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TITLE PAGE

Protocol Title: A Phase IIIb, single-center, double-blind, two-arms, placebo-controlled, randomized, parallel-group clinical trial to evaluate the efficacy and safety of 2-day pre-treatment with fexofenadine in patients suffering from Seasonal Allergic Rhinitis

Protocol Number: LPS17180 (FEXPRESAR)

Amendment Number: Not applicable

Compound: Allegra® (Fexofenadine HCl)

Brief Title: A placebo-controlled study for 2-day pre-treatment with fexofenadine in seasonal allergic rhinitis

Study Phase: IIIb

Sponsor Name: Opella Healthcare Group SAS

Legal Registered Address: 82, Avenue Raspail, 94250 Gentilly, France.

Regulatory Agency Identifier Number(s):

Registry	**ID**
Universal Trial Number (UTN)	U1111-1278-3949

Approval Date: 21 September 2022

Sponsor Signatory

[redacted]

21 September 2022

[redacted]

Date

Medical Monitor name and contact information will be provided separately.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase IIIb, single-center, double-blind, two-arms, placebo-controlled, randomized, parallel-group clinical trial to evaluate the efficacy and safety of 2-day pre-treatment with fexofenadine in patients suffering from Seasonal Allergic Rhinitis

Registry	ID
Universal Trial Number (UTN)	U1111-1278-3949

Rationale:

Previous and pilot studies have suggested that administration of antihistamines a few days or weeks before the pollen season show a greater inhibitory effect on nasal allergy symptoms in patients with allergic rhinitis (AR) than when taken when symptoms appear.[7, 8] Fexofenadine HCl is a second-generation, non-sedating, histamine H1 receptor antagonist (antihistamine) formulated for oral administration and is approved under different strengths and oral pharmaceutical forms for the relief of symptoms associated with AR in adults, adolescents, and children. This proof-of-concept study will assess fexofenadine as a pre-treatment option. The study will be performed under well-controlled conditions of exposure to Ragweed pollen in participants who experienced pollen allergy confirmed by skin prick tests and challenges tests, with the highest dosage of fexofenadine 180 mg. This study will assess the effect of a 2-day pre-treatment regimen of fexofenadine 180 mg once daily in alleviating AR symptoms and possibly even preventing symptoms.

Objectives and Endpoints:

Objectives	Endpoints
Primary • To evaluate the efficacy of fexofenadine 180 mg when started 2 days before the exposure to the allergen in patients suffering from SAR	• The AUC of the TNSS-3 from H0 to H6 at V4
Secondary • To evaluate the efficacy of fexofenadine when started 2 days before the exposure to the allergen in patients suffering from SAR in terms of preventing nasal and ocular symptoms of rhinorrhea, sneezing, and nasal itching, red/burning eyes, tearing, and itchy/watery eyes	• AUC of TOSS from H0 to H6 at V4 • AUC of TNSS-3 from H0 to H12 at V4 • AUC of TOSS from H0 to H12 at V4 • AUC of TNSS-3 from randomization (D1) to V4 (D4) • AUC of TOSS from randomization (D1) to V4 (D4)

Objectives	Endpoints
Secondary (Contd.) • To evaluate the safety of fexofenadine when started 2 days before the exposure to the allergen in patients suffering from SAR	• Frequency of AEs
Exploratory • [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • [redacted]

Abbreviations: AE = adverse event, AUC = area under the plasma concentration time curve, D = day, H = hour, SAR = Seasonal Allergic Rhinitis, TNSS-3 = Total Nasal Symptom Score of 3 symptoms, TOSS = Total Ocular Symptoms Score, TSS = Total Symptom Score, V = visit.

Overall Design:

This is a Phase IIIb, randomized, double-blind, single-center, two-arm, parallel-group, placebo-controlled, proof-of-concept study, outside of Ragweed pollen season. A total of 5 visits to the study site or the Environmental Exposure Unit (EEU) is planned per participant. At Visit 3, participants will be randomized and be in the study for a total of 5 days. No review committee has been appointed for this study.

Two Arms are planned:

- Arm A (active-active): two days of pre-treatment with fexofenadine, then fexofenadine 180 mg during the test pollen challenge
- Arm B (placebo-active): two days of pre-treatment with placebo, then fexofenadine 180 mg during the test pollen challenge

Each participant will be screened, including skin prick tests at Visit 1 (V1). Eligible participants will return to the study site for a 3-hour pollen exposure (standard Ragweed pollen concentration of 3500 ± 500 grains/m^3) at V2 and discharged thereafter. Only those participants with qualifying symptom scores (Total Nasal Symptom Score of 3 symptoms [TNSS-3] ≥4) in the last 90 minutes of the challenge will be eligible to be randomized into the

study. After a washout period of at least 15 days, randomization will occur at V3 (Day 1) in a 1:1 proportion to either Arm A (active-active) or Arm B (placebo-active) group. Randomization may occur within a week after completion of the washout period, where the participants will be instructed not to take the study drug until 2 days before their planned V4. The participants will consume study drug at home, on Day 2 and Day 3. This will be followed by a Ragweed pollen challenge lasting 3 hours (standard Ragweed pollen concentration of 3500 ± 500 grains/m^3) at V4 (Day 4). During this challenge, participants in both Arms will receive a single dose of fexofenadine 180 mg after pollen exposure, at Hour 3. The participants will be discharged after the challenge at V4 (Day 4). Participants will record their symptoms using a diary card (or an e-diary, if applicable) while in the EEU and at home thereafter. On Day 5, all participants will participate in a telephonic visit, which will be recorded as End-of-Study (EOS) Visit. For return of the e-diary, the participants will come to the study site for an in-person EOS Visit.

Number of Participants:

An adequate number of participants will be screened to achieve 96 participants randomized (86 evaluable participants).

Adult patients (18 to 80 years old) suffering from seasonal allergic rhinitis (SAR) provoked by Ragweed pollen, with a 2-year history of SAR with positive skin prick test to Ragweed allergen at screening (≥3 mm) and having a TNSS-3 of ≥4 (with 3 nasal symptoms) at first pollen challenge at Visit 2 will be enrolled. Any participant with history of anaphylaxis to Ragweed pollen, history of asthma or exacerbations in the past 12 months requiring regular inhaled corticosteroids for >4 weeks per year, any oral corticosteroid usage, any emergency department visit for asthma or any asthma-related hospitalization, or history of chronic sinusitis will be excluded.

Intervention Groups and Duration:

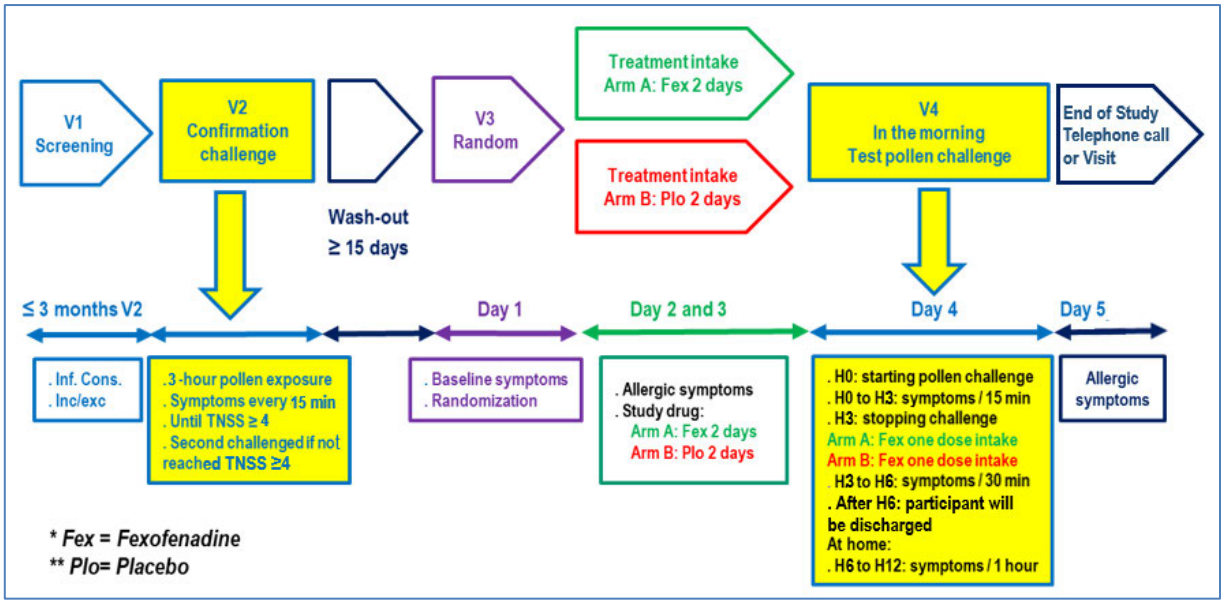
Participants in Arm A (active 2 days) will consume at home, 1 tablet of fexofenadine 180 mg each day in the morning on Day 2 and Day 3, followed by 1 tablet of fexofenadine 180 mg after the pollen challenge on Day 4.

Participants in Arm B (placebo 2 days) will consume at home, 1 tablet of matching placebo each day in the morning on Day 2 and Day 3, followed by 1 tablet of fexofenadine 180 mg after the pollen challenge on Day 4.

Data Monitoring/Other Committee: No

1.2 Schema

Figure 1 Study Schema



Abbreviations: Fex = fexofenadine, FU = follow up, H = hour, Inc/exc = inclusion and exclusion criteria, Inf.Cons. = informed consent, Plo = placebo, TNSS = Total Nasal Symptoms Score, V = visit.

1.3 Schedule of Activities

Table 1 Schedule of Activities

	Screening	Confirmation	Washout	Randomization	Treatment	Pollen Challenge	End-of-study (telephone call or visit)
Day		**Within 3 months after V1**	**≥15 days**	**D1**	**D2 and D3**	**D4**	**D5**
Visits	**V1**	**V2**		**V3**		**V4**	
Informed consent	X						
Inclusion/exclusion criteria	X	X[a]		X[a]		X[a]	
Medical history	X						
Skin prick testing	X						
Urine pregnancy test	X[b]	X[b]		X[b]		Before challenge[b]	
COVID-19 testing[c]		Before challenge				Before challenge	
Physical examination	X					At H6	
Vital signs	X					At H6	
Nasal examination	X					At H6	
Symptoms scoring		X		X	X	X[d]	X
Randomization				X			
Study drug administration					X	X[e] At H3 after challenge	
Diary card (e-diary) completion[f]		X[f]		X[f]	X[f]	X[f]	X[f]
Pollen challenge (EEU)[g]		3-hour pollen exposure[h]				3-hours pollen exposure[i]	
AE recording[j]	X	X	X	X	X	X	X
Concomitant medications[k]	X	X	X	X	X	X	X
Participant satisfaction and recommendation						X[l]	

Abbreviations: AE = adverse event; D = day; COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; EEU = Environmental Exposure Unit; H = hour; Random = randomization; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; Treat = treatment period; V = visit; WO = washout period; WOCBP = women of childbearing potential.

Note: If a participant is not able to visit the study site for any reason (including COVID-19) they should contact the study site by telephone. Adverse event and concomitant medication details may be collected during a telephone call. It may not be possible to collect all clinical laboratory samples or conduct clinical assessments during this time, but any details should be recorded in the eCRF. If alternative arrangements can be agreed for the sample collection or clinical assessments, the details should be documented in the eCRF.

a Exclusion criteria will be re-verified

b For WOCBP only. Urine pregnancy test on V2 and V4 must be performed before challenge.

c COVID-19 rapid antigen test for SARS-CoV-2 infection must be performed before pollen exposure at V2 and V4.

d See Section 4.1.6 for specific time points for symptom scoring at V2 and V4. Scores may be recorded in the e-diary (See Footnote f).

e Participants will have to return their study drug wallet (which was dispensed at V3) before challenge at V4.

f Diary card (or e-diary, if applicable) will be provided at screening and should be completed every day, in the morning. See Section 4.1.6 for specific time points for e-diary completion after discharge on V4. The e-diary will be provided on the participant's own phone or provided device.

g Participants will be exposed to a standard Ragweed pollen concentration of 3500 ± 500 grains/m^3. If in the judgment of the Investigator, symptoms become intolerable the subjects will be removed from the EEU.

h For 3-hour pollen exposure on V2: Pollen exposure begins at H0 and ends at H3.

- H0: Start pollen exposure
- H0 to H3: Allergic symptoms will be recorded every 15 minutes
- H3: Stop pollen exposure and discharge from EEU.

i For 3-hour pollen exposure on V4: Pollen exposure begins at H0 and ends at H3.

- H0: Start pollen exposure
- H0 to H3: Allergic symptoms will be recorded every 15 minutes,
- H3: Stop pollen exposure
- At H3: single dose of fexofenadine180 mg,
- H3 to H6: Allergic symptoms will be recorded every 30 minutes,
- After H6: Participant will be discharged,
- H6 to H12: Allergic symptoms will be recorded every hour at home.

j Adverse events will be collected at every visit.

k Concomitant medications will include rescue medication.

l Participant satisfaction and recommendation will be collected via e-diary. See Section 4.1.6 for time points for this assessment on V4.

2.0 INTRODUCTION

2.1 Study Rationale

If patients have a prior history of seasonal allergic rhinitis (SAR), allergists in the US recommend starting medications to alleviate symptoms before they are expected to begin.[1] Pre-treatment may prevent or reduce allergic rhinitis (AR) symptoms if taken before exposure to a known allergen, or before the allergy season. Taking an H1 histamine receptor antagonist (antihistamine) prior to exposure, might reduce the allergic reaction by stopping the inflammatory cascade and easing AR symptoms.[2]

The Practical Guideline for the Management of Allergic Rhinitis in Japan 2017 recommends that clinicians treat patients with SAR from the beginning of early symptoms, immediately after the start of pollen season. The Chinese clinical guidelines on Allergic Rhinitis published in 2018 states that the use of second-generation antihistamines prior to pollen exposure can improve nasal symptoms and activity by impairment in pollinosis.

Fexofenadine HCl is a second-generation, non-sedating, histamine H1-receptor (H1R) antagonist (antihistamine) formulated for oral administration. It is approved in more than 100 countries worldwide, covering Europe, North America, Central and South America, Australia, Japan, the Middle East, Asia, and Africa. This is a proof-of-concept study assessing the efficacy of fexofenadine as pre-treatment. The study will be performed under well-controlled exposure to Ragweed pollen in an Environmental Exposure Unit (EEU) in participants who experienced pollen allergy confirmed by skin prick tests and challenges tests, with the highest dosage of fexofenadine 180 mg marketed in multiple countries (eg, US and Brazil).

2.2 Background

Allergic Rhinitis is one of the most common types of rhinitis and the most underestimated respiratory condition reported by physicians and patients in terms of prevalence. Its management is often suboptimal and frequently complicated by delayed diagnosis and appropriate treatment. Antihistamines (oral, intranasal) are the most commonly used medications for the relief of AR symptoms, both over-the-counter and by-prescription. Symptom severity and symptom onset were the primary signals to take allergy medications for 47% of adults and 46% of children. Some respondents (12% of adults and 26% of children) started their allergy medications before seasonal symptom onset.[3]

Since SAR due to different allergens is a predictable phenomenon, pre-treatment may benefit these patients as mentioned in the different guidelines.[1, 4]

Currently, applications and websites are available in the public domain, to inform the public about the presence of outdoor allergens such as pollen in the air. More importantly, these can be used to provide data that allows for an accurate prediction of AR symptom development over a period of 48 hours in susceptible individuals and to develop models based on forecasted temperature and concentration of pollen/m^3 to predict hay fever symptoms up to 5 days in advance.[5, 6]

If one has a prior history of indoor or outdoor allergies, allergists recommend starting medications to alleviate symptoms a few days to 2 weeks before they are expected to begin, before the allergy season.

Fexofenadine HCl is a second-generation, non-sedating, antihistamine formulated for oral administration.

The interest of starting the antihistamine treatment before the exposure to the allergen has already been observed, and administration of antihistamines few days or weeks before the pollen season started suggested a greater inhibitory effect on nasal allergy symptoms in patients with AR, than when taken after the symptoms appeared.[7, 8] Accordingly, their administration 2 to 4 weeks before the onset of the pollen season is recommended in patients with pollinosis in Japan. Recently, several lines of evidence have suggested that in addition to their histamine-blocking effect at H1R, antihistamines possess anti-inflammatory activity through a histamine-cytokine network and decrease H1R gene upregulation with suppression of nasal symptoms.[9, 10] A pre-seasonal prophylactic (1 to 4 weeks) treatment with antihistamines suppresses interleukin (IL)−5 but not IL-33 mRNA expression in the nasal mucosa of patients with SAR caused by Japanese cedar pollen, noted in 8 patients versus 17 control patients.[9] These findings suggest that the down-regulation of IL-5 gene expression in collaboration with the suppression of H1R gene expression in the nasal mucosa provides the basis for better therapeutic effects of pre-seasonal prophylactic treatment with antihistamines (Ebastine, Fexofenadine) in patients with pollinosis.

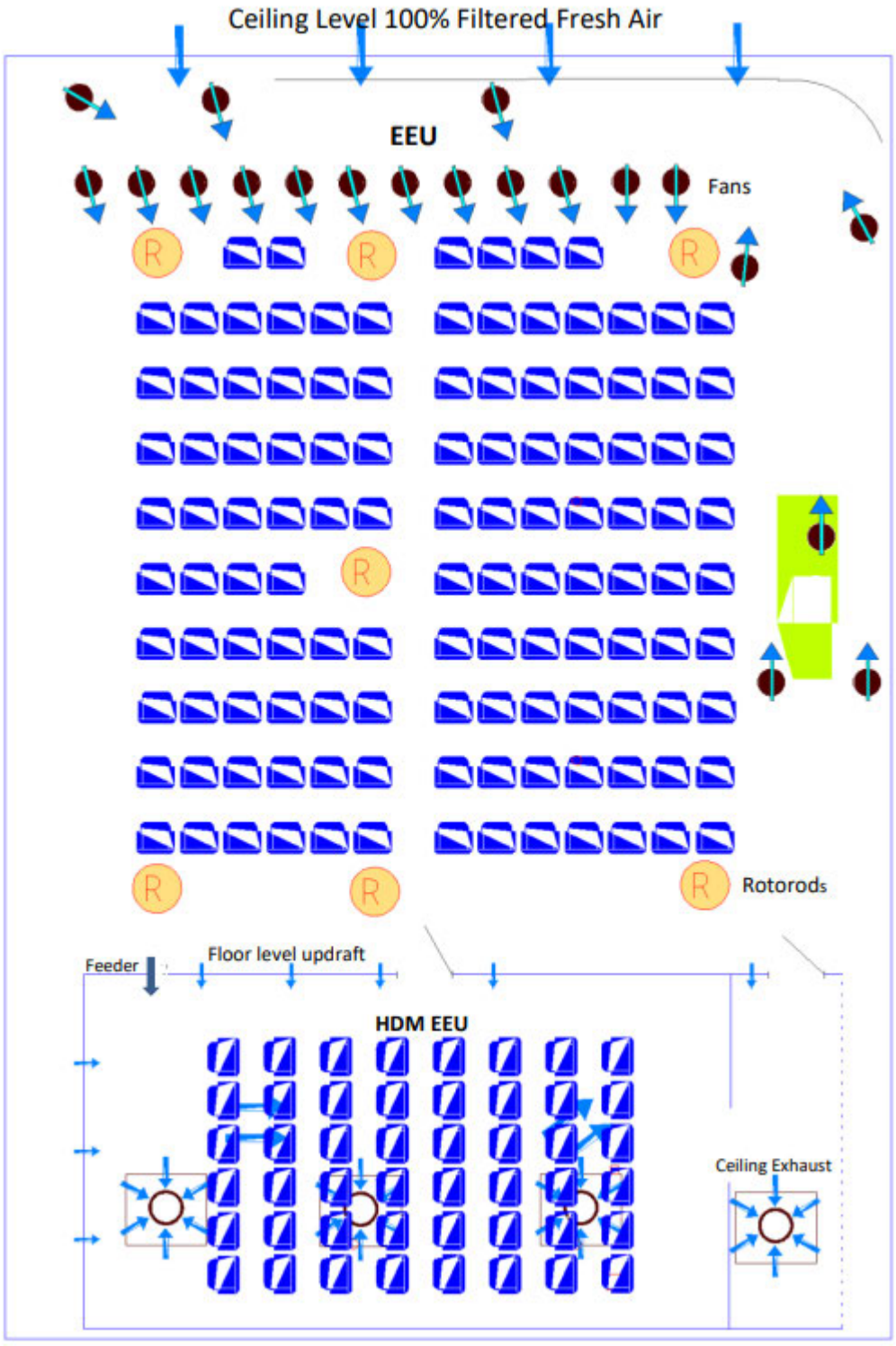
Histamine is a major chemical mediator causing symptoms of pollinosis.[4] Its action occurs mainly through the activation of H1R. Activation of H1R results in the symptoms of AR. The level of H1R gene expression is strongly correlated with the severity of allergy symptoms in patients with pollinosis.[11] Fexofenadine is a well-known, non-sedating antihistamine molecule that binds H1R and prevents histamine binding and subsequent H1R activation. Interestingly, fexofenadine when acting as an inverse agonist, binds the inactive form of H1R and down-regulates constitutive receptor activity, could prevent histamine-induced H1R activation in a more effective manner by shifting the H1R equilibrium toward the inactive state.[12, 13]

In a new in vitro model based on fully reconstituted human nasal epithelium tissue the effect of histamine and relevant biomarkers have been assessed and effect of fexofenadine has been evaluated on inflammatory cytokine, IL-8 and IL-6, as well as the benefits of inverse agonist activity of fexofenadine in prophylactic conditions versus that of concomitant with histamine has been explored. These data suggest that IL-8 and H1R gene expression levels are promising biomarkers of histamine-induced inflammation in human nasal epithelium model. Higher anti-inflammatory activity of fexofenadine (inhibition of IL-8 inflammatory cytokine and down-regulation of H1R gene expression) in prophylactic scenario has been demonstrated; these new findings correlate with inverse agonist fexofenadine mode of action. These data suggest that starting fexofenadine administration prior to allergen exposure before the symptoms appear or while the first symptoms occur could have a protective effect and better control of the intensity of nasal symptoms during allergic episodes.[14]

The study is proposed to be conducted in an EEU. The EEU is a specifically engineered room (Figure 2). The EEU setup includes chairs, feeder, fans, and sampling equipment. A custom-engineered computer and laser-aided system disperses pollen at a single point of delivery. Evaluation of the efficacy of anti-allergic drugs in patients with pollinosis under natural exposure to pollen presents challenges due to unpredictability of various parameters such as pollen concentration, pollen antigenicity, and weather conditions. To overcome these complications, the EEU was developed to meet the criteria of stable environmental conditions including temperature, humidity and pollen concentration, and reproducibility of pollen-induced nasal symptoms. The pollen will be distributed by selectively placed groups of directional fans, over the participant seating area. Ragweed pollen will be sourced from the USA and will be independently tested for fungal and bacterial contamination by a Canadian Center before use in the EEU.[15]

This proof-of-concept study is proposed to assess the effect of a 2-day pre-treatment regimen of fexofenadine 180 mg once daily in alleviating AR symptoms and possibly even preventing symptoms.

Figure 2 Environmental Exposure Unit



Abbreviations: EEU = Environmental Exposure Unit; HDM-EEU = house dust mite unit-Environmental Exposure Unit; R = rotorod.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of fexofenadine may be found in the Summary of Product Characteristics (SmPC).

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, ICH-Good Clinical Practice (GCP), European Union-Clinical Trials Regulations, and applicable regulatory requirements.

2.3.1 Risk Assessment

[redacted]

2.3.2 Benefit Assessment

Potential benefits include contributing to the process of developing a new method of therapy as this study will contribute to the knowledge of AR management for patients and provide evidence of the benefit from pre-treatment for allergy sufferers.

All participants can expect a treatment benefit as they all will have confirmed AR diagnosis, will have demonstrated the occurrence of AR symptoms during the pollen challenge which takes place after screening, and all participants will receive at least 1 dose of fexofenadine during the study, even those in the placebo arm, which they can continue at home after the pollen challenge is over if they wish to. This study may bring a better knowledge about the benefit of pre-treatment for SAR.

[redacted]

3.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints
Primary • To evaluate the efficacy of fexofenadine 180 mg when started 2 days before the exposure to the allergen in patients suffering from SAR	• The AUC of the TNSS-3 from H0 to H6 at V4
Secondary • To evaluate the efficacy of fexofenadine when started 2 days before the exposure to the allergen in patients suffering from SAR in terms of preventing nasal and ocular symptoms of rhinorrhea, sneezing, and nasal itching, red/burning eyes, tearing, and itchy/watery eyes • To evaluate the safety of fexofenadine when started 2 days before the exposure to the allergen in patients suffering from SAR	• AUC of TOSS from H0 to H6 at V4 • AUC of TNSS-3 from H0 to H12 at V4 • AUC of TOSS from H0 to H12 at V4 • AUC of TNSS-3 from randomization (D1) to V4 (D4) • AUC of TOSS from randomization (D1) to V4 (D4) • Frequency of AEs
Exploratory • [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • [redacted]

Abbreviations: AE = adverse event, AUC = area under the plasma concentration-time curve, D = day, H = hour, SAR = seasonal allergic rhinitis, TNSS-3 = Total Nasal Symptom Score of 3 symptoms, TOSS = Total Ocular Symptoms Score, TSS = Total Symptom Score, V=visit.

Estimands: Not applicable.

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase IIIb, randomized, double-blind, single-center, two-arm, parallel-group, placebo-controlled, proof-of-concept study, outside of Ragweed pollen season. Two Arms are planned:

- Arm A (active 2 days): two days of pre-treatment with fexofenadine, then fexofenadine 180 mg during the test pollen challenge
- Arm B (placebo 2 days): two days of pre-treatment with placebo, then fexofenadine 180 mg during the test pollen challenge

A total of 5 visits to the study site or the EEU are planned per participant.

An adequate number of participants will be screened to achieve 96 participants randomized (86 evaluable participants). Each participant will be screened, including skin prick tests at Visit 1 (V1). Eligible participants will return to the study site for a 3-hour pollen exposure (standard Ragweed pollen concentration of 3500 ± 500 grains/m^3) at V2 and discharged thereafter. Only those participants with qualifying symptom scores (Total Nasal Symptom Score of 3 symptoms [TNSS-3] ≥4) in the last 90 minutes of the challenge will be eligible to be randomized into the study. After a washout period of at least 15 days, randomization will occur within a week, at V3 (Day 1) in a 1:1 proportion to either Arm A (active-active) or Arm B (placebo-active) group. Randomization may occur within a week after completion of the washout period, where the participants will be instructed not to take the study drug until 2 days before their planned V4. The participants will consume study drug at home, on Day 2 and Day 3. This will be followed by a Ragweed pollen challenge lasting 3 hours (standard Ragweed pollen concentration of 3500 ± 500 grains/m^3) at V4 (Day 4). During this challenge, participants in both Arms will receive a single dose of fexofenadine 180 mg after pollen exposure, at Hour 3 (H3). The participants will be discharged after the challenge at V4 (Day 4). Participants will record their symptoms using a diary card (e-diary) while in the EEU and at home thereafter. On Day 5, all participants will participate in a telephonic visit, which will be recorded as End-of-Study (EOS) Visit. For return of the e-diary, the participants will come to the study site for an in-person EOS Visit. Any emergency/pandemic concerns in the future will be minimized via use of an e-diary, which is a virtual interface, to document AEs, concomitant medications, symptoms, and the treatment satisfaction questionnaire.

Considering an estimated 10% dropout rate, the number of evaluable subjects for the modified intent-to-treat (mITT) population will need to be 86 participants across both Arms.

4.1.1 Visit 1 (Screening): Within 3 Months Prior Visit 2

The following procedures will be performed:

- Signature of the written Informed Consent
- Inclusion/exclusion criteria verification
- Medical history
- Skin Prick testing to a panel of allergens (Ragweed, dog, cat, *D. pteronyssinus*, *D. farinae*, grass pollens, birch tree pollen)
- Physical examination
- Vital signs
- Nasal examination
- Urine pregnancy testing (for women of childbearing potential [WOCBP] only)
- Prior and concomitant medication recording
- Collection of screening day AEs
- Provision of diary card, ie, electronic Patient-Reported Outcome (e-PRO) diary

4.1.2 Visit 2 (Confirmation Ragweed Pollen Challenge)

Eligible participants will return to the EEU for a 3-hour pollen exposure. The following procedures will be performed:

- Inclusion/exclusion criteria verification
- Coronavirus disease 2019 (COVID-19) testing via a rapid antigen test for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection before challenge
- Urine pregnancy testing (for WOCBP only)
- The participants will be exposed to a standard Ragweed pollen concentration of 3500 ± 500 grains/m^3 for a period of 3 hours (H0 to H3).
- During pollen exposure in the EEU, participants will rate their allergic symptoms every 15 minutes, starting at zero minutes after start of challenge, until 3 hours after start of challenge. Only those participants with qualifying symptom scores (TNSS-3 ≥4) will be eligible to be randomized into the study. In case a TNSS-3 ≥4 is not achieved by H3, the participant can be challenged again if deemed appropriate by

the Investigator. If TNSS-3 ≥4 is still not achieved with the second session the participant is not eligible for study continuation.

- If in the judgment of the Investigator, symptoms become intolerable the participants will be removed from the EEU.
- After 3 hours of challenge: discharge from the EEU
- e-Diary completion
- Concomitant medication recording
- Participants will be questioned with regards to AEs.

Only those participants with qualifying symptom scores (TNSS-3 ≥4) in the last 90 minutes of the challenge will be confirmed for continuing in the study.

4.1.3 Washout Period (≥15 Days)

The following information will be recorded every day preferably in the morning, via e-diary:

- Any AEs
- Concomitant medications

During the washout period of at least 15 days, any antiallergic therapy is forbidden. Please see Section 6.8 for prohibited medications during the study, including the washout period.

4.1.4 Visit 3 (Randomization) Day 1

Randomization may occur within a week after completion of washout period. The following procedures will be performed on Day 1:

- Inclusion/exclusion criteria verification
- Urine pregnancy testing (for WOCBP only)
- E-diary completion
- Concomitant medication recording
- Collection of AEs
- Baseline allergic symptoms scoring
- Randomization will be performed as follows:
    - Arm A: Fexofenadine, one tablet of 180 mg in the morning for 2 days
    - Arm B: Placebo, one tablet in the morning for 2 days

4.1.5 At Home: Day 2 and Day 3 (Study Drug Intake and Diary Card Completion)

The following activities are to be completed at home in the morning on Day 2 and Day 3:

- Diary card (e-diary) completion for:
    - Allergic symptom scores, before drug intake: instantaneous assessments
    - Any AEs
    - Concomitant medications
- Study drug intake

4.1.6 Visit 4 (Test Ragweed Pollen Challenge) Day 4

The following activities are to be completed in the morning:

- Inclusion/exclusion criteria verification
- Urine pregnancy testing (for WOCBP only) before challenge
- COVID-19 testing via a rapid antigen test for SARS-CoV-2 infection before challenge
- Return study drug wallet before challenge
- Symptoms scoring before challenge
- Starting pollen challenge (hour zero [H0]): all participants will be exposed to a standard Ragweed pollen concentration of 3500 ± 500 grains/m^3

If in the judgment of the Investigator, symptoms become intolerable the participants will be removed from the EEU.

- Pollen exposure will last 3 hours (H0 to H3).
    - H0 to H3: symptoms evaluation every 15 minutes
    - At H3: stop pollen exposure
    - At H3 all participants will receive one packet of fexofenadine 180 mg and will be instructed to take one tablet from the pack:
        - Arm A: single dose of fexofenadine 180 mg
        - Arm B: single dose of fexofenadine 180 mg
- H3 to H6: symptoms evaluation every 30 minutes

- At H6:
    - Physical examination
    - Vital signs
    - Nasal examination as per Investigator judgment
- Concomitant medication recording
- Participants will be questioned with regards to AEs
- Participant satisfaction and recommendation
- Discharge from the EEU

Once the participants are discharged, the following procedures will be performed at home on Day 4 (post-test Ragweed pollen challenge):

- Diary card (e-diary) completion:
    - H6 to H12: symptoms evaluation every hour
    - Any AEs
    - Concomitant medications
    - Need of rescue medication
    - Participant satisfaction and recommendation
- The participant can contact the Investigator at any time if necessary

4.1.7 End-of-Study Telephone Call or On-site Visit on Day 5

On Day 5, all participants will participate in a telephonic visit, which will be recorded as EOS Visit. For return of the e-diary, the participants will come to the study site for an in-person EOS Visit. The following will be recorded:

- Allergic symptom scores: instantaneous assessments
- e-Diary card completion
- Return of e-diary in person (if applicable)
- Any AEs
- Concomitant medications, including need of rescue medication

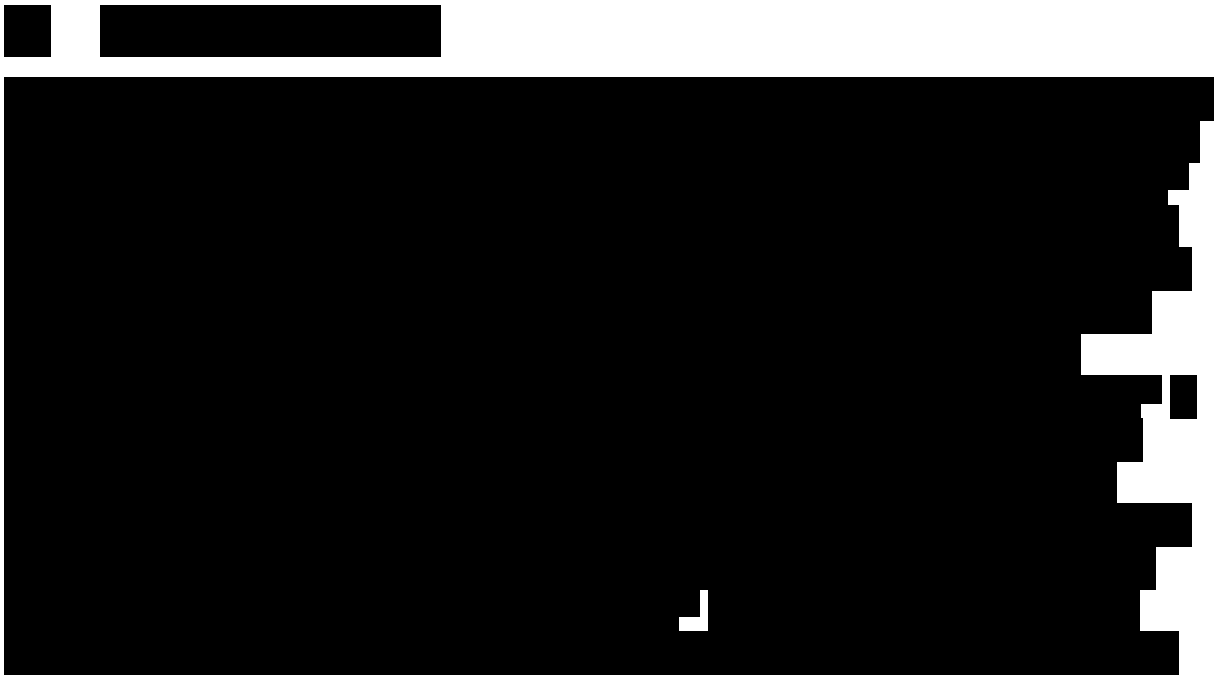
4.2 Scientific Rationale for Study Design

This is a Phase IIIb, randomized, double-blind, single-center, two-arm, parallel-group, placebo-controlled, proof-of-concept study.

A double-blind, randomized, placebo-controlled design is chosen to minimize bias in data collection and interpretation. A washout period of ≥15 days is included between the skin prick test to identify eligible participants and randomization (D1), to prevent carry over of symptoms as well as possible drug effects from previous antihistamine therapy. The patient population to be included in this study is directly relevant to the target population for the intended therapeutic use of the study drug prior to exposure to allergen.

The results of the study will be reported in terms of the statistical significance. It will be important to bridge the gap between statistical and clinical significance to make an informed decision in recommending any intervention.[16] In addition to global ratings, changes in related measures that have established consensus-based thresholds can be used to define the responder threshold for the main criteria measure. In the literature, some different thresholds for the minimum clinically important difference (MCID) have been proposed from 0.5 standard deviation (SD)[17] to 1 SD[18] for the improvement of the Rhinoconjunctivitis Total Symptom Score in grass-pollen-induced AR.

The study will attempt to demonstrate clinical relevance of pre-treatment in the current indication. This requires showing a robust statistical difference when comparing groups with and without pre-treatment. Therefore, the use of placebo in this study is justified and ethical.



[redacted]

4.4 End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all visits of the study including the telephone call/visit on D5.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant is willing to provide written informed consent.
2. Adult patients (18 to 80 years old) suffering from SAR provoked by Ragweed pollen.
3. Patients having a TNSS-3 ≥4 (with 3 nasal symptoms) at first pollen challenge at Visit 2.
4. Having a 2-year history of SAR with positive skin prick test to Ragweed allergen at screening (with a wheal diameter at least 3 mm larger than that produced by the negative control).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. History of anaphylaxis to Ragweed pollen.
2. History of asthma or exacerbations in the past 12 months requiring regular inhaled corticosteroids for >4 weeks per year, any oral corticosteroid usage, any emergency department visit for asthma or any asthma-related hospitalization. Mild asthmatics treated only with pro re nata short-acting β2-agonists, less than 2 doses per week can be enrolled.
3. History of chronic sinusitis, defined as a sinus symptoms lasting greater than 12 weeks that includes 2 or more major factors or 1 major factor and 2 minor factors. Major factors are defined as facial pain or pressure, nasal obstruction or blockage, nasal discharge or purulence or discolored postnasal discharge, purulence in nasal cavity, or impaired or loss of smell. Minor factors are defined as headache, fever, halitosis, fatigue, dental pain, cough, and ear pain, pressure, or fullness.
4. History of systemic disease affecting the immune system such as autoimmune diseases, immune complex disease, or immunodeficiency, where, in the opinion of the study physician, participation in the study would pose a risk or significant effect on the immune system.
5. Presence or history of drug hypersensitivity to fexofenadine and/or its excipients.
6. The use of any investigational drug within 30 days of the EEU procedures.
7. Treatment with any antihistamine within 5 days of screening and within the defined washout period. Subjects receiving build-up injections of pollen allergen immunotherapy are to be excluded, whereas those on stable maintenance dosing can be included.

8. Subjects receiving systemic immunosuppressive treatment should be excluded.
9. Subjects unable to stop the following forbidden treatments/nutriments prior to pollen challenge:
    a. Antihistamines: within 3 days for first-generation antihistamines, within 2 days for second-generation antihistamines.
    b. Intranasal or inhaled corticosteroids: 7 days.
    c. Ocular, intranasal, or inhaled sodium cromoglycate: 14 days.
    d. High doses of systemic corticosteroids: 30 days.
    e. Leukotriene antagonists: 30 days.
    f. Intranasal or systemic decongestants: 3 days.
    g. Tricyclic antidepressants: 7 days.
    h. Any citrus fruits (grapefruit, orange, etc.) or their juices, as well as all fruit juices: 5 days.
    i. Aluminum-and-magnesium containing antacids: 7 days.
    j. Omalizumab/dupilumab: within 6 months
10. Not willing to sit the required time in the EEU during the planned 2 challenge tests. Participants should not be enrolled in any other clinical study.
11. Women of childbearing potential not protected by highly effective method of birth control and/or who are unwilling or unable to be tested for pregnancy (See Section 10.3 for details.)
12. Subjects who, at the discretion of the Investigator, have significant allergy to perennial allergens that cannot be avoided during the study.
13. Subjects with clinically relevant symptoms or a clinically significant illness (in the judgment of the Investigator) in the last 7 days prior to screening through prior to first dosing post pollen challenge at V2. This includes the presence of an active infection requiring systemic antiviral or antimicrobial therapy.
14. History of serious chronic medical conditions which might interfere with treatment or assessments or may pose additional risks from participation in the study.
15. At time of allergen challenge, current symptoms of, or treatment for, an upper respiratory tract infection, acute sinusitis, acute otitis media, or other relevant infectious process; serous otitis media is not an exclusion criterion. Subjects may be re-evaluated for eligibility after symptoms resolve.
16. The presence of any medical condition that the Investigator deems incompatible with participation in the study.
17. Any clinically significant abnormal finding on physical examination or vital signs at screening as deemed so by the Investigator.

18. Any clinically significant physical findings of nasal anatomical deformities (including the presence of nasal mucosal ulceration, nasal polyps, purulent secretions, septal perforation or any other major abnormalities in the nose) which, at the discretion of the Investigator, would interfere with the study procedures.
19. Any history of Grade 4 anaphylaxis due to any cause as defined by the Common Terminology Criteria for Adverse Events (CTCAE) grading criteria ("Life threatening consequences: urgent intervention indicated").
20. History or presence of drug or alcohol abuse at the judgment of the Investigator.
21. Any contraindications to fexofenadine, according to the labeling.

5.3 Lifestyle Considerations

No lifestyle restrictions are required. Participants will be asked to refrain from consumption of any form of alcohol, Seville oranges, Seville orange marmalade, grapefruit, or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 5 days before the start of study drug until after the final dose. Participants will abstain from alcohol for 24 hours prior to V2 and each visit thereafter.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious AE (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5 Criteria for Temporarily Delaying Enrollment, Randomization, or Study Drug Administration

The study schedule includes a visit window up to 3 months post screening, to allow for any emergency situation before randomization into the study.

Once randomized, the participant will be involved in the study for a maximum of 5 days. An e-PRO diary (e-diary) will be available to the participants via a web application on their own device or on a provided device.

The following assessments can be documented remotely, in the event of an emergency/pandemic situation during participation in the study:

- Any AEs
- Concomitant medications
- Allergic symptoms
- Treatment Satisfaction Questionnaire

Frequent and ongoing detailed risk assessments of the impact of the coronavirus infectious disease due to SARS-CoV-2 pandemic on the study will be performed. A risk mitigation plan is in place, which takes into account current knowledge and also potential uncertainties. For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. For details of the contingency plan for maintaining study activities, including site initiation, monitoring, and close-out activities, refer to the study Clinical Monitoring Plan.

The participant should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays, remote collection of data).

6.0 STUDY DRUG(S) AND CONCOMITANT THERAPY

Study drug is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Drug(s) Administered

Table 2 Study Drugs Administered

Study Drug Label	Active drug	Placebo
Study Drug Name	marketed 180 mg fexofenadine HCl	placebo
Study Drug Description	peach, oblong, film-coated oral tablet, with "018" on one side, scripted "e" on the other side.	indistinguishable from active drug
Type	drug	drug
Dose Formulation	tablet	tablet
Unit Dose Strength(s)	180 mg fexofenadine HCl per tablet	0 mg fexofenadine HCl per tablet
Dosage Level(s)	1 tablet once daily	1 tablet once daily
Route of Administration	oral	oral
Use	active drug	placebo
IMP and NIMP/AMP	IMP	IMP
Sourcing	Provided centrally by Sanofi Consumer Health Care	Provided centrally by Sanofi Consumer Health Care
Packaging and Labeling	<u>Randomized, double-blind, placebo-control study part:</u> Fexofenadine HCl 180 mg and matching placebo will be provided as identical film-coated tablets and packaged in child-resistant wallets (containing a blister of 3 tablets of fexofenadine 180 mg or matching placebo – 2 doses and 1 additional tablet in case of loss). <u>Post pollen challenge, open-label study part:</u> Fexofenadine HCl 180 mg will be provided as film-coated tablets and packaged in US commercial Allegra® 5-ct blister packs with open labeling (one pack per participant). The content of the labeling will be in accordance with local regulatory specifications and requirements.	
Current Name	Allegra® (fexofenadine)	Matching placebo

Abbreviations: AMP = auxiliary medicinal product, IMP = investigational medicinal product, NIMP = non-investigational medicinal product.

Table 3 Study Arms

Arm Title	Arm A	Arm B
Arm Type	Active 2 days	Placebo 2 days
Arm Description	During the randomized, double-blind, placebo-control study part, participants will take 1 tablet of fexofenadine 180 mg each day in the morning on Day 2 and Day 3. During the open-label study part, participants will take 1 tablet of fexofenadine 180 mg after the pollen challenge on Day 4	During the randomized, double-blind, placebo-control study part, participants will take 1 tablet of matching placebo each day in the morning on Day 2 and Day 3. During the open-label study part, participants will take 1 tablet of fexofenadine 180 mg after the pollen challenge on Day 4
Associated Study Drug Labels	Active drug	Placebo

6.2 Preparation, Handling, Storage, and Accountability

Allegra® (fexofenadine hydrochloride) tablets should be stored at 15°C to 25°C in a dry place.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study drug.

Until provided to the participants, all study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area at the study site in accordance with the labeled storage conditions with access limited to the Investigator and authorized study site staff. Only participants enrolled in the study may receive study drug, and only authorized study site staff may provide study drug to the participants.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The Investigator, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study drug using the Drug Accountability Form. These forms must be available for inspection at any time.

Any unused/returned study drug should be destroyed at the study site, as per site's standard operating procedures, after study drug accountability, at the end of the study and with Sponsor's approval.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The subject randomization list will be supplied to the study site by the clinical research organization (CRO).

Day 1 to Day 3 (double-blind, placebo-controlled part):

All participants will be centrally assigned to randomized study drug at Visit 3 (Day 1) as per the randomization list. The study site staff will record the subject number allocated at the time of screening and wallet number in the electronic case report form (eCRF). After the individual study drug wallets are assigned, the dispensing staff can ensure their numbers are correct and the participant has not already been randomized. Individual study drug wallets (containing 3 tablets of either fexofenadine or placebo – 2 doses and 1 additional tablet in case of loss) will be dispensed to the participants as assigned. The participants will be instructed by the study staff, to consume 1 tablet of study drug, each on Day 2 and Day 3 at home. The participant will return the used study drug wallet (containing 1 remaining tablet) when they return to the study site on Day 4, before the pollen challenge. Returned study drug should not be re-dispensed.

Day 4 (open-label part, post pollen challenge):

The participants will be exposed to a 3-hour pollen challenge at Visit 4 (Day 4). The study site staff will provide a commercial pack of fexofenadine 180 mg to each participant and instruct the participants to consume only one tablet from the pack. At H3, post pollen challenge, each participant will take the study drug at exactly the same time in the EEU. This time point will be recorded by study staff. The commercial pack of fexofenadine 180 mg with remaining tablets will be returned to the study site staff by each participant before leaving the EEU after completing all assessments at H6.

Stratification

Participants will be randomized to study drug at Visit 2. Stratification of TNSS-3 ≤7/TNSS-3 >7 will be documented in the Statistical Analysis Plan (SAP).

6.3.2 Blinding

This study includes a double-blind study part on Day 1 through Day 3, with limited access to the randomization code. From Day 4 onwards, active study drug will be administered in an open-labeled manner.

Fexofenadine HCl 180 mg and matching placebo will be provided as identical film-coated tablets and packaged in study drug wallets, as described in Table 2. The study site will receive the study drug (fexofenadine and placebo) from the Sponsor. Each study drug wallet will be

labeled in accordance with local Health Authority and Institution requirements. Each study drug wallet will be assigned a Unique Treatment Assignment Number at the time of randomization.

In accordance with the double-blind design, the participants and Investigator will remain blinded to study drug assigned and will not have access to the randomization information (treatment codes) except under circumstances described below.

In case of an AE, the code must only be broken in circumstances when knowledge of the study drug is required for treating the subject. If the code is broken, withdrawal should be discussed on a case-by-case basis. Code breaking can be performed at any time via code-break envelopes. If the blind is broken, the Investigator must document the date, time of day and reason for code breaking.

Method for breaking blind	**Example text to use:**
Blind break (envelopes)	This is a double-blind study in which participants and Investigators are blinded to study drug taken on Day 2 and Day 3. A sealed envelope that contains the study drug assignment for each participant will be provided to the Investigator. The sealed envelope will be retained by the Investigator (or representative) in a secured area. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator may, at his/her discretion contact the Sponsor to discuss the situation prior to unblinding a participant's study drug assignment unless this could delay emergency treatment for the participant. If a participant's study drug assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the Sponsor.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to the Investigator in accordance with local regulations and/or Sponsor policy.

6.4 Study Drug Compliance

All used study drug wallets will be collected by study staff at Visit 4, before pollen challenge, to ensure compliance by tablet counts. Similarly, after the pollen challenge at Visit 4, all open-label, used study drug packs will be collected by study staff to ensure compliance by tablet counts (ie, only 1 tablet taken out of the 5 provided to participants).

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRF.

Noncompliance is defined as taking fewer/more doses than prescribed in the protocol.

A record of the quantity of fexofenadine tablets dispensed to and administered by each participant must be maintained and reconciled with study drug and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5 Dose Modification

Dose modifications are not planned or allowed in this study.

6.6 Continued Access to Study Drug after the End of the Study

The Sponsor will not provide any additional care to participants after they leave the study because such care should not differ from what is normally expected for participants with SAR.

6.7 Management of Overdose

For this study, any dose of fexofenadine HCl greater than 180 mg within a 24-hour time period will be considered an overdose. An overdose (accidental or intentional), ie, symptomatic overdose (serious or nonserious) with the study drug is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as above the maximum recommended dose of 180 mg according to the Allegra®/Telfast® labeling. Of note, asymptomatic overdose should be reported as a standard AE.

The Sponsor recommends that any overdose should be managed by the Investigator as follows:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study drug should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE via a follow-up phone call with the participant until 7 days after Day 5 for AEs and 30 days after Day 5 for both SAEs and AEs of special interest (AESIs).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.8 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- For vaccines (if applicable) include brand name and manufacturer (plus lot number if available)

Any concomitant medications may be considered on a case-by-case basis by the Investigator in consultation with the medical monitor.

6.8.1 Prohibited Medications

The following treatments/nutriments are forbidden before each pollen challenge (See Exclusion criteria 9):

- Antihistamines: within 3 days for first-generation antihistamines, within 2 days for second-generation antihistamines
- Intranasal or inhaled corticosteroids: 7 days
- Ocular, intranasal or inhaled sodium cromoglycate: 14 days
- High doses of systemic corticosteroids: 30 days
- Leukotriene antagonists: 30 days
- Intranasal or systemic decongestants: 3 days
- Tricyclic antidepressants: 7 days
- Any citrus fruits (grapefruit, orange, etc.) or their juices, as well as all fruit juices: 5 days
- Aluminum-and-magnesium containing antacids: 7 days
- Omalizumab/dupilumab: within 6 months

The following medications are prohibited during the study:

- Any antihistamine (during the washout period)
- Beta blockers
- Tricyclic antidepressants

- Monoamine oxidase inhibitors
- Vaccination with live vaccines while on study is prohibited. Administration of inactivated vaccines is allowed (eg, inactivated influenza vaccines or SARS-CoV-2 vaccines).
- Intranasal or inhaled corticosteroids
- Ocular, intranasal or inhaled sodium cromoglycate
- Systemic corticosteroids
- Leukotriene antagonists
- Intranasal or systemic decongestants
- Any consumption of citrus fruits (grapefruit, orange, etc.) or their juices, as well as all fruit juices within 5 days before and during the treatment visit.
- Any administration of aluminum-and-magnesium-containing antacids.

6.8.2 Rescue Medicine

Rescue medication (eg, cetirizine) will be provided to the participants at the discretion of the Investigator, as per clinical judgment in order to manage symptoms. Rescue medication will not be blinded. Separate, open-label packets of marketed drug will be purchased locally by the study site and given to the participants by the study site staff/Investigator, as and when needed.

7.0 DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific study sites or of the study as a whole are detailed in Section 10.1.11.

7.1 Discontinuation of Study Drug

It may be necessary for a participant to permanently discontinue study drug if any of the following criteria are met:

- Important Protocol violation
- Withdrawal of consent by a participant
- Participant is lost to follow-up
- Inadvertent enrollment of a participant
- Pregnancy – see Section 8.3.5
- Termination of the study by the Sponsor

If study drug is permanently discontinued, the participant will remain in the study until EOS on D5. See Section 1.3 for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

If a participant who does not meet enrollment criteria is inadvertently enrolled, that participant must be discontinued from study drug and the Sponsor, or Sponsor designee, must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the participant to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor, or Sponsor designee, to allow the participant to continue in the study.

Participants who discontinue study drug will not be replaced.

7.1.1 Temporary Discontinuation

It may be necessary for a participant to temporarily discontinue study drug, which will be managed by the Investigator on a case-by-case basis.

7.1.2 Rechallenge

It may be necessary for a participant to restart the study drug after temporarily discontinuation, which will be managed by the Investigator on a case-by-case basis.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance, positive COVID-19 test or suspected SARS-CoV-2 infection, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (SoA; Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study drug and the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study site study records.

Participants who voluntarily withdraw are termed dropouts. Dropouts and participants withdrawn due to protocol violations may be replaced following discussion with the Principal Investigator and Sponsor.

Participants withdrawn due to an AE will not be replaced. Subjects who have withdrawn from the study cannot be re-randomized (treated). Their subject and randomization numbers must not be reused.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, via telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local

equivalent methods). These contact attempts should be documented in the participant's study record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Study site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study drug. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Safety results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

8.1 Efficacy Assessments

Participants will score their symptoms as per the United States Food and Drug Administration 2018 guidelines (see Section 10.4), on a scale from zero to 3, where:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living [ADL] and/or sleeping)

The symptoms to be evaluated are rhinorrhea, sneezing, nasal itching, nasal congestion, red/burning eyes, tearing, itchy/watery eyes, and itching of ears/palate or throat.

Composite scores will be determined as per the following:

- Total nasal symptoms score (TNSS-3): the sum of rhinorrhea, sneezing, and nasal itching scores (maximum 9).
- Total ocular symptoms score (TOSS): the sum of red/burning eyes, tearing, itchy/watery eyes scores (maximum 9).

- Total symptoms score (TSS): the sum of rhinorrhea, sneezing, nasal itching, and nasal congestion; red/burning eyes, tearing, and itchy/watery eyes; and itching of ears/palate or throat scores (maximum 27).

8.2 Safety Assessments

The Principal Investigator and staff must register and assess the following variables: AEs, SAEs, AEs leading to discontinuation, and AESIs.

Symptoms assessed for efficacy (including changes in severity): rhinorrhea, sneezing, nasal itching, nasal congestion, red/burning eyes, tearing, itchy/watery eyes, and itching of ears/palate or throat to be considered as AEs as per Investigator's clinical judgment.

8.2.1 Physical Examinations

Physical examination includes at a minimum: head and neck examination, heart and respiratory auscultation; peripheral lymph nodes and abdomen examination.

8.2.2 Nasal Examination

Nasal examination will be performed as follows:

- External inspection: skin changes (eg, skin lesions/ erythema), deformity.
- Internal inspection: nasal mucosa inspection for any abnormalities, nasal cavities alignment:
    - Nasal vestibule: skin changes (eg, ulceration)/ swelling/ asymmetry,
    - Nasal septum: polyps/deviation,
    - Inferior turbinates: asymmetry/inflammation/ polyps.
- Palpation of nasal bones and cartilage for:
    - Alignment,
    - Tenderness or irregularity (if suspicious of fracture in trauma).
- Nasal airflow assessment

8.2.3 Vital Signs

Vital signs include oral body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure. Heart rate, respiratory rate, systolic and diastolic blood pressure will be measured after at least 3 minutes in sitting position.

Vital sign assessments will consist of 1 pulse and 1 blood pressure measurement.

8.2.4 Electrocardiograms

Electrocardiograms will be performed if deemed necessary, as per the Investigator's discretion.

8.2.5 Clinical Safety Laboratory Tests

Routine clinical laboratory testing will be conducted if deemed necessary, as per the Investigator's discretion. A rapid antigen test will be performed before EEU entry, for SARS-CoV-2 infection.

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.6 Pregnancy Testing

Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.

Additional pregnancy testing is not required for this study.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.2.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all SAEs, AEs related to study drug, or AEs that lead to discontinuation from the drug or study (see Section 7.0).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until EOS, at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of the Investigator's awareness of the event, as indicated in Section 10.2 and Section 10.3. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of their awareness of the updated information.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event/cause of death to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting safety reports are provided in Section 10.2 and Section 10.3.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.3.6) will be followed via a follow-up phone call with the participant until 7 days after Visit 5 for AEs and 30 days after Visit 5 for both SAEs and AESIs. Further information on follow-up procedures is provided in Section 10.2 and Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study drug under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, European Union Eudravigilance Database (as applicable), Institutional Review Boards (IRBs)/ Independent Ethics Committee (IECs), and Investigators.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then

file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) and unanticipated adverse device events according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study drug and until 4 days after D5.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy and should follow the procedures outlined in Section 10.3.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication (or elective termination) of a pregnancy for medical reasons will be reported as an AE or SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]) the Investigator will report according to the SAE reporting procedures described in Section 10.3.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor or designee.

Any post-study pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study.

Prior to continuation of study drug following pregnancy, the following must occur:

- The Sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.

- The Investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.3.6 Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

Specific AESI(s) for this study include systemic hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing, and systemic anaphylaxis. Subjects with this diagnosis from Investigator during treatment period are to be advised to avoid use of fexofenadine in the future.

8.3.7 Treatment Satisfaction and Recommendation

The participant's satisfaction of the efficacy of this pre-treatment approach (comparing active drug versus placebo group) will be recorded using a 4-point Numerical Rating Scale:

- 1 = very satisfied
- 2 = satisfied
- 3 = dissatisfied
- 4 = very dissatisfied.

The participant's intention of recommending the pre-treatment approach will be either 'yes' or 'no'.

8.4 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Genetics

Genetics are not evaluated in this study.

8.7 Biomarkers

Biomarkers are not evaluated in this study.

8.8 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.9 Health Economics

Health economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

In order to evaluate the additional benefit in term of efficacy of 2 days pre-treatment before the allergen exposure, the mean area under the plasma concentration-time curve (AUC) of TNSS-3 will be compared between Arm A and Arm B at V4, the following statistical null hypothesis and alternative will be tested:

- H_0: $AUC_{0\text{-}6}$ TNSS-3 of A = $AUC_{0\text{-}6}$ TNSS-3 of B
- H_1: $AUC_{0\text{-}6}$ TNSS-3 of A ≠ $AUC_{0\text{-}6}$ TNSS-3 of B

The study will be positive if the null hypothesis (H_0) is rejected, and the active pre-treatment leads to lowering the symptoms compared to placebo.

9.1.1 Multiplicity Adjustment

The following multiplicity testing procedures will be used to control the type I error:

- The secondary efficacy endpoints will be tested only if the primary endpoint is significant.
- The multiplicity of secondary efficacy endpoints will be handled using Hochberg's step-up test.
- For the other secondary efficacy endpoints and the exploratory efficacy endpoints, p-values will be provided for descriptive purpose only.
- The number of AEs defined as other secondary endpoint will be analyzed only with descriptive statistics (no p-value will be provided).

9.2 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

- Safety population is defined as randomized participants who did receive at least one dose of study drug analyzed according to the treatment actually received.
- The intent-to-treat population will include eligible participants who have been allocated to a randomized treatment regardless of whether the study drug wallet was used or not.

- The mITT population will comprise all eligible, randomized, and treated participants with TNSS-3 evaluation at H0 at V4 and at least a further time point at V4 (main analysis population for the efficacy endpoints).

9.3 Statistical Analyses

9.3.1 General Considerations

In general, the descriptive summary for continuous data will include the number of non-missing observations (n), mean, standard deviation, median, 25th percentile and 75th percentile, minimum, and maximum. The number of subjects with missing data will be displayed when relevant.

In general, categorical data will be summarized for each treatment group using counts (n) and percentages (%). The number of subjects with missing data will be displayed when relevant, but it will not be included in the denominator for the calculation of percentages unless otherwise specified.

Evaluable participants are defined as those who received the Ragweed pollen challenge, with TNSS evaluations at H0 and at least 1 further time point.

The extent of study drug exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

In case of any regional or national emergency declared by a governmental agency during the study, the impact on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of or changes to challenge procedures due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

9.3.2 Primary Endpoint Analysis

All efficacy endpoints analysis will be performed on the mITT population.

The primary analysis will be the comparison of the primary efficacy endpoint (ie, AUC of the TNSS-3 from H0 to H6) between Arm A and Arm B, using an analysis of covariance (ANCOVA) with treatment group as fixed effect and the baseline value of TNSS-3 (ie, at H0 at V4) as covariate. This primary analysis will be conducted on mITT analysis population.

Table 4 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary The AUC of the TNSS-3 from H0 to H6 at V4.	The primary analysis will be the comparison of AUC of the TNSS-3 from H0 to H6 between the Arm A and Arm B, using ANCOVA with treatment group as fixed effect and the baseline value of TNSS-3 (ie, at H0 at V4) as covariate.
Secondary • AUC of TOSS from H0 to H6 at V4 • AUC of TNSS-3 from H0 to H12 at V4 • AUC of TOSS from H0 to H12 at V4 • AUC of TNSS-3 from randomization (D1) to V4 (D4) • AUC of TOSS from randomization (D1) to V4 (D4) • Safety: Frequency of AEs	All secondary endpoints based on the AUC (ie, TSS and TOSS) will be analyzed using an ANCOVA model, with treatment group as fixed effect and the baseline values as covariate. The TNSS-3, TOSS, and TSS will be analyzed using MMRM, with treatment, time point and treatment group by time point interaction as fixed effect with their respective H0 scores as baseline covariate. The TNSS-3, TOSS, TSS, and individual symptom score by time point will be analyzed given the mean and 95% CI. Incidence of treatment-emergent adverse events will be presented in counts and percentages.
Exploratory • [redacted]	The AUC (ie, TSS and TOSS) will be analyzed using ANCOVA of the exploratory endpoints, with treatment group as fixed effect and the baseline values as covariate. The analysis of exploratory endpoints will be conducted on mITT analysis population.

Abbreviations: AE = adverse event, ANCOVA = analysis of covariance, AUC = area under the plasma concentration-time curve, CI = confidence interval, D = day, H = hour, mITT = modified intent-to-treat, MMRM = Mixed Models for Repeated Measures, TNSS-3 = Total Nasal Symptoms Score of 3 symptoms, TOSS = Total Ocular Symptoms Score, TSS = Total Systems Score, V = visit.

Note: A 2-sided alpha-niveau of 5% will be applied for the primary endpoint. Additionally, a 5% significance niveau will be applied for the Hochberg approach.

9.3.3 Secondary Endpoints Analysis

All secondary endpoints based on the AUC (ie, TSS and TOSS) will be analyzed using an ANCOVA of the secondary endpoints, with treatment group as fixed effect and the baseline

values as covariate. The analysis of secondary endpoints will be conducted on the mITT analysis population.

The TNSS-3, TOSS, TSS, and individual symptom score by time point will be analyzed given the mean and 95% confidence interval (CI).

The representation of mean and 95% CI (TNSS-3, TSS, TOSS, and individual symptom score) versus time, by treatment group will be analyzed using Mixed Models for Repeated Measures, with treatment, time point, and treatment group by time point interaction as fixed effect with their respective H0 scores as baseline covariate.

9.3.4 Exploratory Endpoint(s) Analysis

9.3.5 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

The pre-treatment period starts the day of the signed informed consent and ends before administration of study drug.

The treatment-emergent AE period starts at time of administration of study drug ends 3 days after administration of study drug.

All AEs diagnosed by the Investigator will be reported and described.

All AEs will be coded using the version of the Medical Dictionary for Regulatory Activities currently in effect with the Sponsor at the time of the considered database lock.

9.3.6 Study Drug Compliance

A participant will be considered noncompliant if they did not take the planned doses of study drug as required by the protocol. No imputation will be made for participants with missing or incomplete data. The prepared treatment individual package number that has been allocated as per the randomization process and that has actually been administered to the participant will be reported in the eCRF.

Treatment compliance will be summarized by the number and percentage of participants compliant per Arm.

9.4 Interim Analysis

No interim analysis is planned.

9.5 Sample Size Determination

Number of subjects (N) = 96 randomized participants (86 evaluable participants)

All eligible participants will be randomized into 1 out of 2 Arms with the randomization ratio allocation 1:1 as follows:

- Arm A: two days of pre-treatment with fexofenadine, then fexofenadine 180 mg during the test pollen challenge.
- Arm B: two days of pre-treatment with placebo, then fexofenadine 180 mg during the test pollen challenge.

The primary efficacy endpoint is the AUC of TNSS-3 (including rhinorrhea, sneezing, and nasal itching, where each symptom is scored from 0 to 3) from H0 to H6 at Visit 4. The maximum score of TNSS-3 is 9.[2]

The expected benefit of the pre-treatment or the variability of the pre-treatment using the AUC of the TNSS-3 were not published in the literature when the pre-treatment with fexofenadine before allergen exposure has been evaluated.[20] Therefore, given the previous study LPS15332 using TNSS-3, the mean (SD) of the $AUC_{h2\text{-}h12}$ of the TNSS-3 has been estimated to be equal to 26.34 (16.66) on the placebo group and 18.53 (13.73) on the fexofenadine group after 3 hours of pollen exposure in the period 3, thus a common SD, estimated to be equal to 15, has been used for the sample size calculation.[14] An MCID is commonly defined as a 0.55 change on Total Nasal Symptoms Score of 4 symptoms (TNSS-4) when 4 individual symptoms (ie, rhinorrhea, nasal congestion, nasal itching, and sneezing) are measured.[16]

Assuming a common SD=15 and a targeted effect size of 0.70 for the primary endpoint, it will correspond to a difference of AUC of TNSS-3 between Arm A and Arm B of 10.5, which may be interpreted as a difference of TNSS-3 around 2 points between 2 Arms at each time point (which is higher than the MCID of TNSS-3 with 3 individual symptoms). Therefore, at least 86 evaluable patients in both, Arm A and B (ie, included in the mITT population, meaning 43 patients in each arm) are needed to detect a 0.70 effect size for the additional benefit of two days of pre-treatment with fexofenadine on the SAR symptoms with 90% of power and a 2-sided type I error of 5%, using a 2-sample t-test which is assumed to be roughly equivalent

to the primary analysis that will be planned. This sample size has been calculated using EAST6.5 software.

Considering a potential dropout rate of 10% before assessing the primary endpoint, 10 additional patients should be randomized to reach the targeted a total of 86 patients in the mITT population, thus approximately 96 patients will be randomized.

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs, or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study site at which the Investigator has not signed the protocol.

10.1.2 Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study site.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

10.1.3 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4 Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the participants in this study. The terms of the insurance will be kept in the study files.

10.1.5 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study site.

The study record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

10.1.6 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her study records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.7 Committees Structure

No review committee has been appointed for this study.

10.1.8 Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to any relevant database a summary of the results of the clinical study within 1 year from the end of the global clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

10.1.9 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in the eCRF completion guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined in the Clinical Monitoring Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and

requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.

- Details of study monitoring, including action required due to SARS-CoV-2 (COVID-19), will be included in a separate Clinical Operation Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after the completion or discontinuation of the clinical study. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.10 Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the study site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, subject's identity, medical history, nursing notes, physician's notes, etc.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

All data collected in the eCRF should be transcribed directly from source documents. This includes:

- Agreement, date, and signature of informed consent mentioning the study identification
- Subject identification, medical history, associated diseases, and data related to the studied pathology
- Contraception methods for WOCBP
- Previous and concomitant medications
- Study identification
- Date and time of the randomization and study drug administration
- Dates of visits and assessments including the examination report
- Vital signs
- E-diary dispensation date
- E-diary return date
- Study e-diary including symptoms scoring by the subject
- Any AE and follow-up:
  - In case of SAE, the study site staff must file in the source document at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE. The study site staff should make every effort to obtain details of all consultations, hospital records, etc. to document the event. All attempts to obtain information should be noted in the source documents.
- Date of premature study discontinuation (if any) and reason.

10.1.11 Start and Closure of Study and Study Site

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
    - Discontinuation of further study drug development.
- For study site termination:
    - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
    - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
    - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the Regulatory Authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.12 Publication Policy

The study will be performed according to the local legislations and the outcomes will be communicated in congress and in a peer review publication.

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study site will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting for Study Drug

10.2.1 Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence in a clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with that product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of study drug/treatment, whether or not considered related to the study drug/treatment.
Events Meeting the Adverse Event Definition
• Any abnormal safety assessments (eg, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events <u>NOT</u> Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (eg, surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE. • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2 Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

- For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate eCRF.

b. Is life-threatening

- The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- The term congenital anomaly/birth defect means there is suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.2.3 Recording and Follow-up of AE and/or SAE

Adverse Event and Serious Adverse Event Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's study records to the Sponsor or designee in lieu of completion of the applicable/required report form.
- There may be instances when copies of study records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the study records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The intensity of an AE is an estimate of the relative severity of the event made by the Investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE):

AE severity will be evaluated by the Investigator in accordance with the NCI CTCAE v5.0.[a] For AEs that are not adequately addressed in the NCI CTCAE, the Investigator should classify the intensity of the AE using the following guidelines:

- Grade 1: Mild: Aware of sign or symptom, but easily tolerated; no intervention needed.
- Grade 2: Moderate: Discomfort enough to cause interference with usual activity, minimal non-invasive intervention indicated (eg, short course of antibiotics).
- Grade 3: Severe: Medically significant but not immediately life-threatening; incapacitation with inability to work or do usual activity.
- Grade 4: Life-threatening: Refers to an event in which the participant was at risk of death at the time of the event, as judged by the Investigator; urgent/emergent intervention indicated. This

category should not be used for an event that hypothetically might have caused death if it were more severe.

- Grade 5: Fatal outcome.

a Please refer to the CTCAE v5 published on November 2017 at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For causality assessments, events assessed as having a reasonable possibility of being related to study drug will be considered "related." Events assessed as having no reasonable possibility of being related to study drug will be considered "unrelated."
- The Investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of the Investigator's awareness of the information.

10.2.4 Reporting of Serious Adverse Events

Serious Adverse Event Reporting to the Sponsor or Designee via an Electronic Data Collection System

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic data collection system. The study site will enter the event into the electronic data collection system within 24 hours of the Investigator's awareness of the event.
- If the electronic system is unavailable, then the study site will use the paper SAE report form (see next section) to report the event and will enter the event into the electronic data collection system as soon as the system becomes available.
- After the study is completed at a given study site, the electronic data collection system will be taken offline to prevent the entry of new data or changes to existing data.
- If a study site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection system has been taken offline, then the study site can report this information on a paper SAE report form (see next section) to the Sponsor or designee.
- A study specific mailbox will be set up and electronic data capture (EDC) system will be programmed to fire email trigger notifications to the mailbox and the study sites will be given the email address to forward pregnancy reports and back-up SAE paper forms when EDC is down.
- Safety events should be reported to IQVIA at:

  Email: [redacted]

Serious Adverse Event Reporting to the Sponsor or Designee via Paper SAE Report Form

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the paper SAE report form. The study site will submit the SAE report form, via email, within 24 hours of the Investigator's awareness of the event. Facsimile transmission may be utilized as an alternative mode of submission, if necessary.
- Notification of SAE information via telephone does not replace the need for the Investigator to complete, sign and submit the paper SAE report form to the Sponsor or designee within 24 hours of the Investigator's awareness of the event.
- Safety events should be reported to IQVIA at:

  Email: [redacted]

10.2.5 Reporting of Suspected Unexpected Serious Adverse Reactions

Reporting to the Sponsor or Designee via an Electronic Data Collection System

Adverse events which meet ALL of the following criteria:

- Serious
- Unexpected (ie, is not consistent with the currently applicable summary of product characteristics)
- There is at least a reasonable possibility that there is a causal relationship between the event and the study drug

will be classified as SUSARs and should be reported to the relevant ethics committee and to the relevant Health Authorities in accordance with applicable regulatory requirements for expedited reporting. It is the Sponsor's responsibility to report SUSARs to central Ethics Committee and relevant Health Authorities.

10.3 Appendix 3: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

10.3.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    a) Documented hysterectomy.
    b) Documented bilateral salpingectomy.
    c) Documented bilateral oophorectomy.

NOTE: Documentation can come from the study site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female:
    d) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    e) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2 Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal.

• Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device. • Intrauterine hormone-releasing system. • Bilateral tubal occlusion.
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 4 days after study completion.

Pregnancy Testing:

- A WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.
- Additional pregnancy testing should be performed at times specified in the SoA and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of 25 mIU/mL (urine test) will be performed at the study site.

Collection of Pregnancy Information

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery

date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the Investigator will report according to the SAE reporting procedures described in Section 10.2.
- Any post-study pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to the Sponsor or designee as described in Section 10.2. While the Investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study.

Reporting Pregnancy Information

Email transmission of the paper Pregnancy Report Form is the preferred method to transmit safety event information to IQVIA with facsimile as a back-up method, if necessary. A study specific mailbox will be set up and EDC will be programmed to fire email trigger notifications to the mailbox and the study sites will be given the email address to forward pregnancy reports when EDC is down. All pregnancy events should be reported to IQVIA at:

Email: [redacted]

10.4 Appendix 4: Evolution of Seasonal Allergic Rhinitis Symptoms, Following United States Food and Drug Administration Guidelines 2018

Instantaneous Symptoms Scores

Participants will evaluate their symptoms intensity and will score their symptoms using the below rating scale:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Symptoms to be evaluated: rhinorrhea, sneezing, nasal itching, nasal congestion, red/burning eyes, tearing, itchy/watery eyes, and itching of ears/palate or throat.

Composite scores:

- Total Nasal Symptoms Score (TNSS-3): the sum of rhinorrhea, sneezing, and nasal itching scores (maximum 9).
- Total Ocular Symptoms Score (TOSS), the sum of red/burning eyes, tearing, itchy/watery eyes scores (maximum 9).
- Total Symptoms Score (TSS): the sum of rhinorrhea, sneezing, nasal itching, and nasal congestion; red/burning eyes, tearing, and itchy/watery eyes; and itching of ears/palate or throat scores (maximum 27).

Treatment Satisfaction and Recommendation

Participant satisfaction of the efficacy of this pre-treatment approach (compared with the first challenger) will be rated using a 4-point Numerical Rating Scale

- 1 = ‘very satisfied’
- 2 = ‘satisfied’
- 3 = ‘dissatisfied’
- 4 = ‘very dissatisfied’

At the end of the study, the participant’s intention of recommending the pre-treatment approach: ‘yes’ or ‘no’.

10.5 Appendix 5: Abbreviations

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AR	Allergic rhinitis
AUC	Area under the plasma concentration-time curve
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
EDC	Electronic data capture
EEU	Environmental Exposure Unit
EoS	End-of-Study
e-PRO	electronic Patient-Reported Outcome
DSUR	Development Safety Update Report
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
H	Hour
H1R	histamine H1 receptor
HRT	Hormone replacement therapy
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
MCID	minimum clinically important difference
mITT	modified intent-to-treat
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Seasonal allergic rhinitis
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SoA	Schedule of activities
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TNSS-3	Total Nasal Symptoms Score of 3 symptoms
TOSS	Total Ocular Symptoms Score
TSS	Total Symptom Score
V	Visit
WOCBP	Women of childbearing potential

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Signature of Investigator

PROTOCOL TITLE: A Phase IIIb, single-center, double-blind, two-arms, placebo-controlled, randomized, parallel-group clinical trial to evaluate the efficacy and safety of 2-day pre-treatment with fexofenadine in patients suffering from Seasonal Allergic Rhinitis

PROTOCOL NO: LPS17180 (FEXPRESAR)

VERSION: Original Protocol

This protocol is a confidential communication of The Sponsor. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study site in which the study will be conducted. Return the signed copy to IQVIA.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: [redacted]

Investigator Title: _____

Name/Address of Center: [redacted]

Kingston, Ontario, K7L 2V7, CANADA.