AZFL-AES-4-001 / C1D00571

CLINICAL STUDY PROTOCOL

Protocol Title	Clinical Trial to Assess Onset of Action of Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray Delivered in a Single Spray (Dymista) in the Treatment of Allergen-Induced Allergic Rhinitis Symptoms in Comparison to Placebo in an Environmental Exposure Unit (EEU)
Short Title	Dymista Allergen Chamber
Protocol Number	AZFL-AES-4-001
Cliantha Study Code	C1D00571
Product	Dymista
Study Type	Phase IV (post-authorization)
Version	3.0
Protocol Date	27 Jul 2021
EudraCT no.	Not applicable
IND no.	077363
Legal/Filing Sponsor	Meda Pharma GmbH & Co. KG (A Viatris company) Benzstrasse 1, 61352 Bad Homburg, Germany

Confidentiality:

ClinicalTrials.gov Identifier: NCT04652245

DOCUMENT HISTORY

Document Version, Date	Summary of Changes with Rationale
1.0 21 October 2020	Original
2.0 03 March 2021	• To keep generalised wording for COVID-19 testing • To adapt planned study period • To correct end of study defininition in Section 4.1 • To update e-mail addresses from ‘mylan.com’ to ‘viatris.com’
3.0 27 Jul 2021	• To include wash-out period for COVID-19 vaccination • To adapt planned study period • To change signatures from Adobe signature to electronic signature in the sponsor’s document manangement system • To perform administrative changes (update company name from ‘Mylan’ to ‘Viatris’, remove company logo, update department names and job titles, minor clarifications and removal of typographical errors)

PROTOCOL REVISION HISTORY

The following table summarizes the updates made from Protocol Version 1.0 (21 Oct 2020) to Protocol Version 2.0 (03 Mar 2021)

Section: Protocol Synopsis	
From: Study Period Planned: December 2020 – April 2021	**To:** Study Period Planned: December 2020 – July 2021
Rationale to change: Recruitment is delayed due to COVID-19 restrictions and study period needs to be extended to reach the planned number of subjects.	

Section: Study Diagram and Study Schedule of Activities **Table 0-1 Study Schedule** (Footnote 11)	
From: Will be performed within 5 days prior to Visit 2 and Visit 4 to ensure the subjects safety prior to entering the EEU	**To:** Will be performed within 5 days prior to Visit 2 and Visit 4 or on the day of Visit 2 and 4 for a COVID-19 test to ensure the subjects safety prior to entering the EEU
Rationale to change: So as to add an option for COVID-19 testing to be done on the day of Visit 2 and Visit 4 using Health Canada approved Rapid testing kit.	

4.1 Study Population	
From: The duration of the study from screening (Visit 1) to end of study (Visit 5) will last up to 56 days for each subject (duration may be longer if re-priming is required).	**To:** The duration of the study from screening (Visit 1) to end of study (telephone follow-up) will last up to 56 days for each subject (duration may be longer if re-priming is required).
Rationale to change: Correction of the explanation for the end of study given in brackets in accordance with other sections of the protocol (e.g. Synopsis and Section 3.4). Up to now Note to File note was issued for this correction.	

6.2.1 Priming/Screening (Period 1, Visit 2) – Day -1	
From: A COVID screening questionnaire with oral temperature will be performed and results of COVID test (PCR) performed within 5 days prior to this visit will be checked.	**To:** A COVID screening questionnaire with oral temperature will be performed and results of COVID test performed within 5 days prior to this visit or on the day of Visit 2 will be checked.
Rationale to change: So as to add an option for COVID-19 testing to be done on the day of Visit 2 and Visit 4 using Health Canada approved Rapid testing kit.	

6.2.3 Priming EEU (Period 2, Visit 4) – Day 13 (+ 5 Days)	
From: A COVID screening questionnaire with oral temperature will be performed and results of COVID test (PCR) performed within 5 days prior to this visit will be checked.	**To:** A COVID screening questionnaire with oral temperature will be performed and results of COVID test performed within 5 days prior to this visit or on the day of Visit 4 will be checked.
Rationale to change: So as to add an option for COVID-19 testing to be done on the day of Visit 2 and Visit 4 using Health Canada approved Rapid testing kit.	

Table 7.3 1 Clinical Laboratory Variables	
From: • Pregnancy[3] (urine): females of childbearing potential only • FSH[2] (blood): if necessary to document postmenopausal status • COVID[4] (nasopharyngeal/oropharyngeal)	**To:** • Pregnancy[3] (urine): females of childbearing potential only • FSH[2] (blood): if necessary to document postmenopausal status • COVID[4] (nasopharyngeal/oropharyngeal/nasal)
Rationale to change: COVID -19 rapid test are conducted using in nasal swab.	

Table 7.3 1 Clinical Laboratory Variables (Footnote 4)	
From: Performed within 5 days prior to Visit 2 and Visit 4	**To:** Performed within 5 days prior to Visit 2 and Visit 4 or on the day of Visit 2 and 4
Rationale to change: So as to add an option for COVID-19 testing to be done on the day of Visit 2 and Visit 4 using Health Canada approved Rapid testing kit.	

Other Changes
• Table of content and abbrevations list updated along with the version and date of the protocol. • E-mail addresses updated from ‘mylan.com’ to ‘viatris.com’ throughout the protocol.

The following table summarizes the updates made from Protocol Version 2.0 (03 Mar 2021) to Protocol Version 3.0 (27 Jul 2021)

Section: Protocol Synopsis and 4.2.2 Exclusion Criteria (Table for prohibited medication)

Addition:

Prohibited medication	Prior to Screening	During study
COVID-19 vaccination	No restrictions	Within 3 days prior to each allergen challenge[2]

[2] If there is a conflict with the next allergen challenge due to COVID-19 vaccination, a delay of up to 3 days for Visit 2 or Visit 4 is allowed. However, the interval between Visit 2 and Visit 3 or Visit 4 and Visit 5 must not be changed.

Rationale for the addition: Added due to increasing COVID vaccinations in the Canadian population. A 3 days washout after COVID vaccination is considered to rule out possible systemic adverse events that may arise due to the vaccination. Clinically, during this period a subject can possibly experience a systemic side effect to vaccine that can impact their study participation. Any local reaction to the vaccination site is not an issue and can be deemed acceptable for subject to continue with the study.

Section: Protocol Synopsis

From:	To:
Study Period Planned: December 2020 –July 2021	Study Period Planned: December 2020 – January 2022

Rationale to change: Recruitment was delayed due to COVID-19 restrictions and it was not possible to randomize the planned number of subjects within the seasonal non-allergy period. Therefore, it was decided to set the study on hold and to resume after the end of this year's ragweed season (i.e. September 2021 at the earliest).

Section: Protocol Approval

From:	To:
Electronic signature	*See Electronic Signature Manifestation*

Rationale to change: According to sponsor's SOP, signatures should be undertaken within the document management system.

Other Changes (Administrative)

- Removed company logo from the header throughout the protocol.
- Updated company name from 'Mylan' to 'Viatris' throughout the protocol.
- Updated department names and job titles on the Protocol Approval page.
- Minor clarifications and removal of typographical errors.

PROTOCOL SYNOPSIS

Protocol Title	Clinical Trial to Assess Onset of Action of Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray Delivered in a Single Spray (Dymista) in the Treatment of Allergen-Induced Allergic Rhinitis Symptoms in Comparison to Placebo in an Environmental Exposure Unit (EEU)
Short Title	Dymista Allergen Chamber
Protocol Number	AZFL-AES-4-001
Cliantha Study Code	C1D00571
Study Sites	Headquarters: Cliantha Research 1310 Fewster Drive Mississauga, ON L4W 1A4, Canada Location of the allergen chamber: Cliantha Research 4500 Dixie Road Mississauga, ON L4W 1V7, Canada
Study Period Planned	December 2020 – January 2022
Duration of Individual Treatment	The duration of the study will last up to 56 days for each subject (duration may be longer if re-priming is required). In the study, there will be single dose administrations on two separate occasions with at least 14 days wash-out between each treatment
End of Study	Date of last contact of the last subject undergoing the trial
Background and Rationale	Patients with allergic rhinitis have high expectations of anti-allergic treatment (Hellings et al. 2012). Highly effective medications with early onset of action may improve patient's compliance with therapy. Pivotal trials showed that under clinical conditions, Dymista becomes efficacious within the first 30 minutes and more effective than the monoproducts (M1). However, these studies were standard phase III allergic rhinitis efficacy trials and they were not specifically designed to assess onset of action, the primary endpoint was treatment effect over 2-week treatment. The assessment of onset of action was done during 4-hour observation period following the initial administration of trial drug at study sites under indoor conditions with considerably low pollen exposure. Therefore, clinical trial X-03065-3311 using a standardized EEU (synonym to environmental exposure chamber - EEC) model with measurement timepoints starting from 5 minutes after administration was performed. The EEU was used to promote a uniform aerosolization of allergen over time in a highly controlled

	manner with limited confounding environmental factors. In this trial, Dymista started relieving nasal symptoms within 5 min and ocular symptoms within 10 minutes of dosing. All individual nasal and ocular symptoms reached first statistical significance at early time points and thus contributed to the overall effects of Dymista (Bousquet et al. 2018, O1). The aim of the current study is to replicate the results of the fast onset of action for Dymista in a second onset of action study using an EEU model with a similar design but without an active control. The study design and requirements have been adapted from Principles of the U.S. FDA draft guidance "Allergic Rhinitis: Developing Drug Products for Treatment Guidance for Industry" September 2018 for evaluating onset of efficacy (R1).
Primary Objective	• To assess the onset of action of a fixed combination of azelastine hydrochloride and fluticasone propionate nasal spray (Dymista) in relieving the nasal symptoms of seasonal allergic rhinitis (SAR) induced by an allergen challenge in an Environmental Exposure Unit (EEU)
Primary endpoint	For onset of action assessment: • Changes from baseline in TNSS at each post-dose assessment time point (0 to 4 hours p.a.)
Secondary Objectives	• To assess onset of action of Dymista in relieving the ocular symptoms of SAR induced by an allergen challenge in an EEU • To assess onset of action of Dymista in relieving the combined nasal and ocular symptoms of SAR induced by an allergen challenge in an EEU • To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the nasal symptoms (TNSS) with that of placebo • To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the ocular symptoms (TOSS) with that of placebo • To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the combined nasal and ocular symptoms (T7SS) with that of placebo • To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the individual nasal and ocular symptoms with that of placebo • To evaluate time to relevant response to therapy (30% and 50% reduction of TNSS)
Secondary Endpoints	Efficacy: • Changes from baseline in TOSS and total 7 symptoms score (T7SS) at each post-dose assessment time point (0 to 4 hours p.a.) • Time courses of TNSS, TOSS, and T7SS during the 6.5-hour EEU session • Change from baseline in individual nasal symptom scores (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptom scores (itchy eyes, watery eyes, eye redness) at each post-dose assessment time point (0 to 4 hours p.a.) Safety and tolerability: • Adverse events (AEs) • Vital signs

<table>
<tr><td>Methodology</td><td>The study will be a single-center, randomized, placebo-controlled, double-blind, and two-period cross-over trial.

The study will consist of a screening visit (Visit 1), which will take place on Day -28 to Day -2. A priming/screening visit will be performed at Visit 2 (Day -1), where subjects will record their individual nasal and ocular symptoms using an electronic diary (ePDAT™) prior to EEU entry and during a 2-hour ragweed EEU session (see Table 0-2 for time points). At Visit 2, if subjects meet a minimum threshold total nasal symptom score (TNSS) response of ≥ 6 out of a possible of 12 at least twice, with at least one occurring during the last 2 time points, as well as a score of at least 2/3 for runny nose at least twice, with at least one occurring during the last 2 time points, during hours 0-2 in the EEU, they will be eligible to attend Visit 3.

At Visit 3 (Day 1), subjects will record their individual nasal and ocular symptoms using an electronic diary (ePDAT™) prior to EEU entry and during the ragweed EEU session (see Table 0-3) for the first 2 hours. Subjects who meet the predetermined minimum TNSS of ≥ 6 out of a possible 12 at least twice, with at least one occurring during the last 2 time points, as well as a score of at least 2/3 for runny nose at least twice, with at least one occurring during the last 2 time points, during hours 0-2 in the EEU, and with nasal passages that are not completely blocked on either one or both sides as assessed by the Investigator within 30 minutes prior to dosing, will be randomized to a treatment sequence. They will receive a single-dose of the first study treatment approximately 2.5 hours after entering the EEU. The ragweed EEU session will be continued over the next 4 hours with subjects recording their individual nasal and ocular symptoms using an electronic diary (ePDAT™) (see Table 0-3).

Subjects will return to the study site after a period of at least 12 days (+ 5 days). The procedures at Visits 4 and 5 (Period 2) will be identical to Visit 2 and Visit 3, respectively, except that subjects will not need to meet a minimum threshold value for TNSS. Subjects will be assessed for complete nasal blockage within 30 minutes prior to dosing. Any evidence of complete nasal blockage on one or both sides prior to dosing should be documented in the eCRF. Subjects will receive the alternate study treatment in the second period. Throughout the study, the Investigator will adequately treat and follow up on adverse events.</td></tr>
<tr><td>Study Treatment</td><td>
<table>
<tr><th>Study Treatment</th><th>Dose and Mode of Administration</th></tr>
<tr><td>Dymista = fixed drug combination of azelastine hydrochloride and fluticasone propionate nasal spray</td><td>Active Drug: 1 spray per nostril of Dymista for a total dose of 274 mcg azelastine hydrochloride plus 100 mcg of fluticasone propionate</td></tr>
<tr><td>Placebo = nasal spray with no active dose (Dymista vehicle)</td><td>Placebo: 1 spray per nostril of placebo nasal spray</td></tr>
</table>
The blinded study treatment will be given to suitable subjects on Visits 3 and 5 approximately 2.5 hours after the start of the EEU session.</td></tr>
<tr><td>Inclusion/ exclusion criteria</td><td>Inclusion criteria:
To be eligible for the study, a subject must comply with all of the following criteria at screening (Visit 1):</td></tr>
</table>

	1. Provide written informed consent. 2. Male or female subjects (childbearing and non-childbearing potential, non-childbearing potential defined as females with no menstruation for at least 1 year at screening and documented FSH > 35 IU/L) aged 18 to 55 years (inclusive) at screening. 3. History of SAR to ragweed pollen for at least the previous 2 ragweed pollen seasons. 4. Positive skin prick test (SPT) response to ragweed pollen (allergen induced wheal diameter at least 3 mm larger than the negative control). A test performed at Cliantha Research in the previous 12 months may be used to qualify the subject. 5. Willingness to complete all study visits. To be eligible for Visit 2 EEU, a subject must additionally comply with the following criteria: 6. Asymptomatic or with mild symptoms during the baseline recording of symptoms prior to start of the screening EEU (Visit 2): • TNSS ≤ 3/12 with the score for each symptom being less than 2. To be eligible for Visit 3, a subject must additionally comply with the following criteria during Visit 2 EEU: 7. Demonstrate adequate symptomology: • TNSS ≥ 6/12 on at least two ePDAT™ time point assessments during hours 0-2 in the EEU (Visit 2), with at least one occurring during the last two time points. Additionally, subjects will be required to meet a score of at least 2/3 for runny nose at least twice during hours 0-2 in the EEU, with at least one occurring during the last two time points. To be eligible for randomization (Visit 3), a subject must additionally comply with the following criteria: 8. Demonstrate adequate symptomology: • TNSS ≥ 6/12 on at least two ePDAT™ time point assessments during hours 0-2 in the EEU (Visit 3), with at least one occurring during the last two time points. Additionally, subjects will be required to meet a score of at least 2/3 for runny nose at least twice during hours 0-2 in the EEU, with at least one occurring during the last two time points. • No evidence of complete nasal blockage on either one or both sides on anterior rhinoscopy within 30 minutes prior to dosing. **Exclusion criteria:** A subject is ineligible and must not enter the study if any of the following criteria is met: <u>Safety concerns:</u> 1. History of allergic reaction to azelastine hydrochloride or fluticasone propionate or one of the excipients of the study treatments (e.g. benzalkonium chloride, phenylethyl alcohol, microcrystalline cellulose) or a component of the container. 2. History of anaphylaxis, cardiovascular, pulmonary, hepatic, renal, gastrointestinal, hematological, endocrine, metabolic, psychiatric,

neurological, or other disease at screening that may affect subject safety during the study or evaluation of the study endpoints at the discretion of the Investigator and/or designee.

3. Subjects with a current diagnosis of asthma or subjects with measured FEV_1 <75% of the predicted value using Global Lung Function Initiative set from 2012 for references.
4. Pregnant, breast-feeding, or planning a pregnancy during the study and women of childbearing potential not using adequate contraception. Women of childbearing potential not abstinent or using a highly effective method of birth control defined as those which result in a low failure rate (i.e. <1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, hormonal IUDs, barrier methods, or tubal ligation started at least 4 weeks prior to screening.

Lack of suitability for the study:

5. Previous and concomitant treatments: use of prohibited therapies as specified in the following table; use of any medication considered to have an influence on the outcome of the study during the EEU session, at the discretion of the Investigator and/or designee.

Prohibited medication	Prior to Screening	During study
Antihistaminic agents, all presentations	1 week	Not allowed
Theophylline, all presentations	1 week	Not allowed
Cromolyn sodium, all forms Nedocromil sodium	24 hours	24 hours prior to each allergen challenge
Salbutamol, all presentations	No restrictions	6 hours prior to each allergen challenge
Leukotriene modifiers, all presentations	1 week	Not allowed
Corticosteroids (inhaled, oral, intravenous)	4 weeks	Not allowed
Topical corticosteroids (ocular, intranasal)	2 weeks	Not allowed
Corticosteroids, (intramuscular or intra-articular)	12 weeks	Not allowed
Decongestants, all forms	24 hours	Not allowed
Immunotherapy	6 months	Not allowed
Systemic antibiotics	1 week	Within 1 week prior to each visit day
Tricyclic antidepressants and MAO inhibitors[1]	2 weeks	Not allowed
Any cytochrome P450 3A4 inhibiting or inducing drug (e.g. ritonavir, cobicistat, ketoconazole, itraconazole, erythromycin, cimetidine,	14 days	Not allowed

rifampicin, St. John's wort (Hypericum perforatum) etc.)		
COVID-19 vaccination	No restrictions	Within 3 days prior to each allergen challenge[2]

[1] Antidepressants devoid of anticholinergic effects: Fluctin® (Fluoxetine), Seroxat® (Paroxetine), and Trevilor® (Venlafaxine) are permitted during the study period provided the subject has been on a stable dose for 4 weeks prior to screening and there is no change in the dose or regimen during the entire study.

[2] If there is a conflict with the next allergen challenge due to COVID-19 vaccination, a delay of up to 3 days for Visit 2 or Visit 4 is allowed. However, the interval between Visit 2 and Visit 3 or Visit 4 and Visit 5 must not be changed.

6. Subjects with (expected) clinically relevant symptoms at the timing of the scheduled EEU assessments due to concomitant allergies, i.e. history of allergic response to the causative allergen, at the discretion of the Investigator. Subjects with a positive SPT for cats and/or dogs are acceptable if the subject avoids cats and/or dogs for the duration of the study.
7. Concomitant diseases: abnormalities during the screening visit (Visit 1) or Visit 2 that might interfere with study results as determined by the Investigator and/or designee.
8. Presence of a severely deviated septum, septal perforation, structural nasal defect or large nasal polyps causing obstruction as determined by the Investigator.
9. Acute conditions: any acute illness within 7 days prior to the screening visit (Visit 1) or Visit 2, including acute conjunctivitis or any other ocular infection, at the discretion of the Investigator and/or designee.
10. History of increased ocular pressure, glaucoma, cataracts, and/or central serous chorioretinopathy (CSCR).
11. Presence of or ongoing tuberculosis, untreated local or systemic fungal or bacterial infections, systemic viral or parasitic infections or ocular herpes simplex.
12. Recent nasal ulcers, mucosal erosion, nasal surgery, or nasal trauma, that might interfere with study results as determined by the Investigator and/or designee.
13. Exposure to chickenpox or measles within 4 weeks prior to the screening visit or during the study.
14. Acute or chronic sinusitis or non-allergic rhinitis, at the discretion of the Investigator and/or designee.
15. Exposure to another investigational product within the last 30 days prior to screening.
16. History of malignancy within the past five years, except for basal cell skin carcinomas that have been treated with no recurrence for at least 3 months.
17. Neurological or psychiatric disease or drug or alcohol abuse which would interfere with the subject's proper completion of the protocol assignment. Subjects with a positive urine drug screen will be excluded.
18. Subjects undergoing surgical procedures with general anaesthesia within 90

	days prior to screening or who plan to undergo surgery/hospitalization during the study. Administrative reasons: 19. Vulnerable subjects (such as persons who are institutionalized). 20. Positive alcohol or drug test during screening visit (Visit 1) 21. Public health emergency (e.g. COVID-19): subjects not complying to Public health guidelines (e.g. self isolation etc.), at the discretion of the Investigator's and/or designee, or subjects with a positive COVID-test at Visit 2.
Planned Number of Subjects	A total of 216 subjects are to be randomized in the study to show an onset of action at [redacted]
Statistical Methods	**Sample size estimation:** [redacted] a total of 216 randomized subjects should be included in this study. **Statistical analyses :** Adequate descriptive statistics will be provided for each endpoint. Time courses will be displayed graphically. For all endpoints, baseline is defined as the average of the last 2 assessments in the EEU prior to dosing with study treatment. **Primary onset analysis (by time point):** Analysis of changes from baseline at each post dose assessment time point in 0 to 4 hours will be performed using a mixed effect Analysis of Covariance model based on all subjects in FAS population (proc mixed). [redacted] For the active treatment, the onset of action will be defined as the first time point after initiation of treatment when the product demonstrates a greater change from baseline in the primary efficacy endpoint compared to the placebo treatment that proves durable from this point until the end of the last assessed time point (4h). **Other secondary onset analyses:** Following secondary endpoints will be analyzed and reported similar to the analysis method and reporting of the primary endpoint as described above using only the FAS population: • Changes from baseline in TOSS and total 7 symptoms score (T7SS) at each post-dose assessment time point (0 to 4 hours p.a.) • Change from baseline in individual nasal symptom scores (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptom scores (itchy eyes, watery eyes, eye redness) at each post-dose assessment time point (0 to 4 hours p.a.)

	Overall efficacy: [redacted] **Responder analysis:** Time to relevant response to therapy (30% and 50% reduction of TNSS) will be analysed. **Safety analysis:** Safety analysis will include descriptive analysis according to received treatment. **Populations for statistical analyses:** Safety (SAF) population: all subjects who administered at least one dose of study treatment. Subjects will be categorized according to the treatment that they actually received. Full analysis set (FAS) population: This will be the intention to treat (ITT) population (all randomized patients). The per-protocol (PP) set of subjects will be a subset of the FAS population excluding the subjects with major protocol violations that may affect the results of the primary variables. FAS Subgroup with Moderate/Severe Ocular Symptoms: all FAS subjects with baseline TOSS at Visit 3 ≥4.

STUDY DIAGRAM AND STUDY SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Study Conduct Section (6.0) for detailed information on each procedure and assessment required for compliance with the protocol.

Table 0-1 Study Schedule

		Screening	Study treatment				
			Period 1		Period 2		EOS/ET
Visit No		**1**	**2**	**3**	**4**	**5**	**5**[1]
Study procedures	**Day (window)**	**-28 to -2**	**-1**	**1**[2]	**13 (+5)**	**15 (+5)**[2]	**15 (+5)**
Confirm subject ID		●	●	●	●	●	●[3]
COVID screening questionnaire and oral temperature		●	●	●	●	●	●[3]
Written Research Subject informed consent		●					
Review inclusion/exclusion criteria		●	●	●			
Demographic information/social history		●					
Vital signs		●	●[4]	●[4]	●[4]	●[4]	●[5]
Paper diary training[6] and dispensing		●	●	●	●	●[3]	
Paper diary review and collection			●	●	●	●	●[3]
Prior and concomitant medication assessment		●	●	●	●	●	●[3]
Urine pregnancy test (females of childbearing potential only)		●	●		●		
Physical examination, incl. measurement of height and weight		●					
Placebo nasal spray administration training			●		●		
Verbal reminder of dosing technique				●		●	
Nasal inspection with anterior rhinoscopy		●		●[7]		●[7]	
Adverse events (AEs) monitoring[8]		●	●	●	●	●	●
Allergic skin prick test (SPT)[9]		●					
Medical history		●[10]					
Blood and urine sample for clinical laboratory tests		●					●
Spirometry		●					
Urine drug & alcohol screen		●					
COVID test			●[11]		●[11]		
Randomization				●			
Treatment administration							
Dispensing study treatment				●		●	
Dosing				●		●	
EEU							
ePDAT™ training and dispensing			●	●	●	●	
Nasal symptoms using ePDAT™			●[12]	●[13]	●[12]	●[13]	
Ocular symptoms using ePDAT™			●[12]	●[13]	●[12]	●[13]	
At-home							
Record AEs/concomitant medication in the paper diary		●	●	●	●	●	●[3]

[1] May be performed as part of the procedures at Visit 5, if done on the same day.

[2] The treatment administration visit (Visit 3 and Visit 5) should take place 2 days after the priming visit in the respective period (Visit 2 and Visit 4), with one day in between the treatment administration visit and the priming visit. If a subject cannot make Visit 3 or 5 as scheduled because of emergency, re-priming is allowed once per period with a wash-out period of at least 5 days between the priming visits.

[3] Will be performed unless EOS occurs on the same day as Visit 5

[4] Vital signs (blood pressure and heart rate) will be measured in a seated position (after at least 2 minutes of rest) prior to and after the EEU session.

[5] Conducted as part of Visit 5 after the EEU session or at early termination, if applicable.

[6] Training will be provided only at screening

[7] Performed within 30 minutes to dosing.

[8] The adverse event collection period begins at signing of informed consent and ends 5 to 7 days after the last treatment administration. Adverse events collection after EOS/ET visit will be done by phone. An adverse event is considered treatment emergent when occurring in the period from administration of study medication until 5 days (120 h) thereafter.

[9] If documentation within 12 months of screening is not available.

[10] Brief medical history will be sufficient at Visit 1 if medical history was already assessed at general screening within 60 days prior to Visit 2.

[11] Will be performed within 5 days prior to Visit 2 and Visit 4 or on the day of Visit 2 and 4 for a COVID-19 test to ensure the subjects safety prior to entering the EEU

[12] Individual nasal and ocular symptoms will be assessed within 10 minutes prior to the EEU session and during the EEU session at 30, 60, 75, 90, 105, and 120 minutes (+ 5 minutes).

[13] Individual nasal and ocular symptoms will be assessed within 10 minutes prior to entering the EEU session, after entering the EEU session at 30, 60, 75, 90, 105 and 120 minutes (+ 5 minutes) and after dosing at 5, 10, 15 minutes (+ 2 minutes), 30, 60, 90, 120, 150, 180, 210 and 240 minutes (+ 5 minutes).

Table 0-2 Schedule of Assessments in the EEU at Visit 2 and Visit 4

Time [min]	Pre-EEU	30*	60*	75*	90*	105*	120*	Post-EEU
Vital Signs	●							●
ePDAT™ training and dispensing	●							
Placebo nasal spray administration training								●
Nasal symptoms using ePDAT™	●	●	●	●	●	●	●	
Ocular symptoms using ePDAT™	●	●	●	●	●	●	●	

* Deviation window of + 5 minutes

Table 0-3 Schedule of Assessments in the EEU at Visit 3 and Visit 5

Time [min]	Pre-EEU	30*€	60*€	75*€	90*€	105*€	120*€	150/0§	5¥	10¥	15¥	30€	60€	90€	120€	150€	180€	210€	240€	Post-EEU
Administration of study treatment								●												
Vital Signs	●																			●
ePDAT™ training and dispensing	●																			
Nasal symptoms using ePDAT™	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	●	●	
Ocular symptoms using ePDAT™	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	●	●	

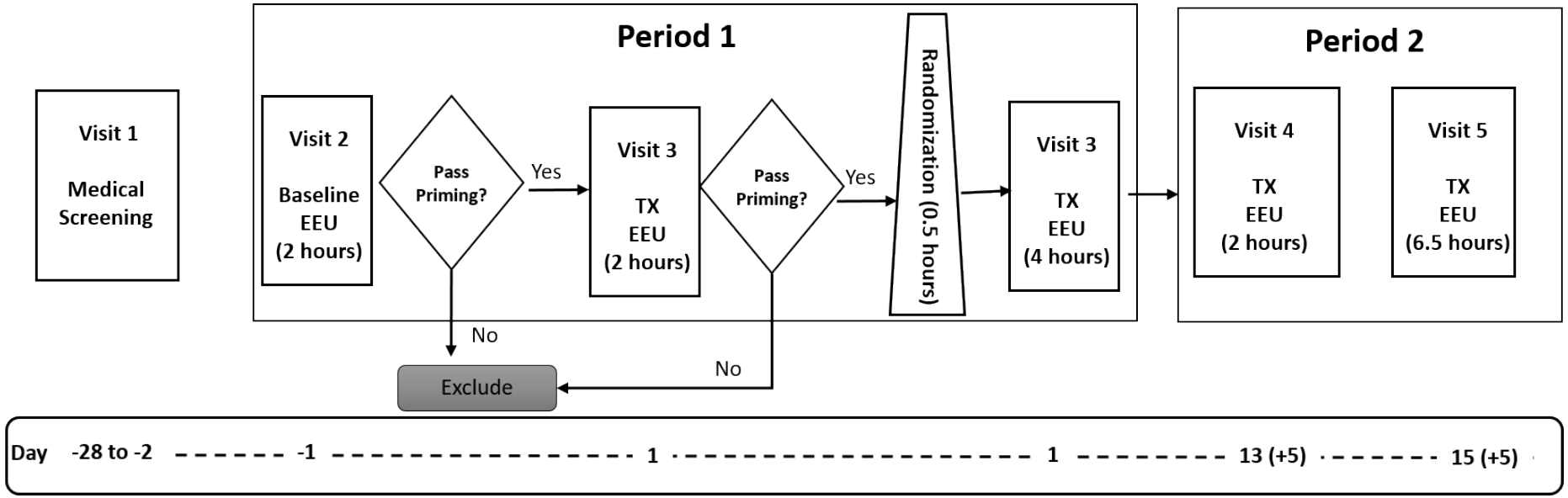
* Prior to dosing

€ Deviation window of + 5 minutes

¥ Deviation window of + 2 minutes

§ Deviation window of ± 5 minutes

Figure 0-1 Study Schematic



PROTOCOL APPROVAL

Protocol Title	Clinical Trial to Assess Onset of Action of Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray Delivered in a Single Spray (Dymista) in the Treatment of Allergen-Induced Allergic Rhinitis Symptoms in Comparison to Placebo in an Environmental Exposure Unit (EEU)
Protocol Number	AZFL-AES-4-001 / C1D00571
Version	3.0
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LIST OF COMMONLY USED ABBREVIATIONS

Abbreviation	*Description*
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
AR	Allergic Rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
COVID	Corona Virus Disease
CRF	Case Report Form
CRO	Contract Research Organization
CSCR	Central Serous Chorioretinopathy
DMP	Data Management Plan
EC	Ethics Committee
EDC	Electronic Data Capture
EEC	Environmental Exposure Chamber
EEU	Environmental Exposure Unit
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EU	European Union
EudraCT	European Clinical Trials Database
ePDAT™	Electronic Patient Data Acquisition Tablet
ET	Early Termination
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume in 1 Second
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
H_1A	H_1-Antihistamine
HEPA	High Efficiency-Particulate Air(filter)
ICF	Informed Consent Form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use
ICTRP	International Clinical Trials Registry Platform
ID	Identification
IEC	Independent Ethics Committee
IgE	Immunglobulin E
INCS	Intranasal Corticosteroid
IRB	Institutional Review Board
ISF	Investigator's Site File

ITT	Intent-to-Treat (Population)
IUD	Intrauterine Device
LEC	Local Ethics Committee
MAO	Monoamine Oxidase
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Model for Repeated Measures
p.a.	(*post applicationem*) post-administration
PAF	Platelet-activating Factor
PI	Principal Investigator
PP	Per-Protocol (Population)
PSRM	Product Safety and Risk Management
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAF	Safety (Population)
SAP	Statistical Analysis Plan
SAR	Saisonal Allergic Rhinitis
SD	Standard Deviation
SDV	Source Data Verification
SE	Standard Error
SOP	Standard Operating Procedure
SPT	Skin Prick Test
T7SS	Total 7 Symptom Score (TNSS + TOSS)
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
TNSS	Total Nasal Symptom Score
TOSS	Total Ocular Symptom Score
TX	Treatment
U.S .	United States
WHO	World Health Organization

1.0 INTRODUCTION

1.1 Indication

Allergic rhinitis (AR) is an upper airway inflammatory disease of the nasal mucosa, resulting from an IgE-mediated immunological response following an allergen exposure. Symptoms of AR include rhinorrhea, sneezing, nasal itching, congestion as well as non-nasal symptoms such as itchy eye, watery eye, red eye and throat and palate itching (Small & Kim 2011). AR is one of the most common of atopic diseases, but by itself, is not life threatening unless accompanied by asthma (Dixon et al. 2006 , Kim et al. 2008). However, AR can affect between 10% and 25% of the world's population and epidemiologic studies indicate that the prevalence of AR is on the rise. Moreover AR causes significant morbidity, substantial economic burden and impairment in quality of life (Stewart et al. 2010).

Seasonal allergic rhinitis (SAR) is typically caused by pollens of specific seasonal plants including tree, grass and ragweed (Small & Kim 2011, Ihler & Canis 2015, Day et al. 2006, Jacobs et al. 2012). Early-phase symptoms occur within minutes of exposure to the allergen in a sensitized individual. Cross-linking of allergen-specific IgE to the surface of mast cells in the nasal mucosa can trigger a cascade of instantaneous events including mast cell degranulation and the immediate release of Type I hypersensitivity mediators such as histamine, leukotrienes and prostaglandins, which can induce acute nasal symptoms (Small & Kim 2011, Sin & Togias 2011, Pawankar et al. 2011). Approximately 30 to 40% of sensitive individuals develop late-phase reaction occurring 4 to 5 hours after the initial allergen exposure. Indolent symptoms can continue due to the continued upregulation of a variety of recruited Type 2 T-helper cells and the production of cytokines (Small & Kim 2011, Min 2010, Pipet et al. 2009). Repeated allergen exposure or "priming" can lead to the development of mucosal inflammation and increased nasal hyper-responsiveness (Sin & Togias 2011, Pawankar et al. 2011).

Therapeutic options available for treatment of AR include avoidance measures, oral/ intranasal antihistamines, intranasal corticosteroids, leukotriene receptor antagonists and allergen immunotherapy. The recently updated Allergic rhinitis and its impact on asthma (ARIA) Guidelines (Bousquet et al. 2020) recommend the use of a combination of intranasal H_1A and INCS for initial therapy as well as for patients previously not sufficiently treated with H_1A and INCS alone. This applies to all AR patients, independent of symptom severity and type of AR (seasonal and/or perennial). Most relevantly, the ARIA guidelines highlight that the combination of intranasal antihistamine and INCS is more effective than INCS alone and is effective within minutes whereas the INCSs may need day(s) to work.

1.2 Background and Rationale

Patients with allergic rhinitis have high expectations of anti-allergic treatment (Hellings et al. 2012). Highly effective medications with early onset of action may improve patient's compliance with therapy. Pivotal trials showed that under clinical conditions, Dymista becomes efficacious within the first 30 minutes and more effective than the monoproducts (M1). However, these studies were standard phase III allergic rhinitis efficacy trials and they were not specifically designed to assess onset of action, the primary endpoint was treatment effect over 2-week treatment. The assessment of onset of action was done during 4-hour

observation period following the initial administration of trial drug at study sites under indoor conditions with considerably low pollen exposure. Therefore, clinical trial X-0365-3311 using a standardized EEU (synonym to environmental exposure chamber – EEC) model with measurement timepoints starting from 5 minutes after administration was performed. The EEU was used to promote a uniform aerosolization of allergen over time in a highly controlled manner with limited confounding environmental factors. In this trial, Dymista started relieving nasal symptoms within 5 min and ocular symptoms within 10 minutes of dosing. All individual nasal and ocular symptoms reached first statistical significance at early time points and thus contributed to the overall effects of Dymista (Bousquet et al. 2018, O1).

The aim of the current study is to replicate the results of the fast onset of action for Dymista in a second onset of action study using an EEU model with a similar design but without an active control.

The study design and requirements have been adapted from Principles of the U.S. FDA draft guidance "Allergic Rhinitis: Developing Drug Products for Treatment Guidance for Industry" September 2018 for evaluating onset of efficacy (R1).

1.3 Investigational Product

1.3.1 Dymista

Dymista is comprised of two active ingredients, azelastine hydrochloride and fluticasone propionate. It is indicated in Canada for the symptomatic treatment of moderate to severe seasonal allergic rhinitis (SAR) and associated ocular symptoms in adults, adolescents, and children aged 6 years and older for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient (M1) and in the US for the relief of symptoms of seasonal allergic rhinitis in patients 6 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief (M2). It is also indicated for relief of the symptoms of perennial allergic rhinitis in many other countries worldwide as well as for symptomatic treatment of allergic rhinitis and rhino-conjunctivitis.

The approved daily dose for Dymista in Canada (M1), in the US (M2), and other countries worldwide is one actuation in each nostril twice daily (morning and evening). The use of Dymista within this trial is in line with the approved dosage recommendation. Subjects will apply Dymista as a single dose of 1 spray per nostril; each spray delivers 137 µg of azelastine hydrochloride and 50 µg of fluticasone propionate.

Warnings and precautions, as well as common side effects of the drug, can be found in the Canadian product monograph (M1).

The components of Dymista, azelastine hydrochloride and fluticasone propionate, possess different modes of action in the treatment of AR symptoms (M1).

1.3.2 Azelastine hydrochloride

Azelastine is a phthalazinone derivative and is classified as a potent long-acting anti-allergic compound that has selective H1-antagonist, mast cell stabilizing and anti-inflammatory

properties. Azelastine has been shown to inhibit the synthesis or release of chemical mediators involved in early and late stage allergic reactions, e.g. leukotrienes, histamine, platelet-activating factor (PAF) and serotonin (M1).

The azelastine hydrochloride in Dymista is administered as a racemic mixture, which possesses no difference in pharmacologic activity. The major metabolite, desmethylazelastine, also possesses H1-receptor antagonist activity (M1).

1.3.3 Fluticasone propionate

Fluticasone propionate is a synthetic trifluorinated corticosteroid with powerful anti-inflammatory action with a high affinity for the glucocorticoid receptor (M1).

The exact mechanism by which fluticasone propionate affects symptoms of AR is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types, such as mast cells, eosinophils, neutrophils, macrophages, and lymphocytes, as well as mediators, such as histamine, and cytokines, involved in inflammation (M1).

1.4 Ethics and Benefit-Risk Considerations

1.4.1 Ethics

The study will be conducted in agreement with the following directives, laws, and guidelines:

- Declaration of Helsinki (R2).
- ICH guideline on Good Clinical Practice (ICH E6 (R2)) Addendum (R3).
- Regulation (EU) 2016/679 of 27 April 2016 (General Data Protection Regulation (R4)
- Applicable regulatory and national legislations.

Cliantha Research will apply for authorisation by competent authorities, as applicable, and for favourable opinion by the IRB. The study will be notified to other locally responsible authorities as applicable. Meda will provide a power of attorney for delegation of responsibilities to authorised persons / institutions.

1.4.2 Benefit-Risk Considerations

The EEU is an established model to assess onset of action of anti-allergic medications. Cliantha Research and its founders have over 15 years of experience in conducting EEU studies. The risks associated with exposure to ragweed pollen in the EEU are limited. While subjects are in the EEU, they will be exposed to ragweed allergens and are expected to experience AR symptoms typically experienced during the ragweed pollen season. In instances where either no treatment or a placebo treatment is administered, the symptoms will not be alleviated during allergen exposure.

Before subjects are exposed to ragweed pollen in the EEU, they will be examined by the study staff for adverse events and administration of concomitant medications and their vital signs will be taken. They will be monitored throughout their stay in the EEU. If subjects

experience any significant changes in their symptoms and well-being, they will be treated as judged necessary by the Investigator and/or designee.

The subjects will also be exposed to:

- The known risks related to the study treatments or the study procedures, and
- Unknown risks that might be related to study treatments or to the study procedures.

The subjects are comprehensively informed about these aspects, and the study is conducted under conditions to ascertain onset of action of the study treatments and to further evaluate the efficacy of the treatments.

Common side effects of Dymista can be found in the Canadian product monograph (M1).

The subjects may indirectly benefit from the study by advancing medical knowledge about the study treatments.

2.0 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary objective

To assess the onset of action of a fixed combination of azelastine hydrochloride and fluticasone propionate nasal spray (Dymista) in relieving the nasal symptoms of seasonal allergic rhinitis (SAR) induced by an allergen challenge in an Environmental Exposure Unit (EEU)

2.1.2 Secondary Objectives

- To assess onset of action of Dymista in relieving the ocular symptoms of SAR induced by an allergen challenge in an EEU
- To assess onset of action of Dymista in relieving the combined nasal and ocular symptoms of SAR induced by an allergen challenge in an EEU
- To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the nasal symptoms (TNSS) with that of placebo
- To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the ocular symptoms (TOSS) with that of placebo
- To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the combined nasal and ocular symptoms (T7SS) with that of placebo
- To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the individual nasal and ocular symptoms with that of placebo
- To evaluate time to relevant response to therapy (30% and 50% reduction of TNSS)

2.2 Endpoints

2.2.1 Primary Endpoint

For onset of action assessment:

a) Changes from baseline in TNSS at each post-dose assessment time point (0 to 4 hours p.a.)

2.2.2 Secondary Endpoints

Efficacy:

b) Changes from baseline in TOSS and total 7 symptoms score (T7SS) at each post-dose assessment time point (0 to 4 hours p.a.)

c) Time courses of TNSS, TOSS, and T7SS during the 6.5-hour EEU session

d) Change from baseline in individual nasal symptom scores (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptom scores (itchy eyes, watery eyes, eye redness) at each post-dose assessment time point (0 to 4 hours p.a.)

Safety and tolerability:

e) Adverse events (AEs)

f) Vital signs

3.0 STUDY DESIGN

3.1 Overall Design

This study will be a therapeutic study performed as a single-center, randomized, placebo-controlled, double-blind, and two-period cross-over trial.

3.2 Rationale for Study Design

The aim of the current study is to replicate the results of the fast onset of action for Dymista from study X-03065-3311 in a second onset of action study using an EEU model with a similar design but without an active control.

An EEU is used to promote a uniform aerosolization of allergen over time in a highly controlled manner. As the assessments will be conducted with limited confounding environmental factors and with consistent allergen exposure, the use of an EEU model is expected to provide a more effective method to assess the onset of efficacy of Dymista compared to a field trial.

The choice of dosage and route of administration is based on study X-03065-3311 and the approved and marketed dosage forms for Dymista used in the study (M1).

The study design and requirements have been adapted from Principles of the U.S. FDA draft guidance "Allergic Rhinitis: Developing Drug Products for Treatment Guidance for Industry" September 2018 for evaluating onset of efficacy (R1).

3.3 Environmental Exposure Unit (EEU)

The EEU is equipped with an environmental control unit / air handling system which provides temperature and humidity controlled HEPA-filtered air into the EEU to create the optimal conditions for aerosolization. Pollen counts are obtained as per Cliantha SOPs regarding EEU operation.

During the EEU sessions, subjects will be exposed to airborne ragweed pollen at an average concentration of 3500 ± 500 grains/m^3 for approximately 2 or 6.5 hours, depending on the visit. While in the EEU, ragweed-allergic subjects are expected to experience nasal and ocular allergy symptoms typically experienced during the ragweed pollen season. Deviations in EEU conditions including pollen counts should be reported to the Sponsor.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the end of study (EOS) visit and last phone contact. Subjects who prematurely terminate from the study will have an Early Termination (ET) visit scheduled as soon as possible.

The end of study is defined as the date of final contact of the last subject undergoing the trial.

4.0 STUDY POPULATION

4.1 Study Population

A total of approximately 216 male and female subjects will be randomized into the study.

Subjects will be selected from non-institutionalized volunteers consisting of members of the community at large.

The duration of the study from screening (Visit 1) to end of study (telephone follow-up) will last up to 56 days for each subject (duration may be longer if re-priming is required). In the study, there will be single dose administrations on two separate occasions with at least 14 days wash-out between each treatment.

4.2 Inclusion and Exclusion Criteria

4.2.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

To be eligible for the study, a subject must comply with all of the following criteria at screening (Visit 1):

1. Provide written informed consent.
2. Male or female subjects (childbearing and non-childbearing potential, non-childbearing potential defined as females with no menstruation for at least 1 year at screening and documented FSH >35 IU/L) aged 18 to 55 years (inclusive) at screening.
3. History of SAR to ragweed pollen for at least the previous 2 ragweed pollen seasons.
4. Positive skin prick test (SPT) response to ragweed pollen (allergen induced wheal diameter at least 3 mm larger than the negative control). A test performed at Cliantha Research in the previous 12 months may be used to qualify the subject.
5. Willingness to complete all study visits.

To be eligible for Visit 2 EEU, a subject must additionally comply with the following criteria:

6. Asymptomatic or with mild symptoms during the baseline recording of symptoms prior to start of the screening EEU (Visit 2):
    - TNSS ≤ 3/12 with the score for each symptom being less than 2.

To be eligible for Visit 3, a subject must additionally comply with the following criteria during Visit 2 EEU:

7. Demonstrate adequate symptomology:
    - TNSS ≥ 6/12 on at least two ePDAT™ time point assessments during hours 0-2 in the EEU (Visit 2), with at least one occurring during the last two time points. Additionally, subjects will be required to meet a score of at least 2/3 for runny nose at least twice during hours 0-2 in the EEU, with at least one occurring during the last two time points.

To be eligible for randomization (Visit 3), a subject must additionally comply with the following criteria:

8. Demonstrate adequate symptomology:
    - TNSS ≥ 6/12 on at least two ePDAT™ time point assessments during hours 0-2 in the EEU (Visit 3), with at least one occurring during the last two time points. Additionally, subjects will be required to meet a score of at least 2/3 for runny nose at least twice during hours 0-2 in the EEU, with at least one occurring during the last two time points.
    - No evidence of complete nasal blockage on either one or both sides on anterior rhinoscopy within 30 minutes prior to dosing.

4.2.2 Exclusion Criteria

A subject is ineligible and must not enter the study if any of the following criteria are met:

Safety concerns:

1. History of allergic reaction to azelastine hydrochloride or fluticasone propionate or one of the excipients of the study treatments (e.g. benzalkonium chloride, phenylethyl alcohol, microcrystalline cellulose) or a component of the container.

2. History of anaphylaxis, cardiovascular, pulmonary, hepatic, renal, gastrointestinal, hematological, endocrine, metabolic, psychiatric, neurological, or other disease at screening that may affect subject safety during the study or evaluation of the study endpoints at the discretion of the Investigator and/or designee.
3. Subjects with a current diagnosis of asthma or subjects with measured FEV_1 <75% of the predicted value using Global Lung Function Initiative set from 2012 for references.
4. Pregnant, breast-feeding, or planning a pregnancy during the study and women of childbearing potential not using adequate contraception. Women of childbearing potential not abstinent or using a highly effective method of birth control defined as those which result in a low failure rate (i.e. <1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, hormonal IUDs, barrier methods, or tubal ligation started at least 4 weeks prior to screening.

Lack of suitability for the study:

5. Previous and concomitant treatments: use of prohibited therapies as specified in the following table; use of any medication considered to have an influence on the outcome of the study during the EEU session, at the discretion of the Investigator and/or designee.

Prohibited medication	Prior to Screening	During study
Antihistaminic agents, all presentations	1 week	Not allowed
Theophylline, all presentations	1 week	Not allowed
Cromolyn sodium, all forms Nedocromil sodium	24 hours	24 hours prior to each allergen challenge
Salbutamol, all presentations	No restrictions	6 hours prior to each allergen challenge
Leukotriene modifiers, all presentations	1 week	Not allowed
Corticosteroids (inhaled, oral, intravenous)	4 weeks	Not allowed
Topical corticosteroids (ocular, intranasal)	2 weeks	Not allowed
Corticosteroids, (intramuscular or intra-articular)	12 weeks	Not allowed
Decongestants, all forms	24 hours	Not allowed
Immunotherapy	6 months	Not allowed
Systemic antibiotics	1 week	Within 1 week prior to each visit day
Tricyclic antidepressants and MAO inhibitors[1]	2 weeks	Not allowed
Any cytochrome P450 3A4 inhibiting or inducing drug (e.g. ritonavir, cobicistat, ketoconazole, itraconazole, erythromycin, cimetidine, rifampicin, St. John's wort (Hypericum perforatum) etc.)	14 days	Not allowed
COVID-19 vaccination	No restrictions	Within 3 days prior to each allergen challenge[2]

[1] Antidepressants devoid of anticholinergic effects: Fluctin® (Fluoxetine), Seroxat® (Paroxetine), and Trevilor® (Venlafaxine) are permitted during the study period provided the subject has been on a stable dose for 4 weeks prior to screening and there is no change in the dose or regimen during the entire study.

[2] If there is a conflict with the next allergen challenge due to COVID-19 vaccination, a delay of up to 3 days for Visit 2 or Visit 4 is allowed. However, the interval between Visit 2 and Visit 3 or Visit 4 and Visit 5 must not be changed.

6. Subjects with (expected) clinically relevant symptoms at the timing of the scheduled EEU assessments due to concomitant allergies, i.e. history of allergic response to the causative allergen, at the discretion of the Investigator. Subjects with a positive SPT for cats and/or dogs are acceptable if the subject avoids cats and/or dogs for the duration of the study.
7. Concomitant diseases: abnormalities during the screening visit (Visit 1) or Visit 2 that might interfere with study results as determined by the Investigator and/or designee.
8. Presence of a severely deviated septum, septal perforation, structural nasal defect or large nasal polyps causing obstruction as determined by the Investigator.
9. Acute conditions: any acute illness within 7 days prior to the screening visit (Visit 1) or Visit 2, including acute conjunctivitis or any other ocular infection, at the discretion of the Investigator and/or designee.
10. History of increased ocular pressure, glaucoma, cataracts, and/or central serous chorioretinopathy (CSCR).
11. Presence of or ongoing tuberculosis, untreated local or systemic fungal or bacterial infections, systemic viral or parasitic infections or ocular herpes simplex.
12. Recent nasal ulcers, mucosal erosion, nasal surgery, or nasal trauma, that might interfere with study results as determined by the Investigator and/or designee.
13. Exposure to chickenpox or measles within 4 weeks prior to the screening visit or during the study.
14. Acute or chronic sinusitis or non-allergic rhinitis, at the discretion of the Investigator and/or designee.
15. Exposure to another investigational product within the last 30 days prior to screening.
16. History of malignancy within the past five years, except for basal cell skin carcinomas that have been treated with no recurrence for at least 3 months.
17. Neurological or psychiatric disease or drug or alcohol abuse which would interfere with the subject's proper completion of the protocol assignment. Subjects with a positive urine drug screen will be excluded.
18. Subjects undergoing surgical procedures with general anaesthesia within 90 days prior to screening or who plan to undergo surgery/hospitalization during the study.

Administrative reasons:

19. Vulnerable subjects (such as persons who are institutionalized).
20. Positive alcohol or drug test during screening visit (Visit 1)
21. Public health emergency (e.g. COVID-19): subjects not complying to Public health guidelines (e.g. self isolation etc.), at the discretion of the Investigator's and/or designee, or subjects with a positive COVID-test at Visit 2.

4.2.3 Randomization Criteria

To be eligible for randomization (Visit 3), a subject must comply with the criteria for randomization mentioned in Section 4.2.1.

4.2.4 Screening Failures

To allow a rough description of the reasons to fail screening, at least the following items need to be documented for these patients in the eCRF: age, sex, ethnicity, race, adverse events, concomitant medications (only if in context with adverse events) and the main reason for not being enrolled / randomized.

4.2.5 Criteria for study drug termination, withdrawal from the study and study termination

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study center. Every effort should be made to retain subjects in the study. When available, a reason for not completing the study will be recorded in the subject source documents and transcribed into the electronic case report form (eCRF).

Withdrawal is understood as premature discontinuation from study procedures after randomization. Drop-outs before randomization are considered as screening failures (see Section 4.2.4). A decision of withdrawal should be communicated with the Sponsor in a timely manner.

If, a subject discontinues from the study prematurely, due to any reason as provided in the below withdrawal criteria, the site should make every effort to follow-up the subject to perform safety and efficacy assessments as per the Study Schedule (Table 0-1).

A subject may be required to terminate study drug for reasons including the following:

- The subject withdraws consent.
- For female subjects, diagnosis of pregnancy or stated intention to become pregnant. All efforts should be made by the site to obtain consent from the pregnant women, so that they are followed until delivery or termination.
- Despite education/reinforcement, the subject shows persistent inadequate compliance with required study visits/procedures, potentially compromising safety monitoring while on study drug based on Investigator's discretion.
- The subject takes prohibited treatment presenting a safety concern to continued dosing with study drug.
- At the Investigator's discretion (it is recommended that the investigator discusses with medical monitor prior to decision), if it is in the subject's best interest due to occurrence of an AE and/or other findings considered to present a safety concern to continued dosing with study drug, and warrants treatment withdrawal.
- If the blind is broken for a subject by the Investigator

The Principal Investigator and/or the Sponsor reserve the right to terminate the study for any reason.

The study will be terminated early if there are significant safety concerns.

Subjects who prematurely terminate from the study will have an Early Termination (ET) visit scheduled as soon as possible.

4.3 Replacement Policy

Subjects who are withdrawn from the study after randomization and after administration of the first treatment will not be replaced.

For subjects who dropped out before randomization due to other reasons than safety and SAR symptoms qualification, re-screening may be possible following discussion with Sponsor or designee or according to pre-defined written procedures, if applicable. If re-screening occurs this will be clearly documented within the site file.

4.4 Lifestyle Guidelines

No specific interaction studies with Dymista and food have been performed. Subjects do not have to follow specific dietary restriction throughout the conduct of study.

In clinical trials, the occurrence of somnolence has been reported in some patients (0.7% of patients) taking Dymista. In isolated cases fatigue, weariness, exhaustion, dizziness or weakness that may also be caused by the disease itself, may occur when using Dymista nasal spray. In these cases, the ability to drive and use machines may be impaired. Alcohol and other central nervous system depressants may enhance this effect and should be avoided (M1).

4.5 Contraception

4.5.1 Females - Non-childbearing Potential

Female subjects of non-childbearing potential must meet at least one of the following criteria:

1. Postmenopausal females, defined as females who have been amenorrheic for at least 1 year and documented FSH > 35 IU/L at screening.
2. Females who have a reported or documented hysterectomy and/or bilateral oophorectomy more than 90 days prior to Visit 3.

All other females will be considered to be of childbearing potential.

4.5.2 Females - Childbearing Potential

Female subjects of child-bearing potential must use an acceptable, highly effective method of contraception (i.e., a method with a failure rate <1% per year when used consistently and correctly) starting at least 4 weeks prior to screening and continuing at least 5 days following the last treatment, such methods include at least one of the following:

- Abstinence (periodic abstinence is not acceptable)
- Tubal ligation
- Intrauterine device of intrauterine system
- Barrier method, like condom, with spermicide
- Male partner who has had a vasectomy for at least 6 months. Male partners with vasectomies of <6 months are NOT considered protected
- Hormonal contraceptives (oral, injected, transdermal or implanted) with the exception of low dose gestagens, i.e. only containing lynestrenol or norethisterone, since they do not inhibit ovulation and are therefore not considered as highly-effective. The subject must remain on the hormonal contraceptive throughout the study and must have been using hormonal contraceptives for an adequate period prior to the study to ensure effectiveness (e.g., 3 months)

4.6 Pregnancy Testing

Urinary pregnancy testing will be performed on all females of childbearing potential as described in the schedule of activities (results will be reviewed and must be negative prior to dosing). In the event of a positive test, the subject will be withdrawn from the study (or will not enter the study if during screening).

Any pregnancy occurring after randomization to study drug will be followed up and reported to the Sponsor as per Section 11.5.4.

5.0 STUDY DRUG

5.1 Investigational Drug

Dymista nasal spray (azelastine hydrochloride and fluticasone propionate nasal spray) will be supplied in glass bottles containing 23 g suspension fitted with a metered-dose nasal spray pump. Each bottle contains at least 120 metered sprays. After priming, the nasal spray pump delivers approximately 137 µg of azelastine hydrochloride and 50 µg of fluticasone propionate per actuation.

The placebo nasal spray will be also supplied in glass bottles containing 23 g suspension fitted with a metered-dose nasal spray pump. Each bottle contains at least 120 metered sprays.

The composition of Dymista and the placebo nasal spray is listed in Table 5.1-1 below.

Table 5.1-1 Composition and Storage Conditions of Dymista and Placebo

	Dymista	Placebo nasal spray (Dymista vehicle)
Active substance(s)	Azelastine hydrochloride 137 µg and Fluticasone propionate 50 µg	-
Excipients	Benzalkonium chloride, Disodium edetate, Glycerol, Microcrystalline cellulose and carmellose sodium, Phenylethyl alcohol, Polysorbate 80 and Purified Water	Benzalkonium chloride, Disodium edetate, Glycerol, Microcrystalline cellulose and carmellose sodium, Phenylethyl alcohol, Polysorbate 80 and Purified Water
Storage	Store between 15°C-30°C	Store between 8°C-25°C
	Storage condition to be applied to the blinded study drug is Store between 15-25°C	
Marketing authorization holder	MEDA Pharmaceuticals Ltd.	-

Canadian commercial Dymista nasal spray will be purchased for use in the study. The placebo nasal spray will be provided by the Sponsor.

The study treatments will be labelled according to Cliantha Research SOPs. The approved labels in the local language(s) will be filed in the TMF of the Investigator and the Sponsor.

The study drugs must not be used after the retest or expiry date. The study monitor will check these dates accordingly and will initiate appropriate measures in due time if study drugs will be needed after that date.

For placebo nasal spray, the certificate of analysis will be filed in the TMF of the Sponsor. Respective documentation (i.e. the "final release" form and study drug shipment record) in the TMF of the Investigator will specify batch number(s), retest date(s), and reference number(s) of the certificate(s) of analysis.

For Canadian commercial Dymista nasal spray, respective documentation (i.e. purchase records and documents specifying batch numbers, expiry dates and the certificate(s) of analysis, if available.) will be filled in the TMF of the Investigator and Sponsor.

5.1.1 Administration of Study Drugs

In each period for Visit 3 and Visit 5, after an approximately 2.5-hour session in the ragweed EEU, each subject will be administered with either one of the following treatments as described in Table 5.1-2 below and according to randomization.

Table 5.1-2 Treatment Administration

Period 1 (Visit 3)	Period 2 (Visit 5)
Treatment A: One spray in each nostril of Dymista nasal spray	Treatment B: One spray in each nostril of placebo nasal spray
Treatment B: One spray in each nostril of placebo nasal spray	Treatment A: One spray in each nostril of Dymista nasal spray

The dosage instructions for Dymista are indicated in the respective Canadian product monograph (M1). Preparation of the spray (including priming the pump) should be done by the member of the study staff who dispenses and will otherwise not be involved in the conduct of the trial.

In the event of any significant dosing errors, the Medical Monitor, or Sponsor study contact should be contacted immediately.

Subjects will be trained on how to use the nasal spray with a training placebo nasal spray at the end of the priming EEU session at Visit 2 andVisit 4.

5.2 Drug Inventory

Canadian commercial Dymista nasal spray will be purchased for use in the study. The placebo nasal sprays will be supplied by the Sponsor and shipped to Cliantha Reseach.

5.3 Study Medication/Device Complaints

In the event the subject has a complaint/concern during study participation regarding the study supplied study medication, they should inform the study staff.

In the event of a complaint/concern regarding any study medication provided by the Sponsor for this study, as a minimum the following information should be sent by the site via e-mail to [redacted]

- Study number
- Principal Investigator name
- Subject ID
- Date of occurrence of incident/complaint
- Description of incident/complaint (facts)
- Confirmation if the complaint caused or resulted in a SAE? If “Yes”, confirmation that the SAE has been reported

Additional information and potentially the return of study medication may be requested by the Sponsor in order to investigate the complaint.

5.4 Storage, Disposition of Unused Study Drug and Drug Accountability

The Investigator, or an approved representative, e.g. pharmacist, will ensure that all investigational products are stored in a secured area under recommended storage conditions and in accordance with applicable regulatory requirements while at the Investigator site.

Study drug should be stored between 15-25°C.

Temperature of storage facilities should be monitored and recorded on a daily basis using validated devices that record maximum and minimum temperatures. Should the storage facility experience any excursion of temperature outside of the labelled storage condition this must be reported immediately to Sponsor or designee. At sites where daily monitoring and recording is not possible at weekends, then on the next working day after the weekend the temperature record (e.g. max/min thermometers) should be checked immediately for any temperature excursions. Devices used for temperature monitoring should be regularly calibrated. Affected material must be placed into quarantine until the impact of the excursion has been assessed and confirmed by Sponsor.

The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the study drug. If Sponsor supplies drug accountability forms these must be used. Alternatively, Sponsor may approve use of standard institution forms. In either case, the forms must identify the study drug, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Sponsor or designee.

At the end of the study, Sponsor will provide instructions as to disposition of any unused investigational product. If Sponsor authorizes destruction at the study site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Sponsor. Destruction must be adequately documented.

The study medication must not be used outside this protocol.

5.4.1 Retained Drug Samples

Not applicable.

5.5 Randomization

At screening, each subject will be assigned a screening number and listed in the *Subject Identification List and Screening/Enrolment Log* (blank form in TMF of the Investigator).

After review of all eligibility criteria and immediately before dispensing the randomized treatment, the subject will be assigned the next available randomization number according to the randomization scheme. The respective control label will be affixed in the respective place on the subject source document.

Cliantha Research will generate the randomization scheme. The randomization scheme will be generated by using SAS statistical software (Version 9.4 or higher; SAS Institute Inc., USA)

The randomization scheme will be kept in a locked cabinet within the pharmacy, with access limited to pharmacy staff only. The pharmacy staff involved in preparing and dispensing of investigational products will be accountable for ensuring compliance to the randomization scheme. The Principal Investigator and study staff will not have access to the randomization scheme during the study conduct until unblinding.

All sequences will be balanced (i.e., the ratio of the sequences will be 1:1, meaning 108 subjects per sequence). Table 5.5-1 represents the randomization sequences.

Table 5.5-1 Randomization Sequence

Sequence	Period 1	Period 2
1	Treatment A : Dymista	Treatment B : Placebo
2	Treatment B : Placebo	Treatment A : Dymista

5.6 Breaking the Blind

Individual decoding may be requested by the Investigator from the pharmacy staff if necessary for medical reasons or regulatory requirements. The Investigator should unblind the individual treatment only to prevent immediate harm to the subject or on request by a regulatory authority or IRB.

If time permits, the Investigator is encouraged to contact the Sponsor prior to breaking the blind. If the blind is broken for any reason, the Investigator must notify the Sponsor immediately about unblinding procedure without medication code (within 24 hours). Upon request by the Sponsor, the Investigator should provide the status of unblinding.

Emergency unblinding envelopes (one envelope for each subject) will be prepared by unblinded pharmacy staff using the randomization scheme. QC/QA of the preparation process will be performed by 1 or 2 additional unblinded staff members. To faciliatate emergency unblinding and ensure subject safety, unblinding envelopes will be kept in a secured area with access limited to Pharmacy staff, the PI and other key designated study staff as specified in the delegation log. Unblinding will be performed by breaking the seal of the envelope, for that specific subject of interest only, and retrieving the treatment code.

The name of the unblinding person, the reason, the subject randomization number, the date and time of unblinding will be documented and confirmed by a signature. The reasons for and the date of unblinding must also be documented in the subject source document and also in the eCRF (if applicable). If possible, all causality and expectedness assessments should be done before breaking the blind. The sole fact that an adverse event is considered serious does not provide sufficient rationale for breaking the blind for a given subject.

5.7 Rescue Medication

Use of rescue medications may result in removal of the subject from the period/study at the discretion of the Investigator. Decision of withdrawal should be communicated with the Sponsor in timely manner. If subjects experience bronchospasm, salbutamol may be administered if judged necessary.

5.8 Concomitant Medications

All concomitant medications taken during the study (from signing informed consent to post-study follow-up) must be recorded with indication, daily dose, and start and stop dates of administration in the subject source documents and transferred into the eCRF. All subjects will be questioned about concomitant medication at each clinic visit and at follow up.

Changes in concomitant treatments should be kept at a minimum to avoid or at least reduce confounding factors.

Indication specific medications taken prior to screening (Visit 1) will be documented as a prior medication.

Subjects will abstain from all prohibited medications as described in the exclusion criteria section of this protocol (Section 4.2.2). Use of prohibited medication during the study will be deemed a protocol deviation and such subjects will be assessed by the Sponsor or designee regarding potential need to early terminate study drug (e.g. for safety reasons – see Section 4.2.5).

For non-pharmacological treatment, procedure, or diagnostic measures, the indication, and start and stop dates will be recorded. Any change since start of screening should be documented as well. Times of hospitalisation (beyond emergency room) or prolongation of hospitalisation will be recorded as an SAE (see Section 11.1).

5.9 Recommended Procedure in a Subject Experiencing Adverse Effects Secondary to Excessive Pharmacological Effects of Study Drug

With the nasal route of administration, overdose reactions are not anticipated.

In the event of overdose after incidental oral uptake (of the whole bottle), disturbances of the central nervous system, which include drowsiness, confusion, coma, tachycardia and hypotension, caused by azelastine hydrochloride may occur based on the results of animal experiments (M1). Of note, in clinical studies, single oral use of azelastine up to 17.6 mg is not associated with relevant safety findings.

There is no known antidote to Dymista. Close observation should be performed and adequate supportive care should be provided (M1) in the event of treatment emergent adverse events.

Other expected adverse reactions associated with the use can be found in the Canadian product monograph (M1).

5.10 Treatment Compliance

All study treatments will be administered by trained subjects during the EEU session under the supervision of the Investigator or the study staff.

5.11 Therapy at End of Study for compassionate use

Not applicable.

6.0 STUDY CONDUCT

Subjects eligible for study recruitment will have the nature, purpose, and risks of the study explained to them by the Investigator and/or designee. They will be provided with a written copy of the informed consent form (ICF) for the study and given sufficient time to consider the study's implications before deciding to participate. Subjects agreeing to participate in the study will sign the ICF and be given a duplicate copy before undergoing any screening procedures. Historical Data of Cliantha Research collected from General Screening may be used (if data obtained within 60 days prior to Visit 2 except for SPT which can be obtained 12 months prior to Visit 2). The data may include: medical history, social history, demographics and SPT. At screening, each subject will be assigned a screening number and listed in the *Subject Identification List* and *Screening/Enrolment Log* (blank form in TMF of the Investigator).

Once a subject enrolls in this trial the site will make every effort to retain the subject for the planned duration of the trial. Clinical trial site staff are responsible for developing and implementing support and retention plans. Elements of this plan may include the following :

- Thorough explanation of the complete clinical trial visit schedule and procedural requirements during the informed consent process and re-emphasis at each clinic visit.
- A simple explanation of the key data and key time points that are critical for the trial's successful analysis, and the importance of all the treatment groups to the overall success of the trial.
- Discussion at screening, and subsequent regular review of possible barriers to clinic visit attendance and full study participation and compliance.
- Collection and maintanance of contact information in the database for subjects which is maintained by Cliantha .
- Use of appropriate and timely study visit reminders.
- In case of missed visits, at least 3 attempts at 3 different timings through phone and if subject is not responding, he/she will declared as lost to follow up..

In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject so that they can appropriately be withdrawn from the study. All contact attempts should be documented in the subject's source documents. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF. Regardless

of site plans to support and retain subjects within the trial, subjects may voluntarily withdraw from the trial for any reason and at any time.

For a subject that completes the study and all procedures it is anticipated that the duration of study would be up to 56 days (duration may be longer if re-priming is required).

For details and timings of assessments, refer to Section 7.0.

6.1 Screening Procedures

Each prospective subject must agree to participate in screening procedures by signing the most recent ICF before any screening or re-screening (if applicable) procedure is initiated. The Principal Investigator or Medical Sub-Investigator will review the inclusion and exclusion criteria to confirm eligibility of each subject prior to enrolment.

6.1.1 Screening (Visit 1)

Subjects will commence screening procedures on Day -28 to -2 to confirm that they meet the selection criteria for the study.

The following procedures will be performed at screening:

- A government issued ID containing an image of the subject or a government issued non-photo ID with a non-government photo ID of the subject will be used to confirm the subject's identification
- A COVID screening questionnaire with oral temperature will be performed before obtaining the Research Subject Informed Consent Form.
- Subjects will be presented with and asked to sign the Research Subject Informed Consent Form. Subjects can discuss issues of concern with the PI/designee. Only patients who sign the informed consent will be evaluated for inclusion and exclusion criteria.
- Collect demographic information and social history
- Record medical history (including surgical history, allergy history and history of asthma) (brief medical history will be sufficient if medical history was already assessed during general screening within 60 days prior to Visit 2)
- Perform vital signs measurement (blood pressure, heart rate, oral temperature and respiratory rate)
- Assessment of any prior medication use within the last 6 months or longer as required as per the table in the exclusion criteria
- Physical examination including an examination of the ears, nose and throat and measurements of height and weight
- Perform a skin prick test (if documentation within 12 months is not available)
- Nasal inspection with anterior rhinoscopy
- Blood and urine samples will be collected for clinical laboratory testing
- Spirometry will be performed

- A urine drug & alcohol screen will be performed
- A urine pregnancy test will be performed (females of childbearing potential only)
- Subjects will be evaluated if they meet the inclusion/exclusion criteria
- Subjects will be trained and provided with a paper diary card to record any adverse events and use of any concomitant medications during their time at home. The subjects will be asked to bring their diary cards with them to the next visit for the review of adverse events and use of any concomitant medications during their time at home.

6.2 Treatment phase

6.2.1 Priming/Screening (Period 1, Visit 2) – Day -1

If the subject meets the eligibility criteria during the screening visit, they will attend a 2-hour priming/screening visit in a ragweed EEU where they will be exposed to ragweed pollen at an average concentration of 3500 ± 500 grains/m^3 for evaluation of the inclusion criteria. Subjects will be regarded to be suitable for this investigation if they are asymptomatic or with mild symptoms during the baseline recording of symptoms prior to start of the EEU session (TNSS of ≤ 3 out of a possible 12, with each symptom being less than 2).

The following assessments will be conducted:

- A government issued ID containing an image of the subject or a government issued non-photo ID with a non-government photo ID of the subject will be used to confirm the subject's identification.
- A COVID screening questionnaire with oral temperature will be performed and results of COVID test performed within 5 days prior to this visit or on the day of Visit 2 will be checked.
- The paper diary card will be collected and reviewed for any adverse events and if subjects have taken any concomitant medications since the last visit. The paper diary card will be stored with the subject source documents.
- A urine pregnancy test will be performed (females of childbearing potential only).
- Subjects will be trained on how to use the electronic diary (ePDAT™) to record their allergy symptoms and the ePDAT™ will be dispensed to subjects prior to the start of the EEU session.
- Subjects will record their nasal symptoms (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptoms (itchy eyes, watery eyes, eye redness) prior to entering the EEU and 30, 60, 75, 90, 105 and 120 minutes (+ 5 minutes) after entering the EEU.
- Vital signs (blood pressure and heart rate) will be measured prior to entering the EEU and after the EEU.
- Subjects will be monitored for adverse events throughout the EEU sessions.

If subjects qualify for Visit 3, the following procedures will be performed after end of the EEU session:

- Subjects will be trained on how to use the training placebo nasal spray.
- Subjects will be provided with a new paper diary card to record any adverse events and use of any concomitant medications during their time at home. The subjects will be asked to bring their diary cards with them to the next visit for the review of adverse events and use of any concomitant medications during their time at home.

The EEU sessions should begin at around the same time (± 2.0 hours) throughout the study for each subject.

In order to be eligible for Visit 3, subjects will be required to meet a minimum threshold TNSS response of ≥ 6 out of a possible of 12 at least twice during hours 0-2 in the EEU, with at least one occurring during the last two time points. Additionally, subjects will be required to meet a score of at least 2/3 for runny nose at least twice during hours 0-2 in the EEU, with at least one occurring during the last two time points. These eligibility criteria do not need to be met at the same time point. Subjects will not be permitted to use rescue medications during the EEU session. If a subject cannot tolerate the EEU, they may leave at any time and will be observed in the clinic. If a subject leaves the EEU early, they will be excluded from the study.

Use of rescue medication may result in the removal of the subject from the study at the discretion of the Investigator.

Subjects are permitted to leave the EEU to use the restroom. Subjects will be advised not to leave the EEU during pollen sampling, within 10 minutes before or during their time point assessments. Subject restroom breaks will be monitored and documented by study staff.

During each EEU session, measurements at the same time point will be done in the following sequence: nasal symptoms and ocular symptoms.

For each EEU session, subjects will be instructed to report their own symptoms and will be informed about the importance of accurate symptom reporting. Subjects who are found to be discussing their symptoms during the EEU session will be reminded that everyone's individual symptoms differ, and asked not to discuss with each other.

6.2.2 Randomization and Treatment Administration (Period 1, Visit 3) – Day 1

Eligible subjects will proceed to Visit 3, where they will attend a visit in a ragweed EEU. The start of the EEU session should begin at around the same time (± 2.0 hours) throughout the study for each subject. The following assessments will be conducted prior to EEU entry:

- A government issued ID containing an image of the subject or a government issued non-photo ID with a non-government photo ID of the subject will be used to confirm the subject's identification.
- A COVID screening questionnaire with oral temperature will be performed.
- The paper diary card will be collected and reviewed for any adverse events and if subjects have taken any concomitant medications since the last visit. The paper diary card will be stored with the subject source documents.

- The use of the ePDAT™ to record allergy symptoms will be reviewed and the ePDAT™ will be dispensed to subjects.
- Subjects will record their nasal symptoms (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptoms (itchy eyes, watery eyes, eye redness).
- A verbal reminder of the dosing technique will be given.
- Vital signs (blood pressure and heart rate) will be measured.

Subjects will then enter the EEU for approximately 6.5 hours and will record their nasal and ocular symptoms. Subjects must meet the predetermined minimum TNSS of ≥ 6 out of a possible 12 at least twice during hours 0-2 in the EEU, with at least one occurring during the last two time points, to be randomized to a treatment sequence. Additionally, subjects will be required to meet a score of at least 2/3 for runny nose at least twice during hours 0-2 in the EEU, with at least one occurring during the last two time points. These eligibility criteria do not need to be met at the same time point. The Investigator or designee will also perform an anterior rhinoscopy within 30 minutes of dosing. If there is evidence of complete nasal blockage on either one or both sides, the subject will be reassessed just prior to dosing. If there is evidence of complete nasal blockage on one or both sides at the second assessment, the subject will be excluded from the study. After the first 2 hours in the EEU, if the subject is eligible for the study, randomization and drug administration will be done during the next 30 minutes within the EEU. The allergen challenge will be then continued for further 4 hours. Subjects that do not meet the eligibility criteria will not be dosed and will be withdrawn from the study.

Subjects will have the following assessments conducted while in the EEU:

- Subjects will record their nasal symptoms (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptoms (itchy eyes, watery eyes, eye redness) at 30, 60, 75, 90, 105 and 120 minutes (+ 5 minutes) after entering the EEU.
- Anterior rhinoscopy within 30 minutes prior to dosing.

Subjects who are deemed eligible to participate in the clinical trial will have the following further assessments conducted while in the EEU:

- Administration of the randomized study treatment approximately 2.5 hours (± 5 minutes) after the start of the EEU session.
- Subjects will continue to record their nasal and ocular symptoms after dosing at 5, 10, 15 (+ 2 minutes), 30, 60, 90, 120, 150, 180, 210 and 240 minutes (+ 5 minutes).
- Vital signs (blood pressure and heart rate) will be measured after exposure in the EEU.
- Subjects will be monitored for adverse events throughout the EEU sessions.

The following procedures will be performed after end of the EEU session:

- Subjects will be provided with a new paper diary card to record any adverse events and use of any concomitant medications during their time at home. The subjects will

be asked to bring their diary cards with them to the next visit for the review of adverse events and use of any concomitant medications during their time at home.

Subjects will not be permitted to use rescue medications during the EEU session. If a subject cannot tolerate the EEU, they may leave at any time and will be observed in the clinic. If a subject leaves the EEU early, they will be excluded or withdrawn from the study.

Use of rescue medication may result in the removal of the subject from the study at the discretion of the Investigator.

Subjects are permitted to leave the EEU to use the restroom. Subjects will be advised not to leave the EEU during pollen sampling, within 10 minutes before or during their time point assessments, or during the 30 minutes post dosing. Subject restroom breaks will be monitored and documented by study staff.

6.2.3 Priming EEU (Period 2, Visit 4) – Day 13 (+ 5 Days)

Subjects will return to the study site after a period of at least 12 days.

Subjects will attend a 2-hour priming visit in a ragweed EEU. The following assessments will be conducted:

- A government issued ID containing an image of the subject or a government issued non-photo ID with a non-government photo ID of the subject will be used to confirm the subject's identification.
- A COVID screening questionnaire with oral temperature will be performed and results of COVID test performed within 5 days prior to this visit or on the day of Visit 4 will be checked.
- The paper diary card will be collected and reviewed for any adverse events and if subjects have taken any concomitant medications since the last visit. The paper diary card will be stored with the subject source documents.
- A urine pregnancy test will be performed (females of childbearing potential only).
- The use of the ePDAT™ to record allergy symptoms will be reviewed and the ePDAT™ will be dispensed to subjects prior to the start of the EEU session.
- Subjects will record their nasal symptoms (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptoms (itchy eyes, watery eyes, eye redness) prior to entering the EEU and 30, 60, 75, 90, 105 and 120 minutes (+ 5 minutes) after entering the EEU.
- Vital signs (blood pressure and heart rate) will be measured prior to entering the EEU and after the EEU.
- Subjects will be monitored for adverse events throughout the EEU sessions.
- At the end of the EEU session, subjects will be trained on how to use the training placebo nasal spray.
- Subjects will be provided with a new paper diary card to record any adverse events and use of any concomitant medications during their time at home. The subjects will

be asked to bring their diary cards with them to the next visit for the review of adverse events and use of any concomitant medications during their time at home.

The EEU sessions should begin at around the same time (± 2.0 hours) throughout the study for each subject.

Subjects do not need to meet a minimum threshold value for TNSS and will receive the next study treatment in the following EEU visit.

Subjects will not be permitted to use rescue medications during the EEU session. If a subject cannot tolerate the EEU, they may leave at any time and will be observed in the clinic. If a subject leaves the EEU early, they will be withdrawn from the study.

Use of rescue medication may result in the removal of the subject from the study at the discretion of the Investigator.

Subjects are permitted to leave the EEU to use the restroom. Subjects will be advised not to leave the EEU during pollen sampling, within 10 minutes before or during their time point assessments. Subject restroom breaks will be monitored and documented by study staff.

6.2.4 Treatment Administration (Period 2, Visit 5) – Day 15 (+5 Days)

Subjects will proceed to Visit 5 where they will attend another visit in a ragweed EEU and for administration of the next scheduled study treatment. The visit should take place 2 days after Visit 4, with one day in between each visit. The start of the EEU session should begin at around the time (± 2.0 hours) throughout the study for each subject.

The following assessments will be conducted prior to EEU entry:

- A government issued ID containing an image of the subject or a government issued non-photo ID with a non-government photo ID of the subject will be used to confirm the subject's identification
- A COVID screening questionnaire with oral temperature will be performed.
- The paper diary card will be collected and reviewed for any adverse events and if subjects have taken any concomitant medications since the last visit. The paper diary card will be stored with the subject source documents.
- The use of the ePDAT™ to record allergy symptoms will be reviewed and the ePDAT™ will be dispensed to subjects.
- Subjects will record their nasal symptoms (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptoms (itchy eyes, watery eyes, eye redness).
- A verbal reminder of the dosing technique will be given.
- Vital signs (blood pressure and heart rate) will be measured.

Subjects will then enter the EEU for approximately 6.5 hours and will record their nasal and ocular symptoms. The Investigator or designee will also perform an anterior rhinoscopy within 30 minutes of dosing. If there is evidence of complete nasal blockage on either one or both sides, the subject will be reassessed just prior to dosing. Any evidence of complete nasal blockage on one or both sides at the second assessment should be documented in eCRF.

Administration of the randomized study treatment will be done approximately 2.5 hours (± 5 minutes) after the start of the EEU session.

The following assessments will be conducted while in the EEU:

- Subjects will record their nasal symptoms (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptoms (itchy eyes, watery eyes, eye redness) at 30, 60, 75, 90, 105 and 120 minutes (+ 5 minutes) after entering the EEU.
- Anterior rhinoscopy within 30 minutes prior to dosing.
- Administration of the next randomized study treatment approximately 2.5 hours (± 5 minutes) after the start of the EEU session.
- Subjects will continue to record their nasal and ocular symptoms after dosing at 5, 10, 15 (+ 2 minutes), 30, 60, 90, 120, 150, 180, 210 and 240 minutes (+ 5 minutes).
- Vital signs (blood pressure and heart rate) will be measured after exposure in the EEU.

The following procedures will be performed after end of the EEU session (unless EOS occurs on the same day as Visit 5):

- Subjects will be provided with a new paper diary card to record any adverse events and use of any concomitant medications during their time at home. The subjects will be asked to bring their diary cards with them to the next visit for the review of adverse events and use of any concomitant medications during their time at home.

Subjects will be monitored for adverse events throughout the EEU sessions. Subjects will not be permitted to use rescue medications during the EEU session. If a subject cannot tolerate the EEU, they may leave at any time and will be observed in the clinic. If a subject leaves the EEU early, they will be withdrawn from the study.

Use of rescue medication may result in the removal of the subject from the study at the discretion of the Investigator.

Subjects are permitted to leave the EEU to use the restroom. Subjects will be advised not to leave the EEU during pollen sampling, within 10 minutes before or during their time point assessments, or during the 30 minutes post dosing. Subject restroom breaks will be monitored and documented by study staff.

6.2.5 Early study drug Termination (ET) visit

Subjects may request termination of study drug or withdrawal from the study at any time, or be required to withdraw or terminate study drug by the Investigator or Sponsor for reasons as per Section 4.2.5. If study drug is terminated or the subject withdraws or is withdrawn, the reason for termination/withdrawal should be established and recorded. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the outcome of subject contact attempt, if possible. The Investigator will contact Sponsor or designee in the event that a subject fails to complete the study or violates the protocol.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

Unless consent is withdrawn, subjects who prematurely terminate study drug will be asked to return to the clinic for an ET visit and will have this scheduled as soon as possible after their last dose of study drug.

At the ET visit, the same assessments as mentioned for end of study (EOS) Visit in Section 6.3 will be conducted.

6.3 End of Study (EOS) Visit - Day 15 (+5 Days)

The end of study examination will be conducted following the EEU session in Visit 5 or on a separate day.

The following assessments will be conducted:

- A government issued ID containing an image of the subject or a government issued non-photo ID with a non-government photo ID of the subject will be used to confirm the subject's identification (unless EOS occurs on the same day as Visit 5)
- A COVID screening questionnaire with oral temperature will be performed (unless EOS occurs on the same day as Visit 5).
- Vital signs (blood pressure and heart rate) that are conducted as part of Visit 5 after the EEU session or at early termination, if applicable.
- Subjects will be monitored for adverse events.
- Subjects will be asked if they have taken any concomitant medications (unless EOS occurs on the same day as Visit 5).
- The paper diary card will be collected and reviewed for any adverse events and if subjects have taken any concomitant medications since the last visit. The paper diary card will be stored with the subject source documents (unless EOS occurs on the same day as Visit 5).
- Collection of blood and urine for clinical laboratory assessments.

6.4 Follow up (telephone call)

Subjects will be followed-up by phone at within 5 to 7 days after last treatment administration.

The following assessment will be conducted:

- Subjects will be asked for occurrence of adverse events since last treatment administration.
- In case of an adverse event, subjects will be asked if they have taken any concomitant medications since last treatment administration prior to or for treatment of the adverse event.

7.0 TREATMENT PROCEDURES AND ASSESSMENT CRITERIA

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator or designated representative will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the Investigator or designated representative will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The Sponsor study team will be informed of these incidents in a timely fashion.

Activities specific to this protocol are expanded upon further below.

7.1 Efficacy Assessment

For timing of methods and assessments see the study schedule in Table 0-1.

7.1.1 Total Nasal Symptom Score (TNSS) and Total Ocular Symptom Score (TOSS) and Total symptom score (T7SS)

The total nasal symptom score (TNSS) is comprised of 4 symptoms from the nose (Table 7.1-1). The sum of the 4 symptom scores will be used as the TNSS. The total ocular symptom score (TOSS) is comprised of 3 symptoms from the eyes (Table 7.1-1). The sum of the 3 symptom scores will be used as the TOSS. The sum of TNSS and TOSS will be used as the total symptom score (T7SS).

Table 7.1-1 Allergic Rhinitis Symptoms

Symptom Class	Symptoms
Nasal Symptoms	Itchy nose, nasal congestion, runny nose, sneezing
Ocular Symptoms	Itchy eyes, watery eyes, eye redness

The nasal and ocular symptoms will be assessed by subjects on the ePDAT™ diary prior to and during their exposure to ragweed allergen in the EEU in Visits 2, 3, 4, and 5 at the time periods specified in the schedule of assessments (Table 0-2 and Table 0-3). A mirror and a picture scale (Figure 7.1-1) will be provided to subjects for assessment of eye redness.

All individual allergic rhinitis symptoms and ocular redness score will be scored on a scale of 0 to 3 as indicated in Table 7.1-2 and in Table 7.1-3 (accompanied with photographic scale in Figure 7.1-1), respectively. The sum of the TNSS will contribute to a score ranging from 0 – 12 and the sum of the TOSS will contribute to a score ranging from 0 – 9. The total 7 symptoms score (T7SS) will be the combination of the TNSS and TOSS, for a combined maximum score of 21.

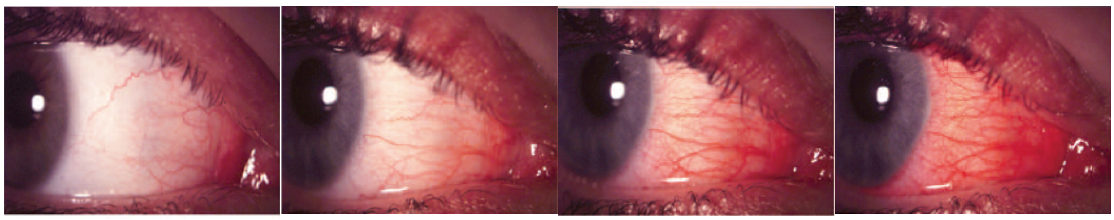
Table 7.1-2 Allergic Rhinitis Symptoms

Scale	Symptoms
0	None (no sign/symptoms evident)
1	Mild (sign/symptom clearly present, but minimal awareness; easily tolerated)
2	Moderate (definite awareness of sign/symptoms that is bothersome but tolerable)
3	Severe (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Table 7.1-3 Ocular Redness Score

Scale	Symptoms
0	None (not experiencing any redness in your eyes)
1	Mild (minimal redness in your eyes)
2	Moderate (more than minimal redness, but you can still see some clear white in your eyes)
3	Severe (Noticeably red or pink eyes or if the whites of your eyes are swollen)

Figure 7.1-1 Ocular Redness Scores



0 None | 1 Mild | 2 Moderate | 3 Severe

7.2 Safety Assessment

7.2.1 Adverse Event Assessment

If a subject reports any symptoms before drug administration, they will be evaluated by medical staff and necessary measurements will be performed. The Principal Investigator or Medical Sub-Investigator will be notified before dosing to determine the course of action.

Findings from screening procedures, e.g., laboratory tests or physical examinations will be recorded as medical history. Clinically significant worsening from the screening procedures will be recorded as adverse events.

Subjects will be routinely queried in regard to the presence or absence of adverse events using open ended questions. The clinic will provide documentation of any adverse events in the subject's eCRF. The adverse event source documentation will minimally include the following information: date and time of assessment, the outcome of the response, and identification of the clinic staff member collecting the information.

No adverse events of special interest will be monitored in this study.

7.2.2 Vital Signs

At screening, vital signs to be recorded are systolic and diastolic blood pressure and heart rate, respiratory rate and oral temperature. Vital signs (blood pressure and heart rate) will also be measured at Visit 2, Visit 3, Visit 4, Visit 5, and EOS/ET visit. Vital signs will be performed before and after the EEU session in each visit. Blood pressure and heart rate will be measured in a seated position (after at least 2 minutes of rest).

Any clinically significant changes in blood pressure and heart rate should be recorded as an AE. If the findings contribute to a clinical diagnosis (such as tachycardia in case of an abnormally increased pulse) this diagnosis should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

7.3 Other Aspects

The following issues are not intended to directly contribute to the assessment of efficacy and safety of the study medication. They will be recorded from each subject at scheduled times during the study (see Table 0-1) and cannot be related to a single treatment period.

7.3.1 Clinical Laboratory Tests

Clinical laboratory tests will be assessed at screening and at the end of study (EOS) or early termination (ET). Additional tests (i.e. pregnancy test, FSH test, COVID test) will be performed during the study as described in Table 7.3-1.

On the laboratory sheets, the Investigator must classify each value outside normal range into the following categories:

- Invalid value; a reason for this judgement must be specified. This classification may require a repeated measurement (e.g. from the same blood sample or a repeated blood draw) depending on the assumed sources of inaccuracy.
- No clinical significance, or attributed to an existing condition unrelated to study treatment.
- Clinical significance (e.g. serious, causing discontinuation, or requiring therapeutic measures) and a respective record in the source documents for AEs. If the findings

contribute to a clinical diagnosis this diagnosis should be recorded as an AE. Findings from screening procedures will be recorded as medical history.

The clinical laboratory tests include the following variables:

Table 7.3-1 Clinical Laboratory Variables

Theme	Variables
Hematology[1]	Leukocytes (white blood cell count) with differential, erythrocytes (red blood cell count), hemoglobin, hematocrit, thrombocytes (platelets)
Electrolytes[1]	Sodium, potassium, chloride
Clinical Chemistry[1]	Blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine transaminase (ALT), glucose, albumin
Urinalysis[1]	Glucose, protein, ketones, bilirubin, blood, nitrites, leukocyte, pH, specific gravity (if blood, nitrites, leukocytes are positive, a microscopic urinalysis will be performed)
Urine Drug & Alcohol Screen[2]	Amphetamines, cannabinoids, cocaine metabolites, opiates, phencyclidine, benzodiazepines, ethanol
Additional tests	• Pregnancy[3] (urine): females of childbearing potential only • FSH[2] (blood): if necessary to document postmenopausal status • COVID[4] (nasopharyngeal/oropharyngeal/nasal)

[1] Performed at screening and EOS/ET
[2] Performed at screening
[3] Performed at screening, Visit 2 and Visit 4.
[4] Performed within 5 days prior to Visit 2 and Visit 4 or on the day of Visit 2 and 4

7.3.2 Spirometry

At screening, spirometry will be performed on all subjects. Subjects must have $FEV_1 \geq 75\%$ of the predicted value to be enrolled in the study.

7.3.3 Demographic Data and Social History

During screening, age, sex, ethnic origin, height, and body weight will be recorded. Body weight will be assessed without shoes. During screening, social history (e.g. drug and alcohol abuse) will be collected.

7.3.4 General Medical History, Concomitant Diseases

Clinically relevant medical history (including drug sensitivities and allergies, major surgeries) and any disease present during screening will be documented under medical history and updated until first exposure to study treatment.

Medical history mentioned in the exclusion criteria, Section 4.2.2, occurring before exposure to the study treatment will be recorded under medical history.

7.3.5 Skin Prick Test

At screening, if prior documentation within the previous 12 months is not available, a skin prick test for a panel of common allergens will be performed:

Positive Control
Negative Control
Short Ragweed
Cat
Dog
Alternaria
Aspergillus fumigatus
Cladosporium cladosporioides
American Elm
Sugar Maple
White Poplar
White Ash
White Birch
White Oak
D. Farinae
D. Pteronyssinus
Grass Mix

7.3.6 Physical Examination

At screening, a physical examination will be performed by the Investigator, or other qualified personnel under the direction of the Investigator. The physical examination will include: general appearance, skin, head, eyes, ears, nose, throat, neck, chest, and cardiovascular, abdominal, neurological, lymphatic, and musculoskeletal systems. The source document will contain the findings of the physical examination and whether or not there are clinically relevant findings and the eCRF will document completion of the examination. Any abnormal finding should be recorded under medical history.

7.3.7 Anterior Rhinoscopy

At screening, the Investigator or designee will perform an anterior rhinoscopy to assess if there are any nasal structural abnormalities that might interfere with study results. At Visit 3 and Visit 5, the Investigator or designee will perform an anterior rhinoscopy within 30 minutes of dosing. If there is evidence of complete nasal blockage on either or both sides, the subject will be reassessed just prior to dosing. Any evidence of complete nasal blockage on one or both sides at the second assessment should be documented in the eCRF.

7.3.8 Pregnancy Testing

A urine pregnancy test (females of childbearing potential only) will be performed at screening and Visit 2 and Visit 4. The results of each pregnancy test will be recorded in the subject source and the eCRF. Additional pregnancy tests may be performed if pregnancy is suspected.

For consequences of a positive pregnancy test see Section 11.5.4.

7.3.9 Blood Volume

Total blood sampling volume for an individual subject is approximately 18 mL (9 mL at screening and 9 mL at EOS/ET). Additional blood samples may be taken for safety assessments, provided the total volume taken during the study does not exceed 500 mL during any period of 30 consecutive days, and the ethics committee/IRB is notified of the blood collection.

7.4 Restrictions

Study restrictions include all items listed in the Lifestyle Guidelines (Section 4.4) and the concomitant medications as described in the exclusion criteria section of this protocol (Section 4.2.2) and will be prohibited throughout the duration of the study. If concomitant medications change during the study, a discussion between the Principal Investigator or a Medical Sub-Investigator along with the Sponsor should occur, and a decision to continue or discontinue the subject will be made based on the medication's pharmacology and pharmacokinetics.

7.5 Mitigation in the event of a public health emergency

In the event of any circumstances impacting the ability of enrolled subjects to attend for scheduled visits at the investigator site, such as travel restrictions imposed due to COVID-19, investigators must notify the Sponsor and make the necessary arrangements to ensure the safety of their enrolled subjects. They should also evaluate whether their subjects should continue in the clinical trial. Those that have not been randomized yet should not continue the study.

Protocol deviations arising under such circumstances (eg, missed or delayed visits, assessments not performed, etc) will be clearly documented in the eCRF and the reasons will be collected.

7.5.1 Pandemic COVID-19 Response Plan

Regulatory authorities have recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may impact the conduct of clinical study. COVID-19 pandemic has created a lot of uncertainty in the current situation and has put subject's safety, protocol compliance and data validity at high risk.

Due to COVID-19 pandemic, challenges may arise for clinical study conduct, for example, quarantines of site personnel/study participants, travel limitations, interruptions to the supply

chain for the IP(s), or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol specified procedures, including administration or use of investigational product, housing duration or adhering to protocol specified visits and laboratory/diagnostic testing.

To accommodate these challenges and mitigate safety risks associated with COVID-19, changes may be required from approved protocol which include (but not limited to) conducting the study in multiple groups, change in study procedures timing, change in subject's housing duration, additional test or parameter may be performed to standard inclusion or exclusion criteria at the discretion of Investigator/designee, etc. The changes made to the procedure will prioritize subject's safety and data validity and integrity. For any significant change, as per regulatory guidelines, a planned protocol deviation will be filled and notified to IRB and/or local regulatory (as applicable).

All participants will be pre-screened prior to enrolment into the study and evaluated for risk factors and symptoms of COVID-19 according to the most recent regional Public Health guidelines available at the time of pre-screening. The screening is conducted through telephone at the time of appointment confirmation and again when the subject arrives at the clinic for any visit.

Additional health checks including body temperature or other vital sign monitoring, etc. may be performed during the study at the discretion of Investigator/designee, even if not specified in the protocol. Subject who is tested positive to COVID-19 during the study will be withdrawn from the study. This subject and other subjects in close contact will be handled as per applicable local Public Health Guidelines.

As the science and regulations are continuously being adapted to the evolving information around the pandemic, additional measures apart from the ones mentioned here may be undertaken to ensure subject safety and appropriate study conduct. The IRB and the sponsor would be informed for their review and approval as applicable.

Risk Mitigation plan/Risk Evaluation and Mitigation strategy will be made to minimize the risk for COVID-19 exposure and to handle possible situations during COVID-19 pandemic.

8.0 DATA MANAGEMENT

A database (EDC) will be created, which reflects the data required to be recorded and analyzed per protocol.

The creation and validation of the EDC system and management of the data will be conducted in accordance with the Division 5 of the Canadian Food and Drug regulations and guidelines (R5) and CFR 21, part 11 of the US regulations (R6). Methods used to ensure the quality and integrity of the data will be documented in the Data Management Plan (DMP), which will be approved by data management and the Sponsor.

The information from the subject source documents will be entered into the EDC system by the site, reviewed by the site's Quality Control group, compared and corrected accordingly. Computerised edit checks on completeness, correctness, plausibility (such as range checks, cross-checks) will be performed according to the study specific data management plan. All

identified discrepancies will be queried utilizing the EDCs query management system. No self-evident corrections (such as spelling and header corrections) will be made by the data manager. Any updates to the data, whether through updates on the page or through the query management system will be recorded in the EDC system's audit trail.

The ePDAT™ data will be transferred to the Cliantha Clinical Data Management group and integrated into the final datasets.

The database will be soft-locked after all source data verification (SDV) has been completed and all SDV queries are resolved and the coding for medical terms (AEs, medical history) and concomitant treatments is completed. The database will be locked when the sets of subjects for analysis are determined.

Unblinding of the study will only be performed after the database has been locked. For unblinding of individual cases see Section 5.6.

9.0 STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. Any further change from final SAP will be reflected in the study Clinical Study Report (CSR).

Statistical analysis and the associated tables, listings and figures will be performed using SAS® (SAS Institute Inc., Cary, USA) version 9.4 or higher at 5% alpha level of significance unless specified.

9.1 Sample Size Determination

Assumptions for parameters were derived from a very similar chamber study of Dymista (X-03065-3311; Bousquet et al. 2018, O1).

[redacted]

[redacted] a total of 216 randomized subjects should be included in this study.

In case a substantial number of subjects could only participate at one treatment period of this cross over study due to public health emergency (COVID-19, etc.) a replacement of patients may be considered in a protocol amendment.

9.2 Populations for Analyses

Safety population (SAF) : all subjects having received at least one dose of the study treatment. The SAF will be used for the analysis of safety data and subjects will be categorized according to the treatment that they actually received.

Full analysis set (FAS) : This will be the intention to treat (ITT) population. These are all randomized patients including subjects who receive incorrect treatment, do not complete the study or do not comply to the protocol, and who are randomized but do not take any study medication..

Per-protocol set (PP) : all subjects in the FAS who had no major protocol violation that would impact on the primary efficacy endpoint. Potential significant protocol deviations are listed below and will be further defined in the SAP. The list of major protocol deviations will be finalized prior to database lock and unblinding as part of the final blind data review (BDR). Data will be summarized and analyzed according to the treatment a subject actually received.

Potential violations that may result in the exclusion of the subject from the per-protocol population include, but are not limited to:

- Not fulfilling all of the inclusion and none of the exclusion criteria during randomization
- Not receiving the treatment to which they were randomized
- Taking prohibited concomitant medications that may affect the primary variables

FAS Subset with Moderate/Severe Ocular Symptoms: all FAS subjects with baseline TOSS at Visit 3 ≥4.

9.3 Statistical Analyses

Adequate descriptive statistics will be provided for each endpoint. Mean time courses for raw values and changes from baseline will be displayed graphically. Demographic data and background characteristics will be displayed descriptively. Baseline measurements of the efficacy variables will be compared descriptively for both treatment periods.

Baseline for each efficacy variable is defined per period (visit 3 and visit 5 separately) as average of the last 2 assessments (105 min and 120 min) of this variable prior to dosing with study treatment. In case one of these two assessments is missing, the baseline will be the remaining value.

9.3.1 Definition of the Primary Efficacy Endpoint

For onset of action assessment:

- Changes from baseline in TNSS at each post-dose assessment time point (0 to 4 hours p.a.)

9.3.2 Primary Analysis of Primary Endpoint

[redacted]

The onset of action is defined as the first time point after initiation of treatment when the product demonstrates a greater change from baseline in compared to the placebo, which proves durable from this time point until the end of the last assessed time point (4h) of this study. Multiple comparisons are handled by hierachical testing from 4h backwards.

9.3.3 Secondary/Sensitivity Analysis of Primary Endpoint

The analysis of the PP population will serve as a sensitivity analysis.

9.3.4 Definition and Analysis of the Secondary Endpoints

Following secondary endpoints will be analyzed and reported similar to the analysis method and reporting of the primary endpoint as described above using only the FAS population:

- Changes from baseline in TOSS and total 7 symptoms score (T7SS) at each post-dose assessment time point (0 to 4 hours p.a.)
- Change from baseline in individual nasal symptom scores (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptom scores (itchy eyes, watery eyes, eye redness) at each post-dose assessment time point (0 to 4 hours p.a.)

[redacted]

Responder analysis: Time to relevant response to therapy (30% and 50% reduction of TNSS) will be analysed by means of Kaplan Meier analysis.

Time course arithmetic mean ± SE curves for raw values (0-6.5 hours) and for change from baseline in TNSS for the post-dose time points 0 to 4 hour will be presented by treatments overlaid each other using the FAS Population.

9.3.5 Missing Data

Missing data will not be replaced. More details might be specified in the SAP.

9.3.6 Sub-Group Analyses

Changes from baseline in TOSS and T7SS will be calculated in a subgroup of subjects with moderate/severe baseline TOSS at Visit 3 as defined in Section 9.2.

9.3.7 Safety Analyses

Analysis of all safety data will be performed on the safety population (SAF) and will be presented by the treatment received.

9.3.7.1 Adverse Events

Adverse events will be coded using latest version of Medical Dictionary for Regulatory Authorities (MedDRA). The occurrence of treatment emergent AEs (TEAEs) and SAEs will be summarized in terms of incidence, as well as in terms of total number of AEs. Analysis of AEs in terms of incidence by severity and by relatedness will also be provided.

Prior and concomitant medications will be listed by subject and coded using the latest version of the WHO Drug Dictionary . Medical history will be listed by subject and coded using the latest version of MedDRA and will be summarized.

9.3.7.2 Vital Signs

Summary statistics of vital signs will be presented for non-treatment days (Visit 1, Visit 2, Visit 4 and EOS/ET Visit). For vital signs during the treatment periods, the Pre-EEU observation will be considered as baseline. During treatment periods, summary statistics for the observed data at Pre- and Post-EEU session as well as the change at Post-EEU session for Visit 3 and Visit 5 will be presented by treatments.

Blood Pressure and heart rate will be listed and descriptively summarized (N, mean, standard deviation, minimum and maximum) by treatment and visit.

9.3.8 Planned Interim Analyses

No interim analysis is planned for this study.

10.0 ADMINISTRATIVE PROCEDURES

10.1 Source Documentation Forms

All clinical data will be recorded by the clinical staff on raw data sheets and/or recorded electronically using validated software. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidance. The Investigator will assume responsibility for

ensuring the completeness and accuracy of all clinical documents independent if sourced on paper or electronically generated.

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

Each page of the subject source will be identifiable by the study number, an identifier for the version, the subject number, and a page number. Completed subject source documents must be dated and signed by the Investigator or authorised study personnel.

The nature and location of all source documents will be documented separately. Source data may be directly captured from devices, transferred from 3rd parties (e.g. laboratory data) or entered manually into eCRF/database.

10.2 Access to Data/Source Documentation

The Investigator or designated representative will permit full access to data and source documentation for the purpose of clinical monitoring, audits, IRB/IEC review and regulatory inspections.

10.3 Final Clinical Study Report and Case Report Forms (CRFs)

A written clinical study report will be provided in accordance with the International Conference on Harmonization (ICH) E-3 guidelines including Annex I (Synopsis) documenting the clinical execution of the study. This report will include a description of important protocol deviations. All protocol deviations will be listed in the appendix. The final report will also include reasons for withdrawals and any necessary treatment(s). The report will also include tables presenting demographics (separate summary tables for enrolled and completed subjects), and adverse events recorded during the study. In addition, the clinical study report will include a Quality Assurance statement, documenting that the report has been reviewed for completeness, accuracy, and compliance with the protocol and applicable local and federal regulations. For final clinical reporting purposes only, adverse events deemed “definite”, “probable” or “possible” will be included in the treatment-related summaries/listings.

Electronic Case Report Forms (eCRFs) containing data transcribed from subject source documents (as appropriate) and copies of other source documents will be supplied by the clinical site. All study staff will be trained to ensure that accurate, consistent, complete, and reliable data is entered into the eCRF unique for each subject.

The Principal Investigator must sign each subject’s eCRF after completion of data entry, signifying that the data entered in the eCRF is complete and accurate. Electronic CRFs will be provided.

10.4 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and well-being of the study subjects requires medical treatment, the study will be conducted as

described in the approved protocol (and amendments, if applicable), GCP and applicable SOPs. In addition, the study will be conducted in accordance with the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted. Any deviation(s) from the protocol will be recorded and presented in the final report (see Section 10.3).

All scheduled events in the study should be conducted at the time(s) specified. Allowed deviation windows are specified in the protocol (see Section 6.0). Tests conducted outside of the allowed deviation windows will be considered a protocol deviation.

10.5 Investigator's qualification

In accordance with ICH E6 (R2), the Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and other relevant documentation requested by the Sponsor, the IRB, or the competent authority.

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates trial-related duties and functions conducted at the trial site. The Investigator/institution should ensure all individuals and parties retained to perform trial-related duties are qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of those study tasks and the generated data.

10.6 Data Handling and Record Retention

All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

A eCRF is required to be completed for each subject. The eCRF is property of the Sponsor and the Investigator must review all eCRFs prior to submission to the Sponsor.

All data collected in the study will be captured and maintained in a secure and validated electronic data capture (EDC) system or collected electronically and provided to clinical data management. Study staff will enter the data into the database as indicated in Section 10.3 with the exception of data collected through an electronic source (e.g., ePDAT™ entries).

The paper diaries are for cumulative documentation of adverse events and use of concomitant medication. They serve as basis of information for the Investigator to transfer relevant information to the eCRF and diary data will not be entered directly into the EDC. Completed diaries will be stored with the subject source documents.

The ePDAT™ data will be transferred to the Cliantha Clinical Data Management group and integrated into the final datasets. In the event of an ePDAT™ failure, paper diary cards will be used as a back-up to collect symptom scores.

Details for all data sources will be provided in the Data Management Plan (DMP).

The Sponsor and the Investigator will each maintain a Trial Master File (TMF) for the "essential documents" as specified by ICH E6 (R2). Sponsor or its designated CRO will provide an Investigator's Site File (ISF) as a part of the TMF to each PI containing a cover page with a description of the required contents for each binder section and any project specific standardized forms . The Sponsor and Investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

When a copy is used to replace an original document (e.g., source documents), the copy should fulfil the requirements for certified copies as specified by ICH E6 (R2).

All records pertaining to the receipt and return of study supplies (particularly study medication) and copies of final case report forms, worksheets, and other pertinent source documents must be retained in accordance with ICH-GCP and the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

The Investigator must obtain in writing the Sponsor's agreement to dispose of any records, even if the retention period has been reached.

10.7 Monitoring

Monitoring of the study will be performed by a monitor independent from the Investigator's site. The Sponsor reserves the right to monitor and/or co-monitor the study in frame of Sponsor oversight.

The sponsor or designee will base the monitoring strategy on a systematic, prioritised, risk-based approach. The extent and details of the monitoring as well as the rationale for the monitoring strategy will be documented in a monitoring plan tailored to the human subject protection and data integrity of the study.

One of the obligations of the monitors is to check the accuracy and completeness of the source documents, the eCRF entries, and other trial-related records against each other (source data verification) as outlined in ICH E6 (R2), this can be completed on site or remotely. Obligations of the monitors are specified in a clinical monitoring plan.

The monitor informs the Investigator of any entry error, omission, or illegibility in the source documentation and eCRF. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the Investigator or by authorised study personnel. The Principal Investigator should guarantee that authorised study personnel are available during monitoring visits.

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor or designee should perform a root cause analysis and implement appropriate corrective and preventive actions.

Monitoring visits will be recorded in a Monitoring visit log at the center of the Investigator. The Monitoring Visit Log will be maintained in the sites ISF. A copy of the log will be

collected at close out and maintained in the Sponsor TMF. The original will be stored in the Investigator's file.

10.8 Confidentiality

Information furnished to Clinical Investigators and IRBs/Ethics Committees will be maintained in confidence by the Clinical Investigator and IRB/Ethics Committee. By signing this protocol, the Investigator affirms to the Sponsor that he/she will maintain, in confidence, information furnished to the IRB/Ethics Committee relevant to this study under appropriate understanding of confidentiality with such IRB/Ethics Committee.

By signing the protocol, the Investigator agrees that within local regulatory restrictions and institutional and ethical considerations, the Sponsor may consult and/or copy source documents (e.g., laboratory reports, workbooks, medical records) in order to verify eCRF data.

Data, including personal data, from source documents may be transferred to Viatris entities or service providers which may be located inside or outside of Canada including, but not limited to, the USA, the European Economic Area (EEA). In such cases, Sponsor ensures that such transfers are carried out in compliance with all applicable data protection laws and regulations and signed Informed Consent Form (ICF).

Personal study related data will be kept confidential. Study documents submitted to the Sponsor, e.g. eCRFs, etc., are only identifiable by pseudonym, i.e. the Subject No. The Investigator will keep in his/her TMF the original of the Subject Identification List and Screening/Enrolment Log (including complete name and date of birth of each subject). To allow compliance with GCP, each subject will be asked for consent regarding the access to his/her personal study related data for monitoring, audits, and inspections as well as regarding transmission and storage of his/her pseudonymous data; a respective statement will be part of the informed consent. The subject has the right to access and rectification of his/her personal data according to the General Data Protection Regulation (GDPR) (R4).

10.9 Ethics and Regulatory Authorities

Guidelines will be followed with regard to the treatment of human subjects in the study, in accordance with the requirements of the Declaration of Helsinki and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E6 (R2)) (R3) in addition to the regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

10.9.1 Institutional Review Board/Ethics Committee

The Investigator is responsible for obtaining initial and continuing review (at intervals not more than once per year) of the study by an IRB/Ethics Committee, or in accordance with applicable government regulations of the country where the study is being conducted as well as the country where the study will be submitted. This study will not enroll any subjects until the IRB/Ethics Committee provides written approval of the protocol and the informed consent to the Investigator. In addition, a copy of the IRB/Ethics Committee approval documents must be provided to the Sponsor prior to enrolling any subjects into the study.

10.9.2 Regulatory Authority

This clinical study protocol, title and a list of investigational sites, IEC(s)/IRB(s) approvals, as well as other relevant documentation will be submitted, as applicable, to the local Regulatory Authorities for review and approval or notification prior to trial start. Upon completion, the Regulatory Authorities will be notified the study has ended, as applicable. The study will only be undertaken in compliance with the local regulatory requirements.

10.10 Informed Consent

A properly executed, written informed consent in compliance with current GCP guidelines and ICH guidelines shall be obtained from each volunteer prior to entering the study. A copy of the informed consent document to be used will be submitted by the Investigator to an independent institutional review board (e.g. IRB or ethics committee) and the Sponsor and/or its agent for review and approval prior to the start of the study. The Investigator shall provide a copy of the signed and dated informed consent to the subject, and a signed and dated copy shall be maintained in the volunteer's medical record.

10.11 Trial Registration

This clinical trial will be registered in a publicly accessible database, which is a primary or partner registry of, or a data provider to, the international clinical trials registry platform of the World Health Organization (WHO ICTRP), before start of recruitment.

10.12 Disclosure and Publication of Clinical Study Data

The disclosure and publication of clinical study data will be detailed in the clinical trial agreement with the Investigators.

10.13 Financing and Insurance

The study will be financed by Meda Pharma GmbH & Co. KG (A Viatris company).

For all patients participating in the trial the Sponsor or the designated CRO has taken out a study-specific insurance in accordance with national legislation, covering liability of the Investigator and Sponsor for damages that occurred in relation to the study. Particular reference is made to the obligations of the insured patient participating in the study, such as immediate notification of any injury that might have occurred during the trial. For further relevant insurance conditions please refer to the copy of the policy and conditions in the TMF of the Sponsor and Investigator.

10.14 Quality assurance and management

This clinical study will be conducted in accordance with Standard Operating Procedures (SOP) of the Sponsor (and/or representatives thereof) and Cliantha Research, the requirements of International Council for Harmonisation Good Clinical Practice Guidelines (ICH GCP (E6 R2), principles provided in Helsinki Declaration, as well as in accordance with the applicable local legislation and regulations of the country where the study is being

conducted. Compliance with the requirements may be provided by audits of the investigational sites and the data obtained in the study.

Audits and inspections may be carried out by the Sponsor's quality assurance department or its designee, local authorities, or authorities, to whom information on this study has been submitted. All documents pertinent to the study must be made available for such inspection after an adequate announcement. Informed consent of patients participating in this study has to include the consent to this access to source documents.

A Quality Management system based on a risk-based approach according to ICH GCP E6 (R 2) addendum (R3) will be implemented to manage quality throughout all steps of the clinical trial. It will include identification of critical processes and data, identification, evaluation, control, review and reporting of risks using appropriate tools in cooperation with the CRO. Risks will be periodically reviewed during the study.

10.15 End of Trial

The end of trial is considered to be the date of last subject last contact or the date of early termination of the study whichever is the later.

11.0 ADVERSE EVENTS AND SAFETY REPORTING

The adverse event collection period begins at signing of informed consent and continues until 5 to 7 days after the last dose of study medication. Adverse events occurring during this period need to be reported to the sponsor according to Section '**Collection and Recording of Adverse Events**.' The investigator is also responsible for notifying the sponsor if he/she becomes aware of any adverse event after the study period has ended and it is considered related to the study medication (i.e. an adverse drug reaction). Once an AE is detected, it should be followed until its resolution or until it is judged by the principal investigator to be stable or permanent.

11.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physical findings, symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

Clinically significant changes from baseline in laboratory assessments, vital signs, and physical examination are to be recorded as adverse events. Clinically significant abnormalities include:

- a result associated with accompanying signs/symptoms

- a result that requires additional diagnostic testing or medical/surgical intervention
- a result that leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- a result considered to be an adverse event by the investigator or sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

- An abnormal safety assessment (e.g. laboratory, vital signs, ECG) associated with a clinical diagnosis that has been recorded as an AE does not require a separate AE entry
- Events meeting the definition of an AE also include:
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug or drug-food interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. (Please refer to Section '**Special Situations**' for further details)
- A symptom or medical complication related to a protocol-mandated intervention, including screening procedures

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening

NOTE: The term **"life-threatening"** in the definition of "serious" refers to an event in which the subject 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.

- requires inpatient hospitalisation or prolongation of existing hospitalisation

Note: In patient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the study drug or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization or accommodation problems and without medical background does not need to be considered an SAE.

Events NOT to be reported as SAEs are hospitalizations for the following:

  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care)
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

Hospitalization also does not include the following: Rehabilitation facilities, Hospice facilities, Respite care (e.g., caregiver relief), Skilled nursing facilities, Nursing homes

- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event.
    - Note: medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject and / or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
    - The seriousness criterion of "medically significant" should **only** be selected when none of the other seriousness criteria apply to the event but the investigator still considers the event as serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Treatment emergent adverse events

Any adverse event that occurs or worsens during a given period after the study medication has been administered. In the present cross-over study an AE is considered treatment emergent when occurring in the period from administration of study medication until 5 days (120 h) thereafter.

Adverse drug reaction

All noxious and unintended responses to an investigational product related to any dose of the investigational product should be considered adverse drug reactions (ADRs). The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an AE is at least a reasonable possibility. All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to an investigational product will be designated as ADRs.

All AEs, with the causal relationship to the study drug reported as "possible", "probable" or "definite" will be considered ADRs. If the relationship to the study drug is not given, then the AE must be treated as if the relationship were "possible."

Expected/Unexpected adverse event

An expected AE is defined as one whose nature, severity or outcome is consistent with the applicable reference safety information described of the study drugs.

An AE is to be considered unexpected if the nature, severity or outcome is not consistent with the applicable product reference safety information.

Preexisting Condition

Any medical condition that is present at the time that the participant is screened will be considered as baseline medical history and not reported as an AE. A baseline or preexisting condition should be recorded as an adverse event only if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

Any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event/Serious Adverse Event

At the last scheduled contact with the subject the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator becomes aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

11.2 Special Situations:

The following situations may by associated with a serious outcome and should be evaluated for expedited reporting to the sponsor.

- Any diagnosis of **Cancer** or **Neoplasm** is to be reported as a serious adverse event.
- **Emergency Room Visits:** Events that result in emergency room visits that do not result in admission to the hospital are not routinely considered to be serious events; however, these events should be evaluated for one of the other serious outcomes (e.g., life-threatening, other serious [medically significant] events).
- **Overdose:** Overdose *per se* will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent; this should be reported regardless of sequelae. signs and symptoms associated with accidental overdose are to be recorded as adverse events or as serious AEs. If adverse events associated with overdose fulfil any of the serious criteria (as defined in section '**Serious Adverse Event**'), a completed SAE report form is required to be submitted.
- Reports of **Drug-drug interaction and Drug Abuse and Medication Errors**: drug interactions or abuse of the study medication must be recorded as AEs. Medication

errors will be captured as protocol deviations while any associated signs or symptoms must be recorded as AEs on the CRF. In addition, any serious consequence of drug interactions, drug abuse, or medication error must be reported immediately if these fulfil any of the SAE criteria.

11.3 Collection and Recording of Adverse Events

During the Adverse Event Reporting Period, the PI or designee (trained qualified study clinic staff) will record all adverse events. At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and in the appropriate adverse event module of the case report form (CRF). Information to be collected includes AE name or term (in standard medical terminology) and final diagnosis, event description, time and date of onset, clinician's assessment of severity, seriousness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), action taken with the study drug, treatment for the event and time (if available) and date of resolution/stabilization of the event.

Any findings from protocol specified safety assessments that are associated with the indication being studied are not to be reported as AEs or SAEs, unless judged by the investigator to be more severe than expected for the subject's condition.

All clearly related signs, symptoms, and abnormal results of diagnostic procedures should be grouped under one diagnosis on the CRF where possible and appropriate.

The clinical course of each event should be followed until resolution or stabilisation. Adverse events that are still ongoing at the end of the study period must be followed up to determine the outcome. Any adverse event that occurs after the study period and is related to the study treatment or study participation should be recorded; and if serious, the investigator should also immediately report it to the Sponsor.

11.4 Classification of an Adverse Event

11.4.1 Severity

The Investigator will assign a severity rating to each AE. For purposes of consistency, the following scale is to be used:

Grade 1 - MILD	Does not interfere with subject's usual function.
Grade 2 - MODERATE	Interferes to some extent with subject's usual function.
Grade 3 - SEVERE	Interferes significantly with subject's usual function.

It is important to distinguish between severe AEs and Serious AEs. Severity is a classification of intensity, whereas an SAE is an AE that meets any of the regulatory specified criteria (see definitions, Serious Adverse Event)

11.4.2 Causality

For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality of each AE.

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. The Investigator must make an assessment of the relationship of each AE (serious and non-serious) to the study treatment(s) and record this relationship in the CRF.

Factors that need to be considered when making a causality assessment include: Temporal relationship, Clinical and pathological characteristics of the event(s), Pharmacological plausibility, Exclusion of confounding factors (medical and medication history), Drug interactions, De-challenge/re-challenge, Dose relationship.

A suspected relationship (definite, probable, possible) between the events and the study medication means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality. The Investigator is responsible for assessing relationship of AEs to study treatment in accordance with the following definitions:

Category	Causality	Description
DEFINITE	Causal relationship is certain	For example: the temporal relationship between drug exposure and the adverse event (AE) onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
PROBABLE	High degree of certainty for causal relationship	For example: the temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely.
POSSIBLE	Causal relationship is uncertain	For example: the temporal relationship between study treatment exposure and the AE onset/course is reasonable or unknown, dechallenge information is either unknown or

		equivocal; could also be explained by disease or other drugs.
UNLIKELY	Causal relationship is improbable	Another explanation is more likely such as disease, environment, or other medication. Does not represent a known reaction to study drug.
UNRELATED/NOT RELATED	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible

For SAEs, if the relationship to the study treatment(s) is considered to be unlikely or not related, an alternative suspected etiology should be provided when possible (e.g., concomitant medications, intercurrent illness/events, study-related procedure).

11.4.3 Expectedness

The Sponsor or its designated representative will be responsible for determining whether an AE is expected or unexpected based on the reference safety information. The reference safety information mentioned in the approved Canadian Product Monograph (M1) will be used in this study for the expectedness assessment of SAEs.

11.4.4 Outcome

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Sponsor or its designated representative.

The outcome at the time of last observation will be classified as:

RECOVERED/RESOLVED where the subject recuperated and is free of any pathological conditions resulting from the prior disease or injury.

RECOVERED WITH SEQUELAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.

NOT RECOVERED/NOT RESOLVED (i.e. ongoing) where the subject has not recuperated from the condition or injury and the event is still considered ongoing

RECOVERING where the subject has begun to recuperate from the condition or injury but the event is considered ongoing at a reduced intensity

FATAL the condition or injury results in the subject's death. The investigator should identify the principal cause of death and assign Fatal outcome to that event. Other concurrent ongoing AE/SAEs present at the time of death would remain Not recovered/Not resolved.

UNKNOWN can be selected if none of the other situations apply or are known. Follow-up should be conducted to obtain one of the preceding outcomes.

11.4.5 Action Taken with the Study Treatment

Action	Description
Treatment interrupted	The treatment was temporarily discontinued
Treatment withdrawn	The treatment was permanently discontinued
Unknown	Not known, not observed, not recorded, or refused
No action taken	The AE did not result in any modification of dose or frequency of dosing
Not applicable	The AE occurred prior to first dose or following last scheduled dose

11.5 Reporting of Serious Adverse Events and Pregnancy Exposures

Investigators and the Sponsor or its designated representative must conform to the serious adverse event reporting timelines, formats and requirements of the various entities to which they are responsible.

11.5.1 Investigator reporting: notifying the study sponsor

Immediate notification of SAEs by the investigator to Viatris PSRM is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Viatris will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Serious adverse events must be reported to the study sponsor within 24 hours of awareness. To report such events, a Serious Adverse Event (SAE) Report form must be completed and signed by the investigator or designee and forwarded to:

Viatris Global Product Safety and Risk Management (PSRM)

Email: [redacted] (primary)

Fax: [redacted] (secondary)

If the initial notification using the completed 'SAE report form' is not possible, the notification may be made via email/fax or over telephone with the following minimum necessary information

- Study identifier
- Study Center
- Subject number
- A description of the event
- Current status (outcome of event-if known and whether study medication is continuing)
- The reason why the event is classified as serious
- Investigator assessment of the causality between the event and study treatment

The investigator should provide further information on the Serious Adverse Event as soon as possible, preferably within 48 hours of awareness. This should include a copy of the completed SAE Report form, and any other diagnostic information and medical records that will assist in the understanding of the event.

Subject identifying information must not be visible on SAE forms or any supporting documentation provided by the Investigator. Any information that could be used to identify the subject (e.g. name, address, medical record number) must be de-identified before submission to Viatris or its designee. The subject's study specific ID number should be recorded on every page of documentation forwarded to the sponsor.

The PI should provide the final diagnosis as the SAE term whenever possible in the SAE report form and CRF. The signs and symptoms should be provided in the narrative only, not as SAE terms. The PI should only list all signs and symptoms as SAE terms if no diagnosis is available at the time of report.

11.5.2 Follow-up

New information and any important missing information from prior reports on a serious adverse event must be provided promptly to the study sponsor. In addition, the Investigator may be requested by Viatris/designee to obtain specific additional follow-up information in an expedited fashion. The investigator should respond to targeted follow-up requests as soon as possible and preferably within 48 hours from receipt of the request.

11.5.3 Investigator reporting: Notification of Ethics Committee

Investigators are responsible for safety reporting to their local Ethics Committee (LEC) and complying with their local EC's reporting requirements. Copies of each report and documentation of LEC notification and receipt will be kept in the investigator's study file.

11.5.4 Investigator Reporting of Pregnancy - notifying the study sponsor

All subjects who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation as detailed in the inclusion and exclusion criteria. Pregnancy testing will be conducted throughout the study, as detailed in the schedule of assessments.

A subject who is found to be pregnant at the screening visit will be excluded from the study and will be a screening failure.

Subjects who have been enrolled in the study should be instructed to contact the Investigator or study staff immediately if pregnancy occurs or is suspected. Early termination visit assessments are required as soon as possible after learning of the pregnancy. Pregnant females will be discontinued from study treatment by the Investigator. A male that has a partner that becomes pregnant during the study will not be discontinued from study treatment.

Details of the pregnancy should be recorded on the Pregnancy Report form and reported to Viatris PSRM within 24 hours of awareness by email [redacted] (primary) or facsimile [redacted] from the time of initial awareness, even if beyond the closure of the clinical database.

The Investigator is also responsible for following the pregnancy every 3 months or until delivery or termination and informing the Sponsor about its outcome. Reports where the embryo or foetus may have been exposed to the study drug(s), should be followed-up in order to collect information on the:

- outcome of the pregnancy,
- outcome for both mother and foetus (malformation/anomalies diagnosed since initial report)
- development of the child after birth (developmental assessment, infant illnesses, hospitalisations, drug therapies, breastfeeding)

Healthy newborns should be followed-up at 1 month after birth to confirm no congenital anomalies were subsequently detected (if possible).

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or termination of a pregnancy for medical reasons will be recorded as an AE or an SAE. A spontaneous abortion is always considered to be a SAE and will be reported to the Sponsor.

Elective termination (i.e., without medical reasons) of an uncomplicated pregnancy is considered an elective procedure and not an AE; nevertheless, Viatris requests the outcome (e.g., elective termination) be reported within 24 hours of awareness and sent as a follow-up on the Delivery and Infant Follow-up Form).

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as at least possibly related to the study treatment, must be promptly reported to Viatris PSRM.

If the study center becomes aware of a pregnancy in a female partner of a male subject, study personnel should contact their clinical research associate to obtain a partner pregnancy ICF. Consent of the pregnant partner must be obtained before any details of the pregnancy can be shared with Viatris or its designated representative. If the pregnant partner provides consent to have the pregnancy followed, the study center should collect the information specified on the Pregnancy Report form and forward the completed form to Viatris PSRM every 3 months until the pregnancy outcome has been obtained.

12.0 REFERENCE LIST

12.1 Published Literature

Bousquet J, Meltzer EO, Couroux P, Koltun A, Kopietz F, Munzel U, Kuhl HC, Nguyen DT, Salapatek AM, Price D. Onset of Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an Allergen Exposure Chamber. J Allergy Clin Immunol Pract. 2018 Sep - Oct;6(5):1726-1732.e6.

Bousquet J, Schünemann HJ, Togias A et al. Allergic Rhinitis and Its Impact on Asthma Working Group. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. J Allergy Clin Immunol. 2020 Jan;145(1):70-80.e3.

Day, J. H., Ellis, A. K., Rafeiro, E., Ratz, J. D. & Briscoe, M. P. Experimental models for the evaluation of treatment of allergic rhinitis. Ann. Allergy. Asthma Immunol. 96, 263–277; quiz 277–278, 315 (2006).

Dixon, A. E. et al. Allergic rhinitis and sinusitis in asthma*: Differential effects on symptoms and pulmonary function. Chest 130, 429–435 (2006).

Hellings PW, Dobbels F, Denhaerynck K, Piessens M, Ceuppens JL, De Geest S. Explorative study on patient's perceived knowledge level, expectations, preferences and fear of side effects for treatment for allergic rhinitis. Clin Transl Allergy. 2012 May 29;2(1):9

Ihler, F. & Canis, M. Ragweed-induced allergic rhinoconjunctivitis: current and emerging treatment options. J. Asthma Allergy 8, 15–24 (2015).

Jacobs, R. L. et al. Responses to ragweed pollen in a pollen challenge chamber versus seasonal exposure identify allergic rhinoconjunctivitis endotypes. J. Allergy Clin. Immunol. 130, 122–127.e8 (2012).

Kim, H., Bouchard, J. & Renzix, P. M. The link between allergic rhinitis and asthma: A role for antileukotrienes? Can. Respir. J. 15, 91–98 (2008).

Min, Y.-G. The Pathophysiology, Diagnosis and Treatment of Allergic Rhinitis. Allergy. Asthma Immunol. Res. 2, 65–76 (2010).

Pawankar, R., Mori, S., Ozu, C. & Kimura, S. Overview on the pathomechanisms of allergic rhinitis. Asia Pac. Allergy 1, 157–167 (2011).

Pipet, A., Botturi, K., Pinot, D., Vervloet, D. & Magnan, A. Allergen-specific immunotherapy in allergic rhinitis and asthma. Mechanisms and proof of efficacy. Respir. Med. 103, 800–812 (2009).

Sin, B. & Togias, A. Pathophysiology of Allergic and Nonallergic Rhinitis. Proc. Am. Thorac. Soc. 8, 106–114 (2011).

Small, P. & Kim, H. Allergic rhinitis. Allergy Asthma. Clin. Immunol. 7 Suppl 1, S3 (2011).

Stewart, M., Ferguson, B. J. & Fromer, L. Epidemiology and burden of nasal congestion. Int. J. Gen. Med. 3, 37–45 (2010).

12.2 Product Information

M1 Canada : Product Monograph Dymista, Azelastine Hydrochloride and Fluticasone Propionate Suspension Nasal Spray, 137 mcg/50 mcg per metered spray. BGP Pharma ULC. Date of Revision: October 3, 2019.

M2 US : Prescribing Information Dymista (azelastine hydrochloride and fluticasone propionate) nasal spray, for intranasal use. MEDA Pharmaceuticals Inc. Revised : 9/2018

12.3 Regulatory Documents

R1 FDA: Allergic Rhinitis: Developing Drug Products for Treatment. Guidance for Industry September 2018

R2 World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, amended by the 64th WMA General Assembly, Fortaleza 2013

R3 ICH E6 (R2): Guideline for Good Clinical Practice (Step 4: November 2016, step 5 (EU: CPMP/ICH/135/95: Note for Guidance on Good Clinical Practice)

R4 Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) Official Journal of the European Union, Vol. L119 (4 May 2016), pp. 1-88

R5 Food and Drug Regulations (C.R.C., c. 870), Health Canada. Available at https://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/page-1.html accessed on 8 Oct 2020.

R6 FDA : Code of Federal Regulations (CFR), Title 21, 21: Part 11 (October 6, 2020)

12.4 Other Proprietary Study Reports and Documents

O1 Study X-03065-3311
Authors: [redacted]
Principle investigator: [redacted]
Title: Clinical trial to assess onset of action of azelastine hydrochloride and fluticasone propionate nasal spray delivered in a single spray (MP-AzeFlu) in the treatment of allergen-induced allergic rhinitis symptoms in comparison to placebo and free combination of fluticasone propionate nasal spray and oral loratadine Sponsor: MEDA Pharma GmbH & Co. KG, Report No.: [redacted]

Document Name : Protocol - AZFL-AES-4-001 - 001277005

Title : AZFL-AES-4-001 Protocol

Status : Approved

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[redacted]	03-Aug-2021 15:46:47	Reviewer
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