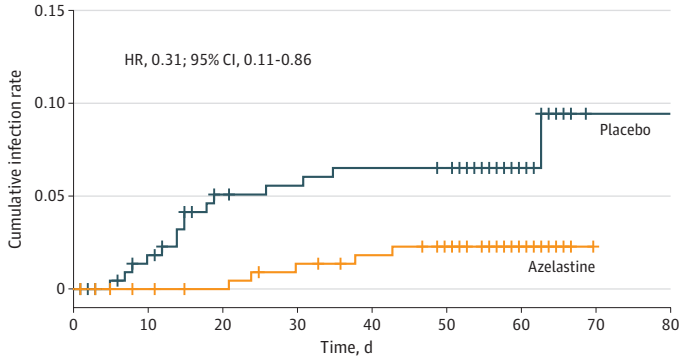
findings were supported by the PP analysis (5 of 179 infections [2.8%] in the azelastine, 13 of 174 [7.5%] in the placebo group; RD, −4.7 percentage points; 95% CI, −9.3 to −0.1 percentage points; *P* = .046; OR, 0.36; 95% CI, 0.12 to 1.02, respectively).

Participants who discontinued the study before completing follow-up were assumed to be uninfected. To assess robustness of the primary finding to missing outcome data, we conducted scenario-based and tipping point sensitivity analyses. Here, statistical significance was lost under some imputation scenarios. However, no scenario resulted in a statistically significant effect favoring placebo (eTable 8, eFigure 4 in Supplement 3).

Several secondary end points related to SARS-CoV-2 corroborated these findings (Table 2). Time-to-event analysis demonstrated a difference in infection rates between the 2 groups with a hazard ratio (HR) of 0.31 (95% CI, 0.11-0.86) (**Figure 2**; eFigure 1 in Supplement 3 for the PP analysis). The incidence of symptomatic SARS-CoV-2 infections was lower in the azelastine group (4 of 227 participants [1.8%]) compared with the placebo group (14 of 223 participants [6.3%]) with a risk difference of −4.5% (95% CI, −8.1% to −0.9%). The mean (SD) time in days to SARS-CoV-2 infection was longer in the azelastine group compared with the placebo group (31.20 [9.26] vs 19.47 [14.77] days) with a mean difference (MD) of 11.73 days (95% CI, 9.45-14.01). The mean (SD) duration of SARS-CoV-2 positivity, as measured by participant-reported RAT, was shorter in the azelastine group (3.40 [1.34] vs 5.14 [2.98] days with an MD of −1.74 [95% CI, −2.17 to −1.31] days).

The incidence of PCR-confirmed human rhinovirus infection was the most frequent non-SARS-CoV-2 infection and here the number of infections was lower in the azelastine group (4 of 227 participants [1.8%]) compared with the placebo group (14 of 223 participants [6.3%], Table 2). Cumulative incidences of rhinovirus infections are displayed in eFigures 2 and 3 in Supplement 3.

Figure 2. Cumulative Incidence of Polymerase Chain Reaction–Confirmed Infection With SARS-CoV-2 Over Time




| No. at risk (censored) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 223 (0) | 215 (5) | 200 (12) | 198 (13) | 196 (13) | 195 (14) | 70 (144) | 1 (207) | 1 (207) |
| Azelastine | 227 (0) | 222 (5) | 220 (7) | 217 (8) | 213 (10) | 210 (13) | 71 (159) | 1 (222) | 0 (222) |

The number at risk is shown below the plot for each treatment arm at different time points. HR indicates hazard ratio.

For other PCR-detected pathogens, including influenza A (H1N1), influenza B, human coronaviruses 229E, NL63, HKU1, OC43, human parainfluenza virus 3, HMPV, human bocavirus, RSV, human adenovirus, and *M pneumoniae*, the number of overall infections was low (n < 10) (Table 2). Influenza A (non-H1N1), human parainfluenza viruses 1, 2, and 4, and human parechovirus, were not detected in either group. Two of the 14 placebo cases who tested positive for rhinovirus also tested positive for enterovirus. As rhinoviruses belong to the genus *Enterovirus* and PCR cross-reactivity may occur, these cases were counted as rhinovirus infections only.

The overall number of PCR-confirmed infections was reduced in the azelastine group compared with the placebo group (21 [9.3%] vs 49 [22.0%]). The total number of participants with laboratory-confirmed infection was also lower in the azelastine group (19/227 [8.4%]) compared with the placebo group (42/223 [18.8%]). Consistently, the mean (SD) number of self-reported illness days was lower in the azelastine group than in the placebo group (1.73 [3.88] vs 2.75 [4.64]). Considering the total length of the study, a lower number of cumulative days of self-reported respiratory illness were observed in the azelastine group (393 of 12 678 total study days, occurring in 67 participants [29.5%]) as compared with the placebo group (613 of 12 443 total study days, occurring in 97 participants [43.5%]).

Because preexisting immunity could influence infection risk, we investigated the association between PCR positivity and baseline serostatus. Among the ITT population, 307 of 450 participants (148 [65.2%] in the azelastine group and 159 [71.3%] in the placebo group) underwent baseline serology testing and showed no difference in nucleocapsid and spike antibody levels between the groups (eTable 2 in Supplement 3). Nucleocapsid-antibody positivity indicating a recent infection[14] was associated with reduced odds of PCR positivity (OR, 0.09; 95% CI, 0.01-0.50; $P$ = .02).

### Safety

The overall incidence of AEs was similar between groups, with 303 events reported in the azelastine group and 367 in the placebo group (**Table 3**; eTable 3 in Supplement 3). AEs assessed by the investigator (T.R., R.B.) as related to the investigational product were more frequent in the azelastine group (94 [0.4 events per participant] vs 41 [0.2 events per participant]), and 61 (26.9%) of participants in the azelastine group experienced at least 1 related AE compared with 25 (11.2%) in the placebo group. This difference largely reflected known adverse effects, including bitter taste (reported by 21 azelastine-treated participants [9.3%] vs 3 [1.3%] in placebo), nosebleeds (15 [6.6%] vs 9 [4.0%]), and tiredness (7 [3.1%] vs 0) (eTable 4 in Supplement 3). Two participants (0.9%) in the azelastine group and 1 participant (0.5%) in the placebo group experiencing AEs discontinued the nasal spray; none of these events were judged to be related to treatment. Serious AEs occurred in 2 participants (0.9%) in the azelastine group—headache recurrent (hospitalization for diagnostic workup) and new diagnosis of Hashimoto thyroiditis—and in 1 participant (0.5%) in the placebo group (knee operation). No serious AE was considered treatment-related, and no deaths were reported.

## Discussion

The data from this double-blind, placebo-controlled study demonstrate that azelastine nasal spray was associated with significantly reduced incidence of laboratory-confirmed SARS-CoV-2 infections in both the ITT and PP populations. Secondary end points further support these findings. Participants applying azelastine had less symptomatic SARS-CoV-2 infections, and an increase in mean time to SARS-CoV-2 infection among infected participants was observed for the azelastine compared with the placebo group. The increase in time to SARS-CoV-2 infection indicates that even in times of higher exposure rates, fewer infections per exposure occurred under treatment compared with placebo. Together, these results suggest that azelastine may provide meaningful protection against SARS-CoV-2 infection in a prophylactic setting. Scenario-based and tipping point analyses demonstrated that the treatment effect was generally robust to missing outcome data with no imputation scenario resulting in a statistically significant effect favoring placebo. The use of a 3 times daily base-

line regimen with optional escalation to 5 times daily in high-risk situations was based on pharmacometric modeling showing increased viral suppression with higher application frequency.[12] Although this modeling was conducted in infected individuals, it supports the mechanistic rationale that sustained and intensified mucosal exposure enhances local antiviral effects, which is relevant to prophylactic use as well. Data on the safety and effectiveness of 2 sprays of azelastine, 0.1%, nasal spray per nostril twice daily for the treatment of moderate to severe seasonal allergic rhinitis[15] as well as the existence of azelastine, 0.15%, nasal spray formulations on the market support the safe use of this medicinal product for longer periods of time.

A reduction in duration of SARS-CoV-2 positivity, as measured by participant-reported RAT, could not be shown in this study. However, such an effect was previously demonstrated in favor of azelastine nasal spray in SARS-CoV-2 infected individuals via quantitative RT-PCR.[10,11]

The reduction of laboratory-confirmed SARS-CoV-2 infections by 67% in the ITT analysis compares well to the efficacy previously reported for vaccines.[16] Monoclonal antibodies, including casirivimab/imdevimab[17] and tixagevimab/cilgavimab,[18] demonstrated efficacy during the pre-Omicron era, but have since lost effectiveness against emerging variants. Although the US Food and Drug Administration recently authorized pemivibart for preexposure prophylaxis in immunocompromised patients, its potency has substantially declined against the latest Omicron sublineages.[19] These challenges highlight the need for alternative approaches, particularly those that are broadly effective against evolving viral variants. Notably, azelastine has demonstrated consistent antiviral activity against all tested SARS-CoV-2 variants in vitro, including the D614G, alpha, beta, delta, and Omicron BA.1 lineages.[5,6] The use of antihistamines for treatment of COVID-19 has been discussed earlier, based on the involvement of histamine pathways during infection and potential direct antiviral effects.[7]

In addition to SARS-CoV-2, azelastine nasal spray showed efficacy against symptomatic rhinovirus infection, the most frequently identified non–SARS-CoV-2 pathogen in this trial. Pharmacological evidence suggests that this effect may be mediated through inhibition of ICAM-1, a major receptor for rhinoviruses.[20] Despite the significant effects of rhinovirus infection on global health, including causing upper respiratory infections and acute exacerbations of chronic pulmonary diseases, there are currently no therapies to treat or prevent rhinovirus infections.[21]

Although the overall incidence of confirmed infections caused by other respiratory pathogens was low in this trial, the pooled analyses of human coronaviruses and all detected respiratory viruses suggest broader antiviral effects of azelastine. In-vitro studies provide evidence of the antiviral activity of azelastine beyond SARS-CoV-2, including endemic coronavirus, influenza and respiratory syncytial virus.[5] Although several modes of action have been described for direct anti-SARS-CoV-2 activities, including interactions with the host cells ACE2- and σ-1 receptors as well as the SARS-CoV-2 protease Mpro,[7,22] a specific panviral mechanism of action remains unknown and indeed a complex interplay of direct and indirect host-cell mediated inhibitory effects seems more likely. The nasal epithelium, as the primary site of viral entry and replication, plays a critical role in the pathogenesis of respiratory viral infections.[23] The ability of locally applied and locally acting azelastine nasal spray to significantly reduce SARS-CoV-2 and overall upper respiratory tract infections underscores the efficacy of topical nasal interventions.

Table 3. Adverse Events in the Safety Analysis Set

| Variable | No. (%) | |
|---|---|---|
| | Azelastine (n = 227) | Placebo (n = 223) |
| Total No. of adverse events | 303 | 367 |
| Total No. of related adverse events | 94 | 41 |
| Participants with ≥1 adverse event | 119 (52.4) | 113 (50.7) |
| Participants with ≥1 related adverse event | 61 (26.9) | 25 (11.2) |
| Participants who discontinued nasal spray due to any adverse event | 2 (0.9) | 1 (0.5) |
| Participants who discontinued nasal spray due to a related adverse event | 0 | 0 |
| Total No. of serious adverse events | 2[a] | 1[b] |
| Total No. of related serious adverse events | 0 | 0 |
| Participants with ≥1 serious adverse event | 2 (0.9) | 1 (0.5) |
| Deaths | 0 | 0 |

[a] Serious adverse events observed in 2 participants were recurrent headache (hospitalization for diagnosis) and a new diagnosis of Hashimoto thyroiditis.

[b] The serious adverse event observed in 1 participant was knee operation.

The safety analysis set included all randomized participants (azelastine, n = 227; placebo, n = 223).

### Limitations

This randomized clinical trial has some limitations. The modest sample size and low incidence of infections for certain pathogens limited the statistical power for subgroup analyses. The PP analysis supported the ITT findings, though its statistical significance should be interpreted with caution given the low number of events. Limitations in the sensitivity of the RAT could have led to underreporting of asymptomatic SARS-CoV-2 infections despite close-meshed testing, in particular for the azelastine group. Such an effect with significant reduction in viral load and lack of symptoms would nevertheless be considered a benefit for the individual and likely result in decreased disease propagation due to the reduction in viral shedding. Symptom-triggered testing for non–SARS-CoV-2 pathogens likely has resulted in underreporting of non–SARS-CoV-2 infections. In addition, the bitter taste of azelastine nasal spray may have unblinded participants, potentially introducing a bias. Conversely, it cannot be ruled out that the placebo had an effect on the probability of infection because rinsing and diluting effects as well as the barrier-stabilizing properties of hypromellose could have contributed to infection prophylaxis.[24] Because this was a single-center trial in a mostly healthy, vaccinated population, the generalizability of the findings to other settings may be limited.

## Conclusions

The findings of this randomized clinical trial suggest that azelastine nasal spray may reduce the incidence of respiratory infections caused by SARS-CoV-2. The established

safety profile, over-the-counter availability, and ease of use of azelastine nasal spray support its potential as a practical, scalable on demand approach to preexposure prophylaxis, particularly in high-risk settings such as large gatherings or travel. Although these findings support the use of azelastine nasal spray as a prophylactic strategy against SARS-CoV-2 infections, larger trials are warranted to confirm efficacy against SARS-CoV-2 and to explore potential benefits against other respiratory pathogens across more diverse populations and settings.

## ARTICLE INFORMATION

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**Group Information:** The CONTAIN Study Group appear listed in Supplement 4.

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