STATISTICAL ANALYSIS PLAN

Protocol title:

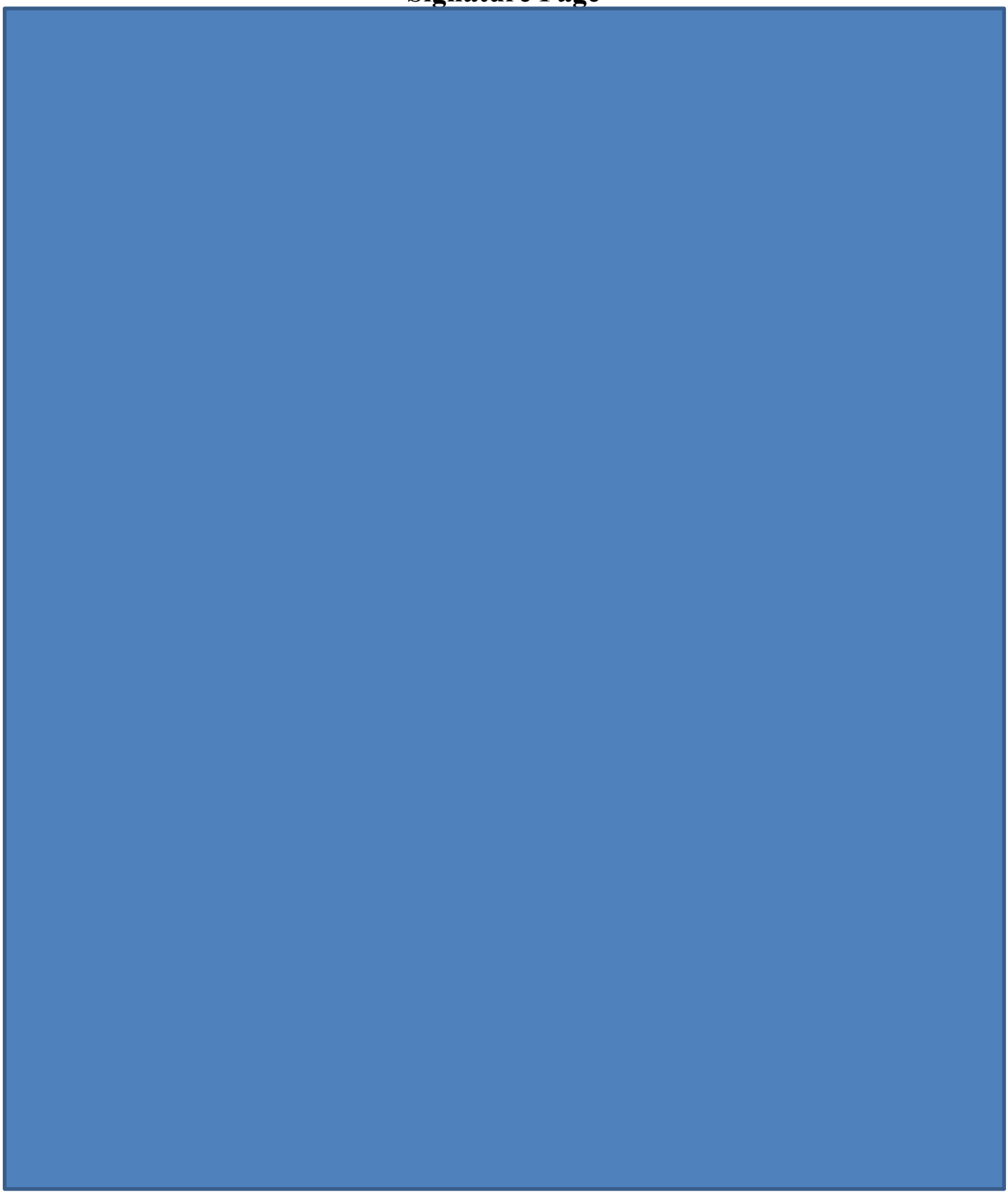
A randomized, double-blind, placebo-controlled, multi-center study of the efficacy and safety of STG320 sublingual tablets of house dust mite (HDM) allergen extracts in adults and adolescents with HDM-associated allergic rhinitis

Protocol Number: SL75.14

ClinicalTrials.gov ID: NCT02443805

Confidential/Proprietary Information

Signature Page



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1. Modification History

Version	Date	Author	Significant Changes from the Previous Authorized Version	Reason for the changes
Version 0	21Apr2016	[redacted]	Creation	Not Applicable
Pre-Final Version V01	23Nov2016	[redacted]	Integration of Protocol Amendment 1: - Update of the determination of sample size section - Addition of secondary endpoints and secondary efficacy analyses - Ranking of key secondary endpoints - Removal of the DSMB - Update of the proposed definition of clinical relevance - Extension of the period of patient recruitment	Integration of Protocol Amendment 1
Pre-Final Version V02	25Sep2017	[redacted]	Update regarding the primary and supportive analyses	Clarification of the primary analysis and addition of a supportive analysis
Final Version	29Oct2018	[redacted]	Remove CIR sensitivity analysis and replace by a MAR sensitivity analysis	Implementation of the method is over the capability of the computer.

2. List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
AR	Allergic Rhinitis
ASS	Adjusted Symptom Score
ATC	Anatomical Therapeutical Chemical
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMH	Cochran Mantel-Haenszel
CP	Controlled Patient
CR	Copy Reference
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CSMS	Combined Symptom and Medication Score
CV	Coefficient of Variation
DRD	Data Review Document
DSMB	Data and Safety Monitoring Board
ETV	Early Termination Visit
FAS	Full Analysis Set
[redacted]	
FEV_1	Forced Expiratory Volume in 1 second
GINA	Global Initiative for Asthma
GLMM	General Linear Mixed Model

Abbreviation	Definition
GRCS	Global Rating of Change Score
H1A	H1 Antihistamine
HDM	House Dust Mite
ICF	Informed Consent Form
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INCS	Intranasal corticosteroid
IP	Investigational Product
IR	Index of Reactivity
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
LLOQ	Lower Limit Of Quantification
LOCF	Last Observation Carried Forward
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model with Repeated Measures
MNAR	Missing Not At Random
NCS	Non Clinically Significant
PNCD	Proportion of Not-Controlled Days
PPS	Per Protocol Set
PSCD	Proportion of Symptom-controlled Days
PT	Preferred Term
RCTSS	Rhinoconjunctivitis Total Symptom Score
RMS	Rescue Medication Score
RQLQ(S)	Standardized Rhinoconjunctivitis Quality of Life Questionnaire
RSS	Rhinoconjunctivitis Symptom Score
RTSS	Rhinitis Total Symptom Score
SAE	Serious Adverse Event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SEM	Standard Error of the Mean
SOC	System Organ Class
SPT	Skin Prick Test
TEAE	Treatment-Emergent Adverse Event
TCS	Total Combined Score
TFLs	Tables, Figures and Listings
TOSS	Total Ocular Symptom Score
UCL	Upper Confidence Limit
ULOQ	Upper Limit Of Quantification
USA	United States of America
VAS	Visual Analogue Scale
WHO-DD	World Health Organization-Drug Dictionary
WPAI + CIQ: AS	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific

3. Introduction

This Statistical Analysis Plan (SAP) outlines and describes the statistical procedures and considerations to be used during the analysis of the STALLERGENES SL75.14 study. It serves as an expansion of the 'Statistics' section of the clinical study protocol.

The SAP includes a description of the statistical methods to be applied and provides templates of the Tables to be produced.

This SAP is based on the clinical study protocol SL75.14 version 7.0 dated 05OCT2017 and the electronic Case Report Form (e-CRF) version 4.0 dated 14OCT2015 as well as the electronic diary (e-diary).

Results will be presented according to the following regulations and norms:

- ICH Guidance on Statistical Principles for Clinical Trials (ICH E9, CPMP/ICH/363/96) step 5 effective from 1 September 1998
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, CPMP/ICH/137/95) step 5 effective from 1 July 1996
- ICH Guidance for Good Clinical Practice (ICH E6 (R2), CPMP/ICH/135/95) step 5, effective from 14 June 2017
- Draft ICH Guidance for General principles for planning and design of multi-regional clinical trials (ICH E17, EMA/CHMP/ICH/453276/2016) step 2b dated 28 July 2016
- Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1) effective from 1 September 2011
- Guideline on Adjustment for Baseline Covariates in Clinical Trials (EMA/CHMP/295050/2013) effective from 1 September 2015
- Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99) effective from 1 March 2003
- Draft Guideline on Multiplicity Issues in Clinical Trials (EMA/CHMP/44762/2017) dated 15 December 2016
- Draft Guideline on the Investigation of Subgroups in Confirmatory Clinical Trials (EMA/CHMP/539146/2013) published on 3 February 2014
- Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases (CHMP/EWP/18504/2006) effective from 1 June 2009

4. Study Objectives

This study is designed to assess the efficacy and safety of 12 months of treatment with 300 IR of STG320 sublingual tablets compared with placebo in adults and adolescents with house dust mite (HDM)-associated allergic rhinitis (AR).

4.1. Primary Efficacy Objective

To evaluate the efficacy of STG320 sublingual tablets at a daily dosage of 300 IR when administered for 12 months to adults and adolescents with HDM-associated AR.

The primary efficacy variable is the average Total Combined Score (TCS), calculated for each patient as the average of the non-missing daily TCSs during the primary evaluation period (i.e., the last 4 weeks of treatment). The daily TCS (scale 0-15) is the sum of the patient's daily Rhinitis Total Symptom Score (RTSS, scale 0-12) and daily Rescue Medication Score (RMS, scale 0-3).

4.2. Secondary Efficacy Objectives

4.2.1. Efficacy of STG320 during the Primary Evaluation Period (Month 12)

To assess the efficacy of treatment with 300 IR of STG320 sublingual tablets compared with placebo during the primary evaluation period on:

- Rhinitis Total Symptom Score (RTSS). The RTSS is the sum of the four rhinitis symptom scores, i.e., itchy nose, sneezing, runny nose, blocked nose
- Rescue Medication Score (RMS)
- Adjusted Symptom Score (ASS, scale 0-12). The ASS is derived from the daily RTSSs, after adjustment for the patient's rescue medication use
- Combined Symptom and Medication Score (CSMS, scale 0-6). The CSMS is derived from RTSS and RMS
- Total Ocular Symptom Score (TOSS, scale 0-6). The TOSS is the sum of the two ocular symptom scores, i.e., itchy/red eyes and watery eyes
- Rhinoconjunctivitis Total Symptom Score (RCTSS, scale 0-18). The RCTSS is calculated as the sum of the four rhinitis symptom scores and the two ocular symptom scores
- The six individual Rhinoconjunctivitis Symptom Scores (RSSs, each scored on a scale of 0-3): itchy nose, sneezing, runny nose, blocked nose, itchy/red eyes and watery eyes
- Rhinoconjunctivitis rescue medication use, overall and by type of treatment
- Visual Analogue Scale (VAS) assessing the intensity of the allergic rhinitis symptoms (ranging from 0 = absence of symptoms to 100 = very severe symptoms)
- Proportion of Symptom-Controlled Days (PSCD), Proportion of Not-Controlled Days (PNCD) and Controlled Patients (CPs)

- Overall Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12) and seven RQLQ(S)≥12 domains
- Health questionnaire EQ-5D-5L (five questions and a VAS)
- Global Rating of Change Score (GRCS, 15-point Likert scale)

4.2.2. Efficacy of STG320 during the Interim Evaluation Periods (Months 3, 6 and 9)

To assess the efficacy of treatment with STG320 300 IR sublingual tablets compared with placebo during the 2-week interim evaluation periods at Month 3, Month 6 and Month 9 on:

- TCS
- RTSS
- RMS
- ASS
- CSMS
- TOSS
- RCTSS
- RSSs
- Rhinoconjunctivitis rescue medication use, overall and by type of treatment
- Overall assessment of allergic rhinitis symptoms by a Visual Analogue Scale (VAS)

4.4. Other Objectives

To assess the effect of treatment with STG320 300 IR sublingual tablets compared to placebo at the end of the treatment on:

- Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI + CIQ: AS)
- Immunological markers: *D. pte*- and *D. far*-specific serum IgE and IgG4

4.5. Safety Objectives

To assess the safety of treatment with STG320 300 IR sublingual tablets on:

- Adverse events (AEs),

- Adverse Events of Special Interest (AESI) (severe anaphylactic reactions, severe laryngopharyngeal disorders, autoimmune disorders and eosinophilic esophagitis)
- Routine safety laboratory tests
- Vital signs
- Spirometry in asthmatic patients
- Physical examination assessments

5. Study Design

5.1. General Description

This is a randomized, double-blind, placebo-controlled, phase III study with two parallel arms conducted in male or female patients, aged 12 to 65 years (inclusive), with HDM-associated AR in 231 centers in the United States of America (USA), Canada, Europe, Israel and Russia.

The trial consists of a 1 to 6-month screening phase (including a run-in period of 5 weeks), a treatment phase of approximately 12 months and a post-treatment follow-up phase of 2 weeks. Therefore, for each patient the study lasts approximately 14 to 20 months.

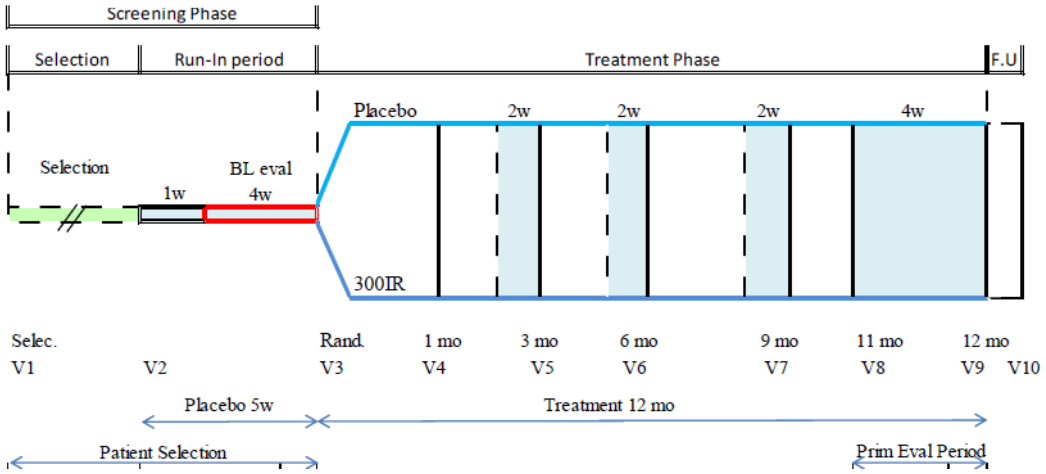
The patients were screened over two enrollment periods, as follows:

- First enrollment period: September 2015 to April 2016
- Second enrollment period: September 2016 to June 2017

A limited shortening of the treatment phase should be considered when necessary in patients screened in late winter or during spring (i.e. from February to June) to avoid the primary efficacy evaluation to be performed when conditions are less favorable for mite exposure and to prevent confounding symptoms due to pollens.

After the screening phase, patients satisfying the inclusion and exclusion criteria are randomized through an Interactive Web Response System (IWRS). Randomized patients are equally allocated to one of the two treatment groups in a 1:1 ratio. During the treatment period, patients receive either STG320 at a dose of 300IR or matching placebo sublingual tablets once a day.

Study schematic diagram:



5.2. Treatments

5.2.1. Treatments Administered

- **During the run-in period**

At Visit 2, each patient eligible for the run-in period is given a run-in period treatment kit consisting of 2 blister pack cards (20 tablets of placebo each).

The first dose should be taken at Visit 2 under the supervision of the Investigator/Co-investigator and the patient monitored for the next 30 minutes. Subsequent doses are to be taken at home, daily, at approximately the same time.

Patients are to take one tablet sublingually per day, for a period of 5 weeks.

- **During the treatment period**

Each randomized patient takes either STG320 sublingual tablets or matching placebo once a day for approximately 12 months (with a minimum of 10 months).

The first dose is to be taken at Visit 3 under the supervision of the Investigator and the patient monitored for the next 30 minutes. Subsequent doses are to be taken at home, daily, at approximately the same time. In the event Investigational Product (IP) intake is interrupted for more than 7 days, it is to be restarted under medical supervision at the dosage of last intake.

The dose is escalated from 100 IR to 300 IR during the first 3 days of treatment period, as follows:

	Initiation period		Maintenance period
	Day 1	Day 2	Day 3 and onward
Active treatment (STG320)	1 tablet of 100 IR	2 tablets of 100 IR (200 IR)	1 tablet of 300 IR
Placebo treatment	1 tablet (P100)	2 tablets (P100)	1 tablet (P300)

At randomization (Visit 3), each randomized patient is given one initiation phase treatment unit (3 blister pack cards of one tablet of 100 IR of STG320 or matching placebo i.e., 3 tablets dispensed) and one maintenance phase treatment unit (5 blister pack cards of 20 tablets of 300 IR of STG320 or matching placebo i.e., 100 tablets).

From Visit 5 (3 months) to Visit 7 (9 months), each patient is given one maintenance phase treatment unit (5 blister pack cards of 20 tablets of 300 IR of STG320 or matching placebo i.e., 100 tablets).

5.2.2. Method of Assigning Patients to Treatment Groups

All patients who have signed an Informed Consent Form (ICF) or Assent Form together with their parent(s)/legal representative in the case of adolescents, receive a screening number allocated in ascending order via an IWRS, whether they are randomized in this study or not.

- **For the run-in period**

At Visit 2, run-in period treatment kit numbers are allocated to patients through IWRS.

- **For the treatment period**

At the end of the run-in period, the center is requested to enter the protocol number, the Investigator site number, the patient-specific screening number, and the randomization status depending on all eligibility criteria observed.

Patients are randomized in a 1:1 ratio to receive either 300 IR of STG320 tablets or matching placebo.

Allocation of patients to treatment groups is performed with a stratification by center through the use of IWRS.

- For each randomized patient, the IWRS assigns the patient to one of the two treatment groups (i.e., randomized treatment group) and allocates two treatment kit numbers (i.e., one for escalation phase and one for maintenance phase). The randomization status (yes, no), the date and number are automatically transferred to the e-CRF by IWRS.
- For screen failed patients (i.e., not randomized patients), only the randomization status is automatically transferred to the e-CRF by IWRS, the reason for non-randomization being provided in the e-CRF by the center.

The connection to IWRS is repeated prior to each dispensation of IP in order to obtain a treatment kit number.

5.2.3. Blinding

- **During the run-in period**

Patients receive placebo tablets. All efforts are taken by study site personnel to not reveal to the patients the placebo nature of the tablets and maintain the single blind.

- **During the treatment period**

After randomization and throughout the study treatment and post-treatment phases, the study is designed as a double-blind study. Therefore, during the treatment phase, patients, investigators and site staff, and all study staff remain blinded. The IP (i.e., active and placebo tablets) are the same with respect to appearance, taste, labeling and packaging.

In the case of medical emergency in which knowledge of the treatment allocation is considered by the Investigator as critical in managing the patient's condition, the Investigator is able to utilize the IWRS and use the unblinding functions. In case of technical issues with the IWRS system, the Investigator is able to contact the responsible person from the Pharmacovigilance department.

Should the blind be broken, the date, the reason for breaking the blind, and the person doing so must be recorded on the source document, and in the appropriate e-CRF page, and STALLERGENES or its representative must be notified immediately.

5.2.4. Data and Safety Monitoring Board (DSMB)

An independent DSMB will be responsible for assuring that study patients are not exposed to unnecessary or unreasonable risks. Specifically, the DSMB will:

- monitor, based on the review of cumulative study data, the overall safety and assess the risk/benefit of the study on a regular basis,
- assess the performance of the study with respect to patient recruitment, ineligibility, relevant protocol deviations and treatment compliance.

5.3. Schedule of Events

Each patient is to attend 10 visits: 2 screening visits, 1 randomization visit, 6 regular follow-up visits (Months 1, 3, 6, 9, 11 and 12) and 1 post-treatment visit (Month 12.5).

Visit 1 involves screening for eligibility. At Visit 2 starts the run-in phase. Visit 3 to Visit 9 comprise the treatment phase and Visit 10 involves the post-treatment follow-up phase.

The following protocol study flow chart provides further details regarding time and schedule of events.

Study Assessments	Screening Phase		Treatment Phase							Post Treatment Follow-up Phase
	Visit 1 Selection	Visit 2 Run-in	Visit 3 Randomization = Visit 2 +5 weeks (+0 to 7 days)	Visit 4 1 mo FU = Visit 3 +30 days (±4 days)	Visit 5 3 mo FU = Visit 3 +90 days (±7 days)	Visit 6 6 mo FU = Visit 3 +180 days (±7 days)	Visit 7 9 mo FU = Visit 3 +270 days (±7 days)	Visit 8 11 mo FU = Visit 3 +323 to 330 days	Visit 9 12 mo FU = Visit 3 +360 to 367 days	Visit 10 2 wk post treat. = Visit 9 +14 days (±7 days)
Informed consent	X									
Patient eligibility	X	X	X							
Medical history, demographics and Prior and Concomitant medication	X									
HDM avoidance measures questionnaire*									X	
Forced Expiratory Volume in 1 second (FEV_1)	X		X***						X***	
Physical examination (incl. vital signs)*	X								X	
Skin prick test (SPT)	X									
[redacted]										
Safety laboratory tests*	X								X	
Immunological markers (IgE, IgG_4) [redacted]*	X								X	
Pregnancy test (urine)	X		X							
Dispensation of placebo tablets for the run-in phase		X								
Randomization			X							
Dispensation of investigational product			X		X	X	X			
Dispensation of rescue medication		X	X	X	X	X	X	X		
Dispensation of epinephrine auto-injector			X							

Study Assessments	Screening Phase		Treatment Phase							Post Treatment Follow-up Phase
	Visit 1 Selection	**Visit 2 Run-in**	**Visit 3 Randomization = Visit 2 +5 weeks (+0 to 7 days)**	**Visit 4 1 mo FU = Visit 3 +30 days (±4 days)**	**Visit 5 3 mo FU = Visit 3 +90 days (±7 days)**	**Visit 6 6 mo FU = Visit 3 +180 days (±7 days)**	**Visit 7 9 mo FU = Visit 3 +270 days (±7 days)**	**Visit 8 11 mo FU = Visit 3 +323 to 330 days**	**Visit 9 12 mo FU = Visit 3 +360 to 367 days**	**Visit 10 2 wk post treat. = Visit 9 +14 days (±7 days)**
Rhinoconjunctivitis Symptoms and Rescue medication use (e-diary) on a daily basis**		**X 1+4 w**			**X 2 w†**	**X 2 w†**	**X 2 w†**		**X 4 w‡**	
VAS (e-diary) on a weekly basis**		**X**			**X**	**X**	**X**		**X**	
RQLQ(S)≥12*			**X**						**X**	
Global Rating of Change Questionnaire*									**X**	
WPAI + CIQ: AS and EQ-5D-5L Health Questionnaire*			**X**						**X**	
Adverse events* and concomitant medication*		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

*: performed at Early Termination Visit in case of premature withdrawal; **: patients having discontinued the treatment before the first interim evaluation period were asked to continue the study (without study treatment) and score their rhinoconjunctivitis symptoms and RM use until Visit 5 ***: FEV_1 only repeated on asthmatic patients at Visit 3 and at the end of study treatment or at early termination visit; †: patients were asked to record their rhinoconjunctivitis symptoms and RM use for 2 weeks before Visit 5, Visit 6 and Visit 7; ‡: patients were asked to record their rhinoconjunctivitis symptoms and RM use during the 4 weeks from Visit 8 to Visit 9.

Notes:

Immunological markers: Serum IgE and IgG_4 specific for *D. pte* and *D. far* allergens should be tested in patients with positive SPT at Visit 1. Testing should be repeated at Visit 9.

Safety Laboratory Tests: Hematology: hemoglobin, hematocrit, red blood cells (RBC), platelets, white blood cells (WBC), differential count (neutrophils, basophils, eosinophils, monocytes, lymphocytes) and Biochemistry: glucose, creatinine, sodium, potassium, chloride, bilirubin (direct, indirect, total), ASAT (SGOT), ALAT (SGPT), GGT, performed at Visits 1 and 9.

E-diary: An electronic diary (e-diary) was dispensed to patients at Visit 2. Patients were asked to bring back the device to the study site at each visit. Patient assessed rhinoconjunctivitis symptoms and rescue medication use daily at the same time after awakening.

Epinephrine auto-injector: At Visit 3, patients were supplied with an epinephrine auto-injector and they were instructed when and how to use it. At each subsequent visit until Visit 9, the Investigator checked if the patient had used this device. If the previously dispensed device had been lost or used for an AE that did not require the patient's withdrawal from the study, a new auto-injector was dispensed.

Visit 8 and Visit 9 dates: For patients who enter the study in late winter or spring (from February to June), Visit 8 and Visit 9 will be anticipated when needed, but should not be earlier than 270 and 300 days after Visit 3, respectively.

5.4. Determination of Sample Size

The primary endpoint is the average TCS defined, for each patient, as the average of the non-missing daily TCSs over the last four weeks prior to the end of the treatment period.

In the European study VO57.07 [*Bergmann et al., 2014*] conducted in 509 patients, the analysis of the average TCS showed a placebo mean of 3.65 and a relative mean difference of -17% between groups with a 95% CI of [-30% ; -3%]. The CV was of 67% in the placebo group and 77% in the active group.

Based on this 95% CI (i.e., [-30% ; -3%]), an expected relative difference *versus* placebo of -20% was considered as a possible and reasonable value for the true relative difference between both groups. Besides, a CV of 75% was assumed to account for a possible higher variability of the data in this international study (i.e., North America, Europe, Israel and Russia).

Thus, assuming a two-sided nominal level of significance of 5%, a relative difference versus placebo of -20%, a placebo mean of 3.65, and a CV of 75%, simulations were performed with a SAS® program (version 9.2) based on 5,000 samples and showed that 739 evaluable patients per treatment group were sufficient to achieve a power of around 80% so as to fulfill both requirements (estimated relative difference versus placebo ≤-15% and upper bound of the 95% CI ≤-10%).

Of note, with the same assumptions and 739 evaluable patients per treatment group, the power of detecting a significant difference between both groups is greater than 99%.

Assuming a drop-out rate of 15% during the study, a total of 1,740 randomized patients (870 patients per group) will be required to ensure that 1,478 patients are included in the primary efficacy analysis. The screen failure rate is estimated at 50%, leading to a planned total number of screened patients of 3,480.

Additional information on the sample size calculation is provided in Appendix 1 (*Section 13.1*).

5.5. Changes from the Clinical Study Protocol

The following changes in the planned analyses will be implemented:

- In the protocol, the primary evaluation period is defined by the 4 weeks prior to the end of the treatment period for patients treated at least 10 months.

  In the SAP, the definition of the primary evaluation period will be based on the time window [- 4weeks; + 4weeks] around the date of last IP intake in order to avoid exclusion of the patients with diary recorded after end of treatment instead of before.

Due to the duration of the treatment period of approximately 12 months and known duration of the effect of immunotherapy, the extended time window is not expected to have an impact on the results for these patients.

6. Study Periods and Time Points

Each patient is to attend 10 visits:

- Visit 1 (Selection) involves screening for eligibility.
- Visit 2 (Run-in) starts the run-in phase.
- Visit 3 (Randomization) to Visit 9 (Month 12, End of treatment) comprise the treatment phase. In case of Early Termination Visit (ETV), all assessments described for Visit 9 are to be done and recorded as Visit 9 in the e-CRF.

  In order to avoid missing symptom and rescue medication scores over the entire treatment period, patients who discontinued treatment before the first interim evaluation period (i.e., Visit 5, after 3 months of treatment) were asked to score their rhinoconjunctivitis symptoms and rescue medication use on the e-diary during the first interim evaluation period, (i.e. off study treatment).
- Visit 10 (Follow-up) involves the post-treatment follow-up phase.

6.1. Evaluation Periods for Records Collected in the e-Diary

Rhinoconjunctivitis symptom scores and rescue medication use are to be recorded daily, and the VAS weekly, at five periods:

- **Baseline evaluation period**: last 4 weeks of the 5-week run-in period.
- **Three interim evaluation periods**: 2 weeks every 3 months after randomization visit (i.e.Visit 3)

  Each interim evaluation period is defined as the 14 days preceding the last daily record within a time window [-14 days; +14 days] around 90, 180, 270 days after randomization visit (i.e., Visit 3):
  - Month 3 (i.e., [76 days; 104 days] after V3) for interim evaluation period 1,
  - Month 6 (i.e., [164 days; 194 days] after V3) for interim evaluation period 2,
  - Month 9 (i.e., [256 days; 284 days] after V3) for interim evaluation period 3

  For interim evaluation period 1, the implementation of this definition follows those steps:

  1. Define the time window (TW) to find out the last daily record:
     TW start date = Visit 3 + 76 days
     TW stop date = Visit 3 + 104 days

  2. Define end date for interim period based on the last daily record within the time window:

Interim period end date = earliest date (date of last daily record within TW, TW stop date).
The interim period end date will be censored at EOS date, in case there are records after this date.

3. Define the start date of the interim period within the time window:
   Interim period start date = latest date (TW start date, interim period end date - 13)

Same steps will be followed for interim evaluation periods 2 and 3.

All patients not prematurely withdrawn before the start of one interim period will be retained for the analysis of that interim period even if no score was recorded (i.e. the number of valid days will be equal to 0 and the average scores will be missing).

- **Primary evaluation period**

The primary evaluation period is defined as the 28 days preceding the last daily record within a time window [-28 days; +28 days] around the last IP intake for patients treated at least 300 days (minimum treatment duration allowed by the protocol).

The implementation of this definition follows those steps, for all patients with a treatment duration of at least 300 days,

1. Define the time window (TW) to find out the last daily record:
   TW start date = last IP intake – 28 days
   TW stop date = last IP intake + 28 days

2. Define end date for primary period based on the last daily record within the TW:
   Primary period end date = date of last daily record within TW
   If no diary available within TW:
   Primary period end date = earliest date (date of last IP intake, EOS date)
   The primary end date will be censored at the EOS date, in case there are records after this date.

3. Define the start date of the primary period as the end date of the primary period - 27 days.

No overlap will be accepted between interim period 3 and the primary period.

All patients not prematurely withdrawn before the start of the primary period will be retained for the analysis of the primary period even if no score was recorded (i.e. the number of valid days will be equal to 0 and the average scores will be missing).

- **Sensitivity primary evaluation period**

The sensitivity primary evaluation period corresponds to the definition initially proposed in the protocol for the primary evaluation period i.e., the 4 weeks prior to the end of the treatment period.

For all patients with a treatment duration of at least 300 days,

- Sensitivity primary period end date = last IP intake
- Sensitivity primary period start date = sensitivity primary period end date - 27

No overlap will be accepted between interim period 3 and the sensitivity primary period.

6.2. Definition of Baseline, Endpoint and Other Time Points for Case Report Form (CRF) Variables

Except adverse events, the following parameters are to be recorded in the e-CRF either before or during Visit 3 (Randomization) or during Visit 9 (Month 12/ETV): spirometry, physical examination, Skin Prick Test (SPT), safety laboratory tests, immunological markers and RQLQ>=12, GRCS, WPAI + CIQ: AS and EQ-5D-5L questionnaires.

- **Baseline** is defined as the last non-missing evaluation recorded before the first administration of IP of the treatment period.
- **Endpoint** is defined as the first non-missing evaluation recorded at or after the Visit 9 (either "Month 12 visit" for patients completing the study or "the early termination visit" for patients not completing the study).

7. Analysis Sets

7.1. Patients Entering the Placebo Run-In Period

This analysis set will include all patients (either randomized or not) who entered the Placebo run-in period and received at least one dose of Placebo.

The analyses of the Placebo run-in Emergent AEs will use this analysis set.

7.2. Safety Set

The Safety Set will include all randomized patients who received at least one dose of the IP of the treatment period.

All safety analyses other than the ones described in *Section 7.1* will use the Safety Set.

7.3. Full Analysis Set (FAS)

In order to be as close as possible to the Intent-To-Treat (ITT) principle, the Full Analysis Set (FAS) will include all randomized patients who received at least one dose of the IP of treatment period and have at least one primary efficacy evaluation during the overall treatment period i.e., at least one day with a valid TCS during one of the evaluation periods.

The FAS will be the primary analysis set for all efficacy analyses (primary, secondary, and exploratory analyses).

7.4. Per Protocol Set (PPS)

The Per Protocol Set (PPS) will include all patients in the FAS who complied with the study protocol without any major protocol deviations and had at least 14 days with a valid TCS during the primary evaluation period.

The primary efficacy analysis and selected secondary efficacy analyses (specified in *Section 10.5.2*) will be replicated in the PPS.

The classification of the protocol deviations as minor or major will be performed during the Blind Review meeting before the unblinding of the data.

8. Variables

8.1. Baseline Variables

8.1.1. Socio-Demographics

The following socio-demographic characteristics are collected at Visit 1:

- Gender
- Age (years) will be calculated relative to the Visit 1 date as follows:
  - If Month of Birth < Month of Visit 1 date then:

    Age (years) = Year of Visit 1 date - 'Year of Birth'.
  - If Month of Birth > Month of Visit 1 date then:

    Age (years) = (Year of Visit 1 date - Year of Birth) - 1.
  - If Month of Birth = Month of Visit 1 date then:
    - If Day of Birth ≤ Day of Visit 1 date then:

      Age (years) = (Year of Visit 1 date - Year of Birth).
    - If Day of Birth > Day of Visit 1 date then:

      Age (years) = (Year of Visit 1 date - Year of Birth) - 1.

  In the case of incomplete birth date the following conventions will be applied during the calculation of age:

  - If Day is missing and Month/Year of Birth are **both** known then the 15th day of the Month will be used (i.e., 15 will be used as the day of Birth),
  - If **only** the Year of Birth is known then the first day of July will be used (i.e., 01JUL will be used as the Day and Month of Birth).

The following categories will also be considered for age:

- adolescent, 12 ≤ age ≤ 17 years,
- adult, age ≥ 18 years.

- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) will be calculated as BMI (kg/m²) = Weight (kg) / [Height (m)]²
- Geographical region (North America [USA and Canada], Rest of the world [Europe, Israel and Russia])
- Ethnic origin (Hispanic or Latino, not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islanders, White and Other)

8.1.2. Allergy Medical History

The allergy medical history is collected at Visit 1. Specific perennial/seasonal or other allergies are pre-specified in the e-CRF with the Investigator having to complete the start and stop dates or whether ongoing, when applicable.

- The duration of HDM AR (years) at Visit 1 will be calculated as follows:

Duration (years) = (Visit 1 date - Start date of the pathology + 1) / 365.25

Missing start date information (Day and/or Month) will be imputed with the latest possible date occurring before Visit 1, as follows:

- If Month is known then the earliest date of (the last day of the Month/Year, Visit 1 date) will be used,
- Otherwise the earliest date of (last day of the Year ('31Dec'), Visit 1 date) will be used.

Those imputation methods considering the latest possible date before Visit 1 correspond to the worst case scenario regarding the inclusion criterion 01 'Having HDM-associated AR (with or without asthma) for at least 1 year'. Indeed, the worst case is the shortest duration to detect all possible protocol deviations.

- Skin Prick Tests (SPTs) and sensitization status

Skin Prick Testing is performed at Visit 1 using the following battery of aeroallergens: *Dermatophagoides pteronyssinus (D.pte)*, *Dermatophagoides farina (D.far)*, cat, dog, cockroach, *Aspergillus, Cladosporium*, *Parietaria,* and *Alternaria* and other geographically relevant, potentially confounding aeroallergens as well as positive (histamine dihydrochloride) and negative (saline diluent) controls.

For each allergen, the test is considered positive when the largest wheal diameter is at least 5 mm greater than that of the negative control. The tests are considered valid when the positive control induces a wheal diameter of at least 3 mm and negative control induces a wheal diameter less than 2 mm.

The size of the wheals (mm) for each tested allergen is measured and recorded in the e-CRF by the investigator. The interpretation (positive / negative) is automatically calculated within the e-CRF as per protocol.

In case of retest, the SPT results of concerned patients will be reviewed during the Blind Review meeting to decide the test to be retained for the baseline analysis.

Due to the numerous allergen terms reported in the e-CRF by the investigators, the allergen terms will be recoded or grouped during the medical review for homogenization.

The sensitization profile (mono- versus poly-sensitization) will be derived from the readings of SPTs on site. Patients will be categorized as:

- Mono-sensitized if they are positive to HDM-allergen(s) *(D.pte* and/or *D.far)* only,
- Poly-sensitized if they are positive to HDM-allergen(s) and at least one other allergen.

- The duration of HDM associated allergic asthma (Years) at Visit 1 will be calculated using the same convention as for the HDM AR.
- The asthma status (Yes, No) is assessed at Visit 1. In case of presence of asthma, the GINA treatment step according to the GINA guidelines [*Global Initiative for Asthma – GINA 2014*] is reported.
- Spirometry is performed at Visit 1 in all patients and at Visit 3 in asthmatic patients. FEV_1 (L) and percentage of FEV_1 predicted value (%) are collected.

8.1.3. Medical History

Medical history is collected at Visit 1 by the Investigator in terms of medical conditions, start date and end date or whether ongoing.

Medical conditions will be coded using version 18.1 of the Medical Dictionary for Regulatory Activities (MedDRA) and grouped as follows:

- Previous medical conditions defined as medical history findings that started and ended before or on Visit 1.
- Concomitant medical conditions defined as medical history findings that started before Visit 1 and are ongoing at Visit 1.

If the end date and ongoing status are missing then the medical conditions will be considered as concomitant.

8.1.4. Other Baseline Characteristics

8.1.4.1 Childbearing Potential

For female patients, the childbearing potential form is completed by the Investigator.

If the patient is not of childbearing potential status, the reason (pre-menarche, menopause since at least 2 years, total hysterectomy, bilateral oophorectomy / ovariectomy, bilateral tubal ligation, other) is provided.

Otherwise, if the patient is sexually active, the most efficient contraceptive method used (hormonal birth control (orally, injectable or by implant, for at least 2 months before enrollment), intrauterine device, male condom or diaphragm used with spermicide, monogamous relationship with a vasectomized partner) is provided.

8.1.4.2 Urinary Pregnancy Test

At Visits 1 and 3, a urinary pregnancy test is performed on all females of childbearing potential.

8.2. Prior and Concomitant Therapies

8.2.1. Medications

During the trial, any medication intake is reported by the Investigator in terms of drug name (generic name), total daily dose, route, start and end date or whether ongoing, and indication for use.

Medications will be coded using version SEP2015 of the World Health Organization - Drug Dictionary (WHO-DD). Preferred Anatomical Therapeutic Chemical (ATC) classification will be performed (ATC levels 1 and 3).

Medications will be grouped and presented as follows:

- Prior medications defined as medications that started and ended before the first administration of IP of the treatment period.
- Concomitant medications defined as medications either ongoing or ended on or after the first administration of IP of the treatment period.

If the stop date and 'ongoing' are missing then the medication will be considered as concomitant.

At Visit 3, patients are supplied with an epinephrine auto-injector and instructed when and how to use it. At each subsequent visit until Visit 9, the Investigator checks if the patient has used this device or not.

The GINA treatment step at Visit 3 and Visit 9 (either "Month 12 visit" for patients completing the study or "the early termination visit" for patients not completing the study) will be determined from the concomitant medications.

8.2.2. Procedures

During the trial, any surgical or diagnostic procedure is reported by the Investigator in terms of type of procedure, start date, stop date or whether ongoing, and indication.

Procedures will be coded using version 18.1 of the MedDRA, and grouped as follows:

- Prior procedures defined as procedures that started and ended before the first administration of IP of the treatment period.
- Concomitant procedures defined as procedures either ongoing or ended on or after the first administration of IP of the treatment period.

If the stop date and 'ongoing' are missing, then the procedure will be considered as concomitant.

8.3. Treatment Exposure and Treatment Compliance

The overall treatment exposure (days) of treatment period will be calculated as:

Treatment Exposure (days) = 'last administration of IP date' – 'first administration of IP date' + 1.

Partial or missing date of last administration of IP will be imputed with the latest possible date occurring before the end of study, as follows:

In case of partial date of last administration of IP, (i.e. Month and Year are known) then the earliest date of (the last day of the Month/Year, End of study date) will be used,

In case of missing date of last administration of IP (e.g., in most cases, patients lost to follow-up or withdrawing their consent), then the date of Visit 9 will be used if available, otherwise the date of end of study will be used.

Those imputed values will be used to assess the overall treatment compliance of the patients. The overall treatment compliance (%) of treatment period will be calculated as follows:

$$\text{Treatment compliance (\%)} = 100 \times \frac{\text{('Number of tablets dispensed' – 'Number of tablets returned/not used')}}{\text{'No. of tablets the patients should have taken'}}$$

The 'Number of tablets the patient should have taken' during the actual treatment period will be equal to the treatment exposure + 1 tablet(s), as one tablet has to be taken daily except on the second day of the initiation period when two tablets have to be taken.

The 'Number of tablets dispensed' refers to the overall number of tablets dispensed all along the treatment period at Visits 3, 5, 6 and 7.

At each visit after IP is dispensed, the patients have to return all unused IP as well as any empty boxes and blisters. Any information regarding IP not returned on site at the visit (tablets lost, thrown away, forgotten or not taken) can be reported in the e-CRF as a comment.

The 'Number of tablets returned/not used' refers to the sum of

- the overall number of tablets returned all along the treatment period at Visits 4, 6, 7 and 9
- and the overall number of tablets reported as comment in the e-CRF as not returned and not used. This number will be assessed during the Blind Review meeting with the clinical team based on all comments reported by the investigator in the Drug accountability panel.

If a patient does not return the dispensed tablets at any visit and does not provide any information regarding his/her IP intake in the comment section of the e-CRF, the compliance will not be calculated. However, if the number of tabs returned during the escalation period is missing, this number will be considered equal to 0 for the compliance calculation (of note among the 3 tablets of the escalation period, one was taken on site under medical supervision).

Once compliance assessed, patients will be classified as:

- Compliant (overall compliance ≥ 80%)

- Non-compliant (overall compliance < 80%)

The non-compliant category includes patients with a missing compliance.

8.4. Primary Efficacy Variable

The primary efficacy variable is the average TCS (aTCS), calculated for each patient and each evaluation period (i.e., baseline, interim and primary) as the average of the non-missing daily TCSs during the corresponding period. The changes in aTCS from baseline to each evaluation period will also be calculated.

The daily TCS is the sum of the patient's daily RTSS (*Section 8.5.1*) and daily RMS (*Section 8.5.2*).

If the RTSS or the RMS for a given day is missing, then the TCS for that day will be considered missing.

In case of two distinct records were completed on a same date but at different time, the first record will be retained for the analysis.

The daily TCS and average TCS range from 0 to 15 (lower is better).

For descriptive purpose only, the baseline aTCS will be categorized as:

- < median of the baseline aTCS calculated on all randomized patients
- ≥ median of the baseline aTCS calculated on all randomized patients

For sensitivity analyses, the baseline average TCS used by investigator to confirm patient eligibility at randomization visit (Visit 3) will be used.

8.5. Secondary Efficacy Variables

Unless otherwise specified, the secondary efficacy variables will be calculated for each evaluation period (i.e., baseline, interim and primary). The way to handle two distinct daily records on a same date but at different time will be the same as for the primary variable.

8.5.1. Rhinitis Total Symptom Score (RTSS)

The daily RTSS is defined as the sum of the four rhinitis symptom scores (i.e., itchy nose, sneezing, runny nose, and blocked nose) evaluated daily by the patient.

The patient assessment addresses symptom intensity over the previous 24 hours and is performed at the same time every morning, using a 4-point scale:

0 = no symptoms,

1 = mild symptoms (symptom clearly present, but minimal awareness; easily tolerated),

2 = moderate symptoms (definite awareness of symptom that is bothersome but tolerable),

3 = severe symptoms (symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

If any of the four individual rhinitis symptom scores for a given day is missing, then the RTSS for that day will be considered missing.

The average RTSS will be calculated for each patient as the average of the non-missing daily RTSSs during each evaluation period.

The daily RTSS and average RTSS range from 0 to 12 (lower is better).

8.5.2. Rescue Medication Score (RMS)

The daily RMS is based on the assumptions that an intranasal corticosteroid (INCS) is more effective than an H1 antihistamine (H1A) and an oral corticosteroid is more effective than an INS, leading to a derived ordinal scale:

0 = absent,

1 = oral associated or not with topical (ocular drops) non-sedative H1A,

2 = INCS with or without oral or topical (ocular drops) H1A,

3 = oral corticosteroids with or without INCS or oral or topical (ocular drops) H1A.

If rescue medication data for a given day are missing, then the RMS for that day will be considered missing.

The average RMS will be calculated for each patient as the average of the non-missing daily RMSs during each evaluation period.

The daily RMS and average RMS range from 0 to 3 (lower is better).

8.5.3. Adjusted Symptom Score (ASS)

The daily ASS is derived from the daily RTSSs, after adjustment for the patient's rescue medication use. It is patient-specific, and will take into account that patients are permitted to make use of any of the three categories of rescue medication [*Grouin et al.,2011*].

The ASS is derived as follows:

- ASS and RTSS are equal the first valid day: $ASS_1 = RTSS_1$.
- If a patient did not take rescue medication at day d and the day before (d-1) then: $ASS_d = RTSS_d$.
- If a patient took rescue medication at day d, then the ASS_d will equal the higher value between the RTSS at day d and the ASS of the previous day.

$$ASS_d = \max (RTSS_d, ASS_{d-1})$$

$$ASS_{d+1} = \max (RTSS_{d+1}, ASS_d)$$

Missing data management:

- If the $RTSS_d$ is missing, then the ASS_d is missing
- If the information on rescue medication intake is missing, then: $ASS_d = RTSS_d$
- If a patient takes rescue medication at day (d) and $RTSS_{d-1}$ is missing, then: $ASS_d = RTSS_d$

The patient estimates the intensity of his/her rhinitis symptoms retrospectively over the previous 24 hours. When he/she takes a rescue medication like antihistamine or nasal corticosteroids, this rescue medication may impact the symptom score assessment on the day of intake and also on the following day. For oral corticosteroids, impact on symptoms probably lasts more than 24 hours and an adjustment for more than 2 consecutive days could be considered. However, by doing so, the adjustment may be overestimated.

The average ASS will be calculated for each patient as the average of the non-missing daily ASSs during each evaluation period.

The daily ASS and average ASS range from 0 to 12 (lower is better).

8.5.4. Combined Symptom and Medication Score (CSMS)

The daily CSMS combines the patient's daily RTSS and RMS, assuming equivalent importance of symptoms and medication scores [*Pfaar et al.,2014*]. Since the RMS ranges from 0 to 3 and the RTSS ranges from 0 to 12, in order to obtain comparable scales, the CSMS will be calculated as follows:

$$CSMS = RTSS/4 + RMS$$

The average CSMS will be calculated for each patient as the average of the non-missing daily CSMSs during each evaluation period.

The daily CSMS and average CSMS range from 0 to 6 (lower is better).

8.5.5. Total Ocular Symptom Score (TOSS)

The daily TOSS is the sum of the two ocular symptom scores (i.e., itchy/red eyes and watery eyes) evaluated daily by the patient using a 4-point scale (0: Absence, 1: Mild, 2: Moderate, 3: Severe).

If any of the two individual ocular symptom scores for a given day is missing, then the TOSS for that day will be considered missing.

The average TOSS will be calculated for each patient as the average of the non-missing daily TOSSs during each evaluation period.

The daily TOSS and average TOSS range from 0 to 6 (lower is better).

8.5.6. Rhinoconjunctivitis Total Symptom Score (RCTSS)

The daily RCTSS is defined as the sum of the four rhinitis symptom scores (i.e., itchy nose, sneezing, runny nose, and blocked nose) and two ocular symptom scores (i.e., itchy/red eyes and watery eyes) evaluated daily by the patient.

If any of the six individual rhinoconjunctivitis symptom scores for a given day is missing, then the RCTSS for that day will be considered missing.

The average RCTSS will be calculated for each patient as the average of the non-missing daily RCTSSs during each evaluation period.

The daily RCTSS and average RCTSS range from 0 to 18 (lower is better).

8.5.7. Six Individual Rhinoconjunctivitis Symptom Scores (RSSs)

The severity of the six RSSs (i.e., itchy nose, sneezing, runny nose, blocked nose, itchy/red eyes and watery eyes) during the previous 24 hours is evaluated daily by the patient.

The average of each of the six individual RSSs will be calculated for each patient as the average of the non-missing daily RSSs during each evaluation period.

The daily RSSs and average RSSs range from 0 to 3 (lower is better).

8.5.8. Rhinoconjunctivitis Rescue Medication Use

The rhinoconjunctivitis rescue medication use (yes, no), overall and by category of rescue medication (oral antihistamine, topical (ocular drops) antihistamine, any antihistamine, intranasal corticosteroid, oral corticosteroid), is recorded daily by the patients on the e-diary.

For each patient, the proportion of days with rhinoconjunctivitis rescue medication use overall and for each rescue medication category will be calculated in each evaluation period.

The dichotomous variables for patients using rhinoconjunctivitis rescue medication (overall and for each category of rescue medication) at least once during the evaluation period are defined for each patient and for each evaluation period as follows:

- 'Yes' for patients with at least one day of rescue medication use
- 'No' otherwise.

8.5.9. Visual Analogue Scale (VAS)

At the end of each week of the evaluation periods, patients assess the intensity of their allergic rhinitis symptoms over the previous week on the e-diary using a VAS, ranging from 0: absence of symptoms to 100: very severe symptoms [*Jamison et al.,2002; Bousquet et al.,2009*].

In case of two distinct records are completed on a same date but at different times:

- The VAS is planned to be collected every 7 days during the evaluation period. If the patient starts scoring the daily scores on day 6 before midnight and stops after midnight, the VAS page fires up by default, and the patient can save this VAS score. On day 7, the page fires up again as expected and the patient scores a second time the VAS. Only record done on day 7 will be retained for analysis.

- In case of replacement of an e-diary, the first record will be retained for the analysis because the second record is done with the replacement e-diary.

The average VAS will be calculated for each patient as the average of the non-missing weekly VAS scores during each evaluation period.

The weekly VAS and average VAS range from 0 to 100 (lower is better).

8.5.10. Proportion of Symptom-Controlled Days (PSCD)

The $PSCD_{2\text{-}0}$ is defined for each patient during each evaluation period as the proportion of days (%) in the evaluation period where RTSS≤2 and no rescue medication is used (RMS=0).

8.5.11. Proportion of Not-Controlled Days (PNCD)

The PNCD is defined for each patient as the proportion of days (%) in the evaluation period with:

- at least one individual symptom score = 2 and RMS > 0, or
- at least two individual symptom scores = 2 whatever the RMS, or
- at least one individual symptom score = 3 whatever the RMS.

8.5.12. Controlled Patients (CP)

The dichotomous variable for patients controlled for at least three quarters of the days in the evaluation period (i.e., $CP75_{2\text{-}0}$) is defined for each patient and for each evaluation period as follows:

- 'Yes' for patients with at least 75% of the days with RTSS≤2 and no rescue medication used (i.e., RMS=0)
- 'No' otherwise.

8.5.13. Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12) Scores

The RQLQ(S)≥12 is used for both adult and adolescent patients at Visit 3 and Visit 9. It consists of 28 questions, evaluated on a 7-point Likert scale, ranging from 0 to 6 (lower being better) and weighted equally [*Juniper et al.,1999*].

The questions are divided into 7 domains:

- Activities (3 items),
- Sleep (3 items),
- Non-nose/eye symptoms (7 items),
- Practical problems (3 items),
- Nasal symptoms (4 items),
- Eye symptoms (4 items),
- Emotions (4 items)

The score for each domain is the mean of the items in that domain (provided that all items of the domain are completed), while the overall score is the mean of all items (provided that all 28 items are completed).

These rhinoconjunctivitis quality of life variables will be calculated at baseline and endpoint. The changes from baseline to endpoint will be also calculated.

8.5.14. EQ-5D-5L Generic Health-Related Quality of Life Questionnaire

The EQ-5D-5L is assessed at Visit 3 and Visit 9. It describes the patients' health state using 5 questions, evaluated on a 5-point scale ranging from 1 to 5 (lower being better), assessing the following 5 dimensions:

- Mobility,
- Self-care,
- Usual activities,
- Pain/Discomfort,
- Anxiety/Depression.

The patients also self-rate their overall health on a VAS ranging from 0: the worst health you can imagine to 100: the best health you can imagine [*Herdman et al.,2011*].

These generic quality of life variables will be assessed at baseline and endpoint.

The 5 dimensions will be dichotomized into 'no problem' (i.e. level 1) vs 'mild to extreme problems' (i.e. levels 2 to 5) and the EQ-5D-5L Index value (using the conversion of health state to index score by country when available or that in UK otherwise) will be calculated.

8.5.15. Global Rating of Change Score (GRCS)

The GRCS is assessed at Visit 9. This score is a global assessment of the treatment efficacy compared to the baseline evaluation period on the following 15-point Likert scale [*Juniper et al.,1994*]:

- Symptom improvement:
  - 1 = Almost the same, hardly any better at all
  - 2 = A little better
  - 3 = Somewhat better
  - 4 = Moderately better
  - 5 = A good deal better
  - 6 = A great deal better
  - 7 = A very great deal better
- No change (score of 0)
- Symptom worsening:
  - 1 = Almost the same, hardly any worse at all
  - 2 = A little worse
  - 3 = Somewhat worse
  - 4 = Moderately worse
  - 5 = A good deal worse

6 = A great deal worse

7 = A very great deal worse

8.6. Exploratory Variables

8.6.2. Rhinitis Exacerbations

A rhinitis exacerbation during an evaluation period is defined as a day where the patient has a daily TCS score of 5 or more with at least one of the four rhinitis symptoms rated severe.

8.6.3. Asthma Events

Before database lock, a medical review of all adverse events reported during the treatment period (i.e. TEAEs) will be performed. The list of MedDRA Preferred Terms (PT) considered as 'asthma and asthma-related events' are listed below:

- Cough
- Asthma
- Dyspnea
- Dyspnoea
- Wheezing
- Bronchospasm
- Asthma exercise induced
- Chest pain
- Non-cardiac chest pain

- Chest discomfort
- Asthmatic Crisis
- Breath sounds abnormal
- Pulmonary function test decreased

Asthma event (yes, no) will be equal to 'yes' if the patient has reported at least one event listed as 'asthma and asthma-related event' during the treatment period.

8.6.4. Candidate Biomarkers

The candidate biomarkers to be assayed will be listed in a separate document.

8.7. Other Variables

8.7.1. Valid Days

During each evaluation period (i.e., baseline, interim and primary periods (including the sensitivity primary period)), a day is defined as valid if the rhinoconjunctivitis symptom scores and the rhinoconjunctivitis rescue medication use are available (i.e., non-missing).

The number of valid days will be classified as follows:

- "0 day", "1 to 7 days", "8 to 14 days" for the three interim periods and
- "0 day", "1 to 7 days", "8 to 14 days", "15 to 21 days" and "22 to 28 days" for the baseline and primary periods.

The proportions of valid days (%) over each period will be calculated as follows:

$$\text{Proportion of valid days (\%)} = 100 \times \frac{\text{Number of valid days during the period}}{\text{14 or 28 depending the evaluation period}}$$

The number of days between the date of the first administration of IP and the start date of each evaluation period will also be calculated.

8.7.2. Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI + CIQ: AS) Scores

The WPAI + CIQ: AS questionnaire is assessed at Visit 3 and Visit 9. It consists of 9 questions divided in 3 parts [*Reilly et al., 1996*]:

- Work performance (4 questions, Q1 to Q4),
- School performance (4 questions, Q5 to Q8),
- Impact of allergic rhino-conjunctivitis on the daily activities (1 question, Q9).

Seven scores, expressed as percentages, will be calculated at baseline and endpoint from the questions as follows:

- Percent work time missed due to allergy: (Q3/Q2) × 100
- Percent impairment while working due to allergy: (Q4/10) × 100

- Percent overall work impairment due to allergy: {(Q3/Q2) + [(1 - (Q3/Q2) × (Q4/10)]} × 100
- Percent class time missed due to allergy: (Q7/Q6) × 100
- Percent impairment in the classroom due to allergy: (Q8/10) × 100
- Percent overall classroom impairment due to allergy: {(Q7/Q6) + [(1 - (Q7/Q6) × (Q8/10)]} × 100
- Percent activity impairment due to allergy: (Q9/10) × 100

These seven scores will be calculated (provided that all items of the scores are completed) at baseline and endpoint. The changes from baseline to endpoint will be also calculated.

If one of the seven scores has a value greater than 100%, the questionnaire will not be retained for the analysis.

8.7.3. HDM Avoidance Questionnaire

The HDM avoidance questionnaire is answered at Visit 9. It consists of 8 questions related to the HDM avoidance measures implemented by patients at their residence since the start of the study.

Patients with at least one HDM avoidance measure implemented since the start of the study will be those who answer 'Yes' to one of the 8 items.

8.7.4. Immunological Markers

Blood samples are collected at Visit 1 and Visit 9 for immunological markers assays (*D. pte* and *D. far* specific serum IgE and IgG_4) which are performed centrally.

Values reported with symbols like:

- Value '<Lower Limit of Quantification (LLOQ)', will be analyzed as = LLOQ/2,
- Value '>Upper Limit of Quantification (ULOQ)', will be analyzed as = ULOQ.

Fold-changes from baseline to endpoint will be calculated (ratio endpoint to baseline).

For descriptive purpose, baseline HDM (i.e., *D. pte* and *D. far*) specific serum IgE levels will be categorized as:

- At least one (*D. pte* and/or *D. far*) specific serum IgE value ≥ 17.5 kU/L
- Both (*D. pte* and *D. far*) specific serum IgE values < 17.5 kU/L

8.8. Safety Variables

The safety of the IP is evaluated by monitoring the patient's AE profile for the duration of the study, AESI, routine safety laboratory tests, vital signs, spirometry for asthmatic patients and physical examination assessments.

8.8.1. Adverse Events (AEs)

During the trial, all AEs experienced by the patient are recorded by the Investigator in terms of symptom/diagnosis, start and stop date and time (time being recorded for AEs with a duration less than 24 hours), time to onset after the previous IP intake, severity, occurrence, seriousness, outcome, action taken (with the IP or other if any) and relationship with IP (either IP of the run-in period or IP of the treatment period depending on the date of start of the AE).

AEs will be coded using version 18.1 of the MedDRA.

AEs will be grouped as follows:

- A Pre-TEAE defined as an AE that started on or after the Informed Consent signed at Visit 1 (i.e. minimum date of Informed Consent date and Visit 1) and before the first administration of IP of the Placebo run-in period.
- A Placebo Run-in Emergent AE defined as an AE that started on or after the first administration of IP during the Placebo run-in period and before the first administration of IP of the treatment period.
- A Treatment-Emergent AE (TEAE) defined as an AE that started on or after the first administration of IP of the treatment period and up to 30 days after the last administration of IP of the treatment period, inclusive.
- A Post-TEAE defined as an AE that started at least 31 days after the last administration of the IP of the treatment period.

  If the start date is missing, the AE will be considered as a TEAE. If the end date is missing, the AE will be considered ongoing.

AE leading to premature study withdrawal will be defined as AE with 'Action taken with study treatment' equals to 'drug withdrawn' and with 'main reason for study withdrawal' on the 'end of study' page or with reason for non-randomization on the 'randomization status' page of the e-CRF equals to 'Adverse event'.

AE leading to premature IP discontinuation will be defined as AE with 'Action taken with study treatment' equals to 'drug withdrawn' and with 'main reason for study treatment withdrawal' on the 'end of treatment' page or with reason for non-randomization on the 'randomization status' page of the e-CRF equals to 'Adverse event'.

Of note, AE leading to premature study withdrawal/ premature IP discontinuation is a Placebo Run-in Emergent AE or a TEAE depending on the nature of the last IP taken (the Placebo of the run-in period or the IP (STG320 or Placebo) of the treatment period).

AESIs were defined in the protocol as any symptoms evoking one of the 4 following clinical pictures:

- Severe anaphylactic reactions,
- Severe laryngo-pharyngeal disorders,
- Autoimmune disorders,
- Eosinophilic esophagitis.

The following AE variables will also be calculated:

- Onset day = ('AE start date' – 'first administration date of IP') + 1, provided that AE start date was on or after the date of first administration of IP.
- Resolution day = ('AE end date' – 'first administration date of IP') + 1, provided that AE end date was on or after the date of first administration of IP.

  The first administration date of IP to be considered for onset and resolution days will depend on the nature of the adverse event (Placebo Run-in Emergent AE or TEAE). Onset and resolution days will remain missing for Pre- and Post-TEAEs.

- Duration (days) = ('AE end date'-'AE start date') +1.

Nor duration nor resolution day will be calculated for ongoing AEs.

Handling of missing data/incomplete dates:

In situations where an AE has a missing severity and/or relationship, a worst-case scenario will be applied. That is, missing severities will be imputed as 'Severe', while missing relationships will be imputed as 'Suspected'.

Of note, AE start time and end time were to be collected only if the duration of the AE was less than 24 hours. In case of partial dates / times of AEs, the following conventions will be considered for the analysis using the adequate first administration date of IP according to the nature of the adverse event (Placebo Run-in Emergent AE or TEAEs):

1. Partial AE start date and time

- If the AE **start day and month** are missing and the AE start year is known:
  - If the year is the same as the year of the first administration of IP, the AE start day and month will be imputed using the day and month of the first administration of IP (if this leads to a date after the AE end date, the AE end date will be used instead).
  - Otherwise the AE start day and month will be imputed using the first day and month of the year (if this leads to a date after the AE end date, the AE end date will be used instead; if this leads to a date before the date of ICF signed at Visit 1, the minimum of ICF and Visit 1 dates will be used instead).
- If the AE **start day** is missing and AE start month and year are known:
  - If the AE start year and month are the same as the month and year of the first administration of IP, the AE start day will be imputed using the day of the first administration of IP (if this leads to a date after the AE end date, the AE end date will be used instead).
  - Otherwise the AE start date will be imputed using the first day of the month (if this leads to a date before the date of ICF signed at Visit 1, the minimum of ICF and Visit 1 dates will be used instead).).
- For AEs during less than 24 hours, if AE **start time** is missing and AE start date is known:
  - if AE start minutes are missing and AE start hour is known, AE start minutes will be replaced by '00',

- if AE start minutes are not missing and AE start hour is missing, AE start hour will be replaced by '00',
- if AE start hour and minutes are missing, time will be replaced by '00:00'.

2. Partial or missing AE end date and time

- If the AE **end day and month** are missing and the AE end year is known, the AE end date will be imputed using the last day of the AE end year (if this leads to a date after the last contact / last visit date, the last contact / last visit date will be used instead).
- If the AE **end day** is missing and the AE end month and year are known, the AE end day will be imputed using the last day of the AE end month (if this leads to a date after the last contact / last visit date, the last contact / last visit date will be used instead).
- If AE **end date** is completely missing and the AE is not ongoing, the AE end date will be imputed using the last contact / last visit date.
- For AEs during less than 24 hours, if the AE **end time** is missing and AE end date is known:
  - if AE end minutes are missing and AE end hour is known, AE end minutes will be replaced by '59',
  - if AE end minutes are not missing and AE end hour is missing, AE end hour will be replaced by '23',
  - if AE end hour and minutes are missing, time will be replaced by '23:59'.

8.8.2. Laboratory Parameters

Blood samples for safety laboratory testing are collected at Visit 1 and Visit 9 for:

- Hematology: hemoglobin, hematocrit, red blood cells (RBC), platelets, white blood cells (WBC), differential count (neutrophils, basophils, eosinophils, monocytes, lymphocytes
- Biochemistry: glucose, creatinine, sodium, potassium, chloride, bilirubin (direct, indirect, total), ASAT (SGOT), ALAT (SGPT), GGT

Safety laboratory tests are performed centrally.

Laboratory values will be categorized as 'Low', 'Normal' and 'High' according to the laboratory reference ranges and the clinical significance (CS: Clinically Significant and NCS: Non Clinically Significant) reported by the Investigator.

Laboratory values classified as 'Low' or 'High' will be regarded as abnormal values.

Shift from baseline will be derived by combining the baseline and endpoint categories relative to the laboratory normal reference ranges ('Low', 'Normal', 'High').

The same conventions as for immunological markers (*Section 8.7.4*) regarding values with symbols '<LLOQ' or '>ULOQ' will be used.

8.8.3. Vital Signs

Vital signs (Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) in mmHg, and, Pulse Rate (PR) in bpm) are measured at Visit 1 and Visit 9 after a 5-minute rest.

For each parameter, the clinical interpretation of the Investigator (Normal, Abnormal NCS and Abnormal CS) of the measured value is reported in the e-CRF.

8.8.4. Spirometry for Asthmatic Patients

Spirometry is performed at Visit 3 and Visit 9 in asthmatic patients. FEV_1 (L) and percentage of FEV_1 predicted value (%) are collected.

8.8.5. Physical Examination

A physical examination is performed according to common medical practice at Visit 1 and Visit 9. Abnormalities in physical examination are reported either as AEs or as medical history.

9. Statistical Methods

9.1. General Methodology

Statistical analyses will be performed by [redacted] using SAS® for Windows, version 9.4, SAS Institute, Cary, North Carolina, USA.

Analysis datasets used will be in Clinical Data Interchange Standards Consortium Analysis Data Model (CDISC-ADaM) format, according to the Analysis Data Model, Final Version 2.1, Analysis Data Model Implementation Guide, Final Version 1.0 and Analysis Data Model Data Structure for Adverse Event Analysis, Final Version 1.0. Analysis datasets will be derived from data in standard CDISC Study Data Tabulation Model (CDISC-SDTM) format (SDTM v1.3 according to SDTM Implementation Guideline 3.1.3).

All variables will be presented descriptively by treatment group or by treatment group and overall (all patients) when appropriate.

The following summary statistics will be presented:

- Categorical (qualitative) variables: Absolute frequencies (n), relative frequencies (%), 95% two-sided Confidence Intervals (CIs) for each category of the studied parameter where appropriate, number of non-missing values ('Total') and number of missing values.
  Percentages will be calculated within each treatment group or overall using the number of non-missing values as denominator. Otherwise, the denominator will be specified in a dedicated footnote.
- Continuous (quantitative) variables: Number of patients (n), number of missing values, mean, SD, 95% two-sided CI of the mean, median, lower quartile (Q1: 25th percentile) and upper quartile (Q3: 75th percentile), minimum and maximum.
- Continuous (quantitative) variables with positive values only and log-normal (or close to log-normal) distribution (e.g., immunological markers): Number of patients (n), number of

missing values, geometric mean, 95% two-sided CI of the geometric mean, median, lower quartile and upper quartile, minimum and maximum.

All inferential tests will be two-sided tests. The probability of a type I error (α) will be set at 0.05 and the confidence level will be set at 0.95 for CI, unless otherwise specified.

Based on historical data, the density plot of combined symptom and medication scores is commonly right-skewed and the square root transformation normalizes the data. Therefore, statistical analysis of the primary efficacy variable and of secondary variables with a right-skewed distribution will be conducted on square root transformed data.

As the sample size is large, parametric methods will be used with adjustment for covariates, unless otherwise specified. In addition, supportive non-parametric analyses will be conducted to check the consistency of the results and to investigate the impact of the skewness and outliers on the results.

9.2. Reporting Rules

All statistical outputs including TFLs will be configured for US letter and A4 format, landscape oriented, with the following margins:

- Top = 3.2 cm ; Bottom = 2.5 cm,
- Right side = 2.8 cm ; Left side = 2.8 cm,

The font used will be Courier New 8pt for tables and figures, and Courier New 7pt for listings.

Unless otherwise specified, all statistical tables provided by treatment group will first present the results in the active group (STG320 300IR) and then the results in the placebo group. The column 'overall' displaying all patients (all treatment groups combined) will be presented where appropriate.

All patient data listings will be produced as selected data supportive of statistical tables/figures, including derived/calculated variables. These patient data listings will be provided for randomized patients and will be sorted by treatment group (according to randomization) and patient ID (Unique Patient number/Gender/Age at Screening/key symbols in case of exclusion from specific analysis sets) unless otherwise specified. A footnote specifying the key symbols will be systematically provided.

The following rules to display the statistical results in the TFLs will be applied:

- Categorical (qualitative) variables:

  Only modalities met at least once in the analysis datasets will be provided in the frequency tables. Percentages equal to 100 will be reported as '100%', percentages equal to 0 will not be reported and all other percentages will be rounded to one decimal place.

- Continuous (quantitative) variables:

  As a general rule, minimum, maximum and any individual value will use the same number of decimal places as the original data; means and 95% CI, and quartiles will be reported rounded to one more decimal place than the original data; second order moment (e.g., SD and Standard Error of the Mean - SEM) will be reported rounded to two more decimal places than the original data.

For the sake of legibility/readability, the number of decimal places could be reduced or increased. Such variables handled in a different manner are detailed in the relevant subsections below.

- Other estimated parameters not on the same scale as the raw data will be reported according to the common usage (e.g., 4 decimals for correlation coefficient, 2 decimals for odds-ratio).
- Other percentages than frequencies (e.g., relative mean difference) will be reported with one decimal place.
- P-values:

  All p-values will be rounded to four decimal places and reported with a leading zero as '0.0001'. P-values <0.0001 will be reported as '<0.0001'.

- Dates:

  All date values will be presented as 'YYYY-MM-DD' (i.e., SAS ISO 8601 format). Partial and missing dates whatever their imputation rules will be displayed as reported in the analysis datasets (i.e., 'YYYY-MM' for partial date with missing day, 'YYYY---DD' for partial dates with missing month, 'YYYY' for partial dates with both month and day missing, and, blank for complete missing dates).

- Missing values:

  All missing values for both numeric and character variables will be left as blank in the patient data listings.

9.3. Protocol Deviations

Protocol deviations are defined as 'major' if they have an influence on the primary outcome. A major deviation will lead to the exclusion of a patient from the PPS.

Protocol deviations will be classified during the Blind Review meeting. The meeting will take place before the database lock when all data of the study are available.

The Data Review Document (DRD) pre-final version including listings of protocol deviations and patient profiles or listings of individual patients by topic (i.e., with all raw data) will be provided to review and classify each protocol deviation as major or minor during the Blind Review meeting. The analysis sets will be finalized according to the classification of protocol deviations.

The following criteria will be used to determine the protocol deviations:

- Inclusion/exclusion criteria:

Inclusion Criteria at Visit 1

Number	Criteria	Status
I01	Have house dust mite (HDM)-associated allergic rhinitis (AR) (with or without asthma) for at least 1 year based on the presence of: • Symptoms for 4 or more consecutive weeks in the previous year and for at least 4 days per week during those weeks. • Symptoms requiring regular intake of symptomatic treatment(s). Symptoms evaluated as "troublesome" by the patients or impairing their daily activities, leisure or sport, school or work or involving sleep disturbance.	Major/ Minor
I02	Have given signed informed consent to participate, after having been informed of the nature and aims of the study, in accordance with local regulation and requirements.	Major/ Minor
I03	Male or female outpatients 12 to 65 years of age.	Major/ Minor
I04	Sensitized to *D. pteronyssinus (D. pte)* and/or *D. farinae (D. far)* defined as skin prick test wheal diameter at least 5 mm greater than the negative control and HDM-specific serum IgE ≥3.5 kU/L.	Major/ Minor
I05	Willing to and capable of completing the e-diary, study questionnaires and scales.	Major/ Minor

Exclusion Criteria at Visit 1

Number	Criteria	Status
E01	A history of rhinitis, rhino-conjunctivitis or asthma to allergens other than HDM, likely to result in rhinitis symptoms during the baseline and primary evaluation periods (i.e., 4 weeks of evaluation between September and January). Specifically, when the following are present: • documented sensitization (positive Skin Prick Test [wheal diameter at least 5 mm greater than the negative control] or allergen specific serum IgE >3.5kU/L) and history of clinically relevant symptoms to allergen(s) other than HDM • anticipated exposure to such allergen(s) during the baseline and primary evaluation periods (i.e., the 4 weeks of evaluation between September and January) For example, the following patients are to be excluded: - patients sensitized to cat or dog allergens and regularly exposed to these animals - patients sensitized to perennial allergens, such as aspergillus, cladosporium, alternaria, cockroach - patients sensitized to seasonal allergens such as parietaria, ragweed or mugwort, if these allergens are endemic in the region during the baseline and primary evaluation periods.	Major/ Minor
E02	Any diagnosed nasal (other than HDM allergic rhinitis) or oral disease that could interfere with the efficacy or safety assessments, such as nasal polyposis, recurrent chronic rhino-sinusitis (at least 2 isolated episodes per year in the 2 previous years, each episode lasting more than 8 weeks) or a history of chronic oral inflammation or current active oral inflammation from any etiology (e.g., oral lichen planus, oral ulceration or oral mycosis) and/or oral wounds.	Major/ Minor

Exclusion Criteria at Visit 1

Number	Criteria	Status
E03	Recent nasal surgery (i.e., within the previous 6 months).	Major/ Minor
E04	Partly controlled or uncontrolled asthma defined in the Global Initiative for Asthma 2014 guidelines (GINA 2014) as the presence of daytime asthma symptoms more than twice/week or nocturnal symptoms/awakening or need for reliever/rescue treatment more than twice/week or FEV_1 <80% of predicted or personal best value.	Major/ Minor
E05	Asthma therapies consistent with GINA treatment Step 3, Step 4 and Step 5 i.e., the preferred controller medication consists of inhaled corticosteroid (ICS) combined with long-acting beta (β)-2 agonist (LABA) according to GINA classification 2014. Eligible asthmatic patients will be those with asthma, controlled by treatment(s) consistent with GINA 2014 treatment Steps 1 or 2 [i.e., reliever treatment with as needed short acting β2-agonist with or without controller treatment consisting of low dose inhaled corticosteroid (i.e., ≤400 µg of budesonide/day or equivalent dose of other corticosteroid) or leukotriene receptor antagonist or low dose theophylline].	Major/ Minor
E06	Experienced a life-threatening asthma attack or an asthma exacerbation that resulted in Intensive Care Unit (ICU) hospitalization.	Major/ Minor
E07	Requiring continuous treatment with systemic corticosteroids for any indication.	Major/ Minor
E08	Requiring continuous treatment with β-blockers or with Monoamine Oxidase Inhibitors (MAOIs).	Major/ Minor
E09	Received an immunosuppressive treatment within 3 months prior to screening.	Major/ Minor
E10	Received allergen immunotherapy (AIT) by any route: - for house dust mites: AIT for more than 1 month within the 5 years before screening - for other allergen(s): ongoing or recently stopped (within 6 months) AIT.	Major/ Minor
E11	Any history of anaphylaxis after previous allergen immunotherapy, exposure to allergen(s) or of unknown cause.	Major/ Minor
E12	A history of hypersensitivity to STG320 or its excipients or contraindication to the use of rescue medications (i.e., antihistamines and corticosteroids).	Major/ Minor
E13	Female with positive urine pregnancy test or lactating or expecting to conceive within the duration of the study.	Major/ Minor
E14	Sexually active female of child-bearing potential without medically accepted contraceptive method: hormonal birth control (orally, injectable or by implant, for at least 2 months before enrollment), intrauterine device, male condom or diaphragm used with spermicide, monogamous relationship with a vasectomised partner. Women are considered not to have childbearing potential prior to menarche or at least 2 years after menopause or if they have had a bilateral tubal ligation or a total hysterectomy or bilateral oophorectomy or ovariectomy.	Major/ Minor
E15	Unable or unwilling to comply with the study protocol requirements, including those who anticipate significant changes in their daily environment in relation to HDM exposure or who are likely to travel for extended periods of time during the main efficacy assessment period.	Major/ Minor

Exclusion Criteria at Visit 1

Number	Criteria	Status
E16	Patients with past or current disease(s) which, as judged by the Investigator, may affect the patient's participation in or the outcome of this study. These diseases include, but are not limited to, cardiovascular disease, malignancy, active tuberculosis, hepatic disease, renal disease, hematologic disease, neurologic or psychiatric disease, severe autoimmune disorder, immunodeficiency or immunologic disease and endocrine disease.	Major/ Minor
E17	Patients with a history of eosinophilic esophagitis or with current severe or persistent gastroesophageal symptoms including dysphagia or chest pain.	Major/ Minor
E18	Contraindications to allergen specific immunotherapy.	Major/ Minor
E19	Patients with history of drug or alcohol abuse.	Major/ Minor
E20	Participation in any clinical study within 30 days prior to the selection visit.	Major/ Minor
E21	Possible dependency of the patient on sponsor or investigators/subinvestigators or study personnel.	Major/ Minor

Inclusion Criterion at the end of the run-in/baseline evaluation period

Number	Criteria	Status
I06	Patients with an average TCS ≥5 (on a scale of 0 to 15) over the baseline evaluation period.	Major/ Minor

Of note, the inclusion criterion I06 is met provided that the number of valid TCSs during the baseline period is ≥14.

- Other deviations:
  - Patients who had their blinded randomization code broken
  - Patients not treated according to the randomization schedule
  - Patients with an overall compliance <80%
  - Patients who took forbidden medications (prior and/or concomitant)
  - Patients with visit time windows not respected
  - Other deviations detected by the monitoring team

9.4. Adjustments for Covariates

By adding covariates, the model's precision could be improved due to a possible reduction in the unexplained variability of the average TCS.

The baseline value of the primary outcome i.e., the baseline average TCS, will be included in the model as a continuous covariate.

Unless otherwise specified the following categorical covariates will be included in the analysis models:

- Age class (adolescent, adult): possible confounding factor
- Gender (male, female): possible confounding factor
- Sensitization status (mono-, poly-sensitized): possible prognostic factor
- Asthma status (yes, no): possible prognostic factor
- Center or pooled center (*Section 9.7*): stratification factor

A patient data listing of all covariates will be provided.

9.5. Handling of Dropouts or Missing Data

The pattern of missing data over the treatment period will be described by treatment group in the randomized set using a Kaplan-Meier plot of the probability of remaining in the study from randomization (*Section 10.1*), overall and by enrollment period.

If any of the individual rhinoconjunctivitis symptom scores or rescue medication data for a given day are missing, the derived scores using the missing individual data for that day will be considered missing. Average scores will be calculated using the non-missing days in the respective evaluation period.

To evaluate the extent of missing TCS daily data, the proportion of valid TCS days during the primary period will be summarized by treatment group in the FAS (*Section 10.7.1*).

In order to prevent missing data during the entire treatment period, patients who discontinue treatment before the first interim evaluation period (i.e., before 3 months of treatment) are asked to continue the study (without study treatment intake) until Visit 5 (i.e., until the end of the first interim evaluation period). All patients are asked to score their rhinoconjunctivitis symptoms and rescue medication use on the e-diary during the first interim evaluation period, off study treatment.

The following sensitivity analyses of the primary efficacy variable (after SQRT transformation) will be performed to assess the robustness of the primary analysis with regard to missing data:

- A multiple imputation method using missing at random (MAR) assumptions. For each analysis, 30 imputed datasets will be generated with the interim evaluation periods and the primary period as longitudinal measures. This imputation method considers that withdrawals have a similar distribution to that observed in their own treatment group.
- A Mixed Model with Repeated Measures (MMRM) using an unstructured covariance matrix with each interim evaluation period and the primary period as repeated measures and including a term for the interaction ‘treatment by period’. This multivariate model applies a missing at random (MAR) assumption and is a direct likelihood method in which information from the observed data is used via the within-patient correlation structure to provide information about the unobserved data
- Pattern-mixture model with reference-based imputation method using missing not at random (MNAR) assumptions. For each analysis, 30 imputed datasets will be generated with the interim evaluation periods and the primary period as longitudinal measures. The Copy Reference (CR) imputation method which considers that withdrawals from the active

group have a similar distribution to that observed in the placebo group [*O'Kelly & Ratitch, 2014*] will be implemented.

- A Last Observation Carried Forward (LOCF) as a single imputation method that imputes the last measured outcome value for patients who either drop out or for whom the final outcome measurement is missing. Since an improvement over time is expected with the active treatment and the patients tend to withdraw earlier in the active group, this approach can be considered as conservative. For patients who discontinued treatment before the first interim evaluation period (i.e., Visit 5, after 3 months of treatment), the last measured outcome will be the one performed 'off study treatment' during the first interim evaluation period or the baseline outcome otherwise.

Unless otherwise specified, missing values for other variables will not be replaced.

9.6. Interim Analyses

No interim analysis will be performed.

9.7. Multicenter Studies

Due to the high number of centers and small numbers of patients within centers, a pooling of the centers will be considered to ensure a sufficient number of patients in each treatment group at each level of the covariate 'pooled center'. The pooling was performed during the Blind Review meeting according to the geographic area, the number of randomized patients and the number of patients with an available average TCS during the primary period. The list of pooled centers with site numbers included in each pool is detailed in the DRD).

The centers included in each pooled center will be presented in a dedicated table in the disposition of patients (*Section 10.1*).

9.8. Multiple Comparisons/Multiplicity

Hypothesis testing for the primary endpoint and for the key secondary endpoints (i.e., the ranked secondary endpoints) will be carried out in a hierarchical order.

The primary endpoint will be tested first at the two-sided alpha level of 0.05. If the primary endpoint is statistically significant, a stepdown sequential closed testing procedure for the six ranked secondary endpoints will be performed to control the overall type I error.

The first ranked secondary endpoint will first be tested at the two-sided alpha level of 0.05. If this endpoint is significant, then the second ranked secondary endpoint will be tested, otherwise the testing procedure will be stopped. The same procedure will be applied to the successive ranked secondary endpoints.

The six ranked secondary endpoints are the following:

- 1. Rhinitis Total Symptom Score (RTSS) during the primary evaluation period
- 2. Overall score of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at the end of the treatment period

- 3. Rhinoconjunctivitis Total Symptom Score (RCTSS) during the primary evaluation period
- 4. Blocked nose symptom score during the primary evaluation period
- 5. Proportion of Symptom-Controlled Days (PSCD, proportion of days with RTSS≤2 and no rescue medication use) during the primary evaluation period
- 6. Rescue Medication Score (RMS) during the primary evaluation period

If a ranked secondary endpoint does not reach statistical significance, the analysis of the subsequent ranked secondary endpoints will be performed for exploratory purposes only.

The analysis of the non-ranked secondary endpoints will be considered supportive and will contribute to document the consistency of the study results; confidence intervals and statistical tests will be of descriptive nature.

9.9. Examination of Subgroups

Descriptive statistics of the primary efficacy variable during each evaluation period will be provided at each level of each covariate. To this end, the categorical baseline average TCS variable will be considered (*Section 8.4*).

Interactions between each covariate and the treatment group will be investigated for the primary efficacy variable. Separate exploratory models will be fitted similarly to the primary efficacy model and including an additional term for interaction between the covariate and the treatment group.

In case of significant interaction between a categorical covariate and the treatment group, an interaction plot will be displayed and discussed in section 16.1.9 of the CSR.

Regardless of the interaction test conclusion, scatter plots of baseline average TCS against average TCS during the primary evaluation period will be displayed by treatment group.

For exploratory purposes, a similar subgroup analysis will be performed by:

- Enrollment period (2015/2016, 2016/2017)
- [redacted]
- Race (*Section 8.1.1*)
- Geographical region (North America, Rest of the world)
- Baseline *D. pte*- and/or *D. far*-specific serum IgE levels (≥17.5 kU/L, <17.5 kU/L)
- At least one HDM avoidance measure implemented since the start of the study (At least one, None)
- Potential confounding sensitization (without potential confounding sensitizations, with potential confounding sensitizations). Patients with potential confounding sensitization are patients sensitized to allergens other than HDM and who might have been exposed to those allergens during the run-in or the primary efficacy assessment periods, those allergens can be perennial allergens (e.g. aspergillus, cladosporium, cockroach), cat or dog allergens, or seasonal allergens with pollination period that potentially overlapped with the run-in or the

primary efficacy assessment periods. Those patients present either a major or a minor deviation to exclusion criterion no. 01 (see DRD section 4.1.2.1).

10. Statistical Analysis

All analyses performed by treatment group in the randomized set, FAS and PPS will be done according to the randomization list.

SAS code for each type of inferential analysis is provided in Appendix 13.2.

10.1. Disposition of Patients

Patient disposition will be presented overall and by enrollment period as follows:

- The date that the first informed consent was signed (by the patient himself or parent(s)/legal representative depending on age of the patient), the date that the first patient entered the run-in period (Visit 2), the date that the first patient was randomized, the date that the first patient was treated with IP of the treatment period, the date that the last patient was treated with IP of the treatment period, and the date that the last patient completed the last visit (Visit 10 or end of study in case of withdrawal) for all screened patients by randomized treatment group and overall.
- The number and percentages of screened patients, patients entering the run-in period, randomized patients and patients treated with IP of the treatment period by country and center for all screened patients by randomized treatment groups and overall. The same table will also be provided by pooled center and by center in each pooled center.
- The number and percentages of screen failures (at selection, during run-in period and overall) as well as each reason for screen failures for all screened patients all treatment groups combined.
- The number and percentages of treated with IP of the treatment period, completed and non-completed patients, as well as patients present at each study visit by treatment group and overall in the randomized set.
- The number and percentages of patients who did not complete the study along with a summary of the primary reasons for early study discontinuation by treatment group and overall in the randomized set. The same table will be provided for patients who did not complete the treatment period.
- A Kaplan-Meier plot by treatment group of the probability of remaining in the study from randomization in the randomized set.
- The number of patients allocated to each analysis set, the number of patients who were excluded from an analysis set along with the main reason for exclusion by treatment group and overall in the randomized set. Percentages will be provided for all treatment groups combined. Since patients in FAS and PPS are analyzed according to the randomized treatment group while patients in Safety Set are analyzed according to the treatment group actually received, percentages by treatment group will be provided only if the randomized and actual groups are the same.

- The number and percentage of patients with at least one major protocol deviation overall and by main category of deviation as defined in *Section 9.3* by treatment group in the randomized set.

The following patient data listings will be provided:

- All patient key dates (inform consent and/or assent, randomization, first and last administration of IP of the treatment period, visit dates, date of discontinuation if any) as well as the final completion status (withdrawn or complete)
- Screen failures
- Withdrawn patients after randomization
- Analysis set allocation and reason for exclusion
- All deviations (minor and major) detected along the study

10.2. Baseline Variables

Unless otherwise specified, the baseline characteristics will be summarized descriptively by treatment group and overall.

All baseline variables will be provided in patient data listings in the Randomized Set.

10.2.1. Socio-Demographics

Socio-demographic characteristics (gender, age (years), age category, height (cm), weight (kg), BMI (kg/m²), geographical region, ethnic origin and race) will be summarized descriptively in patients entering the Placebo run-in period, the Safety Set, the FAS and the PPS.

A corresponding patient data listing will be displayed in patients entering the Placebo run-in period.

10.2.2. Allergy Medical History

Duration of the HDM AR (years), incidence of patients with positive SPT results by allergen, baseline sensitization status, baseline HDM-specific serum IgE levels (≥17.5 kU/L, <17.5 kU/L), duration of HDM asthma (years), asthma status and patient's asthma GINA treatment step for patients with concomitant asthma, FEV_1 (L and percentage of predicted value) will be summarized descriptively for the Safety Set, the FAS and the PPS.

The incidence of patients with positive SPT results will be provided in separate tables. The detailed results of SPTs will be displayed in a specific listing.

10.2.3. Medical History

Previous and concomitant medical conditions including the studied pathology will be presented for the Safety Set as the number of mentions [m], number and percentage (n, %) of patients by MedDRA System Organ Class (SOC) and Preferred Term (PT). Sorting will be done by descending frequency of SOC, and by descending frequency of PT within each SOC, all treatment groups combined.

A corresponding patient data listing will be displayed with a dedicated flag to distinguish previous medical conditions from concomitant ones.

10.2.4. Other Baseline Characteristics

Childbearing potential and urinary pregnancy test will be provided in patient data listings.

10.3. Prior and Concomitant Therapy

10.3.1. Medications

Prior and concomitant medications will be presented for the Safety Set as the number of mentions [m], number and percentage of patients (n, %) by ATC Class levels 1 (one digit) and 3 (4 digits).

Prior medications will be described by treatment group and overall. These medications will be sorted by descending frequency of ATC Class Level 1, and by descending frequency of ATC class level 3 within each ATC Class Level 1, all treatment groups combined.

Concomitant medications will be described by treatment group. These medications will be sorted by descending frequency of ATC Class Level 1, and by descending frequency of ATC class level 3 within each ATC Class Level 1, in the active group.

A corresponding patient data listing, including epinephrine auto-injector use, will be displayed with a dedicated flag to distinguish prior medications from concomitant ones. The epinephrine auto-injector use will be detailed in section 10.8.1.2.

10.3.2. Procedures

Prior and concomitant procedures will be presented for the Safety Set as the number of mentions [m], number and percentage (n, %) of patients by MedDRA SOC and PT.

Prior procedures will be described by treatment group and overall. These procedures will be sorted by descending frequency of SOC, and by descending frequency of PT within each SOC, all treatment groups combined.

Concomitant procedures will be described by treatment group. These procedures will be sorted by descending frequency of SOC, and by descending frequency of PT within each SOC, in the active group.

A corresponding patient data listing will be displayed with a dedicated flag to distinguish prior procedures from concomitant ones.

10.4. Treatment Exposure and Treatment Compliance

Treatment exposure (days) and treatment compliance classes (‘compliant’ or ‘non compliant’) will be described by treatment group for the Safety Set, the FAS and the PPS.

Treatment interruptions will be provided in a separate patient data listing.

10.5. Efficacy Analyses

All efficacy analyses will be performed in the FAS except supportive or sensitivity analyses either performed on the PPS or the Randomized Set.

10.5.1. Primary Efficacy Variable

Primary efficacy analysis

The average TCS during each evaluation period will be summarized descriptively. The square root of the average TCS during the primary evaluation period will be analyzed in the FAS using an Analysis of Covariance (ANCOVA) with treatment group as main effect and pooled center, the square root of the baseline average TCS, age class (adolescent, adult), gender, asthma status (yes, no) and sensitization status (mono-, poly-sensitized) as covariates. Patients in the FAS having no efficacy evaluation during the primary period (i.e., no valid assessment) will not be part of the primary analysis. They will be included in the sensitivity analyses to assess the robustness of the primary analysis with regard to missing data.

The LS means of SQRT-transformed average TCS will be assessed in each treatment group. The back-transformed LS means will be calculated in each treatment group. The point estimate, i.e., the difference of LS means, will be calculated from the back-transformed LS means. The corresponding relative LS mean difference (%) will be derived as follows:

Relative LS mean difference (%) = [(active LS mean - placebo LS mean) / placebo LS mean] x 100

All 95% CIs will be calculated using bootstrap method with 10,000 replications and 1234 as seed value.

Statistical hypotheses

The null hypothesis (H0) is:

There is no statistically significant difference between the active and placebo groups for the primary efficacy endpoint i.e., the average TCS in the FAS during the primary evaluation period.

The alternative hypothesis (H1) is:

There is a statistically significant difference between the active and placebo groups for the primary efficacy endpoint.

The active treatment group will be claimed significantly different from the placebo group if the p-value for the between-treatment comparison is statistically significant at the α level ($p \leq 0.05$).

Clinical relevance

[redacted] the clinical relevance of the efficacy results on the primary endpoint is pre-defined as follows:

- the relative difference of the average TCS versus placebo should be ≤-15%, and

- the upper bound of the 95% CI of the average TCS relative difference versus placebo should be ≤-10%

Supportive analyses

- The primary efficacy analysis will be repeated in the PPS.
- The average TCS will be analyzed in the FAS during the primary evaluation period using a Wilcoxon rank-sum test (non-parametric method). The point estimate, i.e., the difference in medians, will be calculated and the corresponding relative median difference (%) will be derived as follows:

  Relative median difference (%) = [(active median - placebo median) / placebo median] x 100

  All 95% CIs will be calculated using bootstrap method with 10,000 replications and 1234 as seed value.
- The average TCS will be analyzed in the FAS during the primary evaluation period without using the SQRT transformation. Only the 95% CI of the relative difference will be calculated using bootstrap method with 10,000 replications and 1234 as seed value.

Sensitivity analyses

- Sensitivity analyses to assess the impact of missing average TCSs during the primary evaluation period will be investigated in the Randomized Set as detailed in *Section 9.5.* These analyses will include multiple imputation of missing data under MAR assumptions and under MNAR assumptions using control-based imputations (Copy Reference method), a MMRM under MAR assumption with an unstructured covariance matrix and single imputation of missing data using the LOCF method.
- The primary efficacy analysis will be repeated in the FAS using the sensitivity primary period as initially proposed in the protocol i.e. the 4 weeks prior to the end of the treatment period (sensitivity primary evaluation period, defined in *Section 6.1*).
- The primary efficacy analysis will be repeated in the FAS using the baseline average TCS used by the investigator for randomization as covariate (see *Section 8.4)*

Summary statistics

The average TCS during each evaluation period will be summarized descriptively and graphically by treatment group in the FAS.

The average TCS during the primary evaluation period will also be described:

- In the PPS
- In the Randomized Set with imputation of missing data using LOCF method.

Subgroup analyses

The average TCS during the primary evaluation period will be summarized descriptively per treatment group by each level of each covariate and subgroup defined in *Section 9.9*.

Subgroups analyses will be performed as detailed in *Section 9.9*.

A forest plot, displaying the treatment effects across covariates and subgroups, will be produced.

10.5.2. Secondary Efficacy Variables

The six ranked secondary endpoints will be tested in the following order as detailed in *Section 9.8*:

- 1. Rhinitis Total Symptom Score (RTSS) during the primary evaluation period
- 2. Overall score of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at the end of the treatment period
- 3. Rhinoconjunctivitis Total Symptom Score (RCTSS) during the primary evaluation period
- 4. Blocked nose symptom score during the primary evaluation period
- 5. Proportion of Symptom-Controlled Days (PSCDs, proportion of days with RTSS≤2 and no rescue medication use) during the primary evaluation period
- 6. Rescue Medication Score (RMS) during the primary evaluation period

The analysis of the non-ranked secondary endpoints will be considered supportive and will contribute to document the consistency of the study results; confidence intervals and statistical tests will be of descriptive nature.

10.5.2.1 Average Rhinitis Total Symptom Score (RTSS)

The average RTSS during the primary evaluation period will be analyzed as per the average TCS using the corresponding baseline score (including non-parametric analysis but excluding the sensitivity and subgroup analyses). As RTSS is a component of the primary efficacy variable, its analysis will be repeated in the PPS.

Average RTSS will be summarized descriptively during each evaluation period in the FAS and in the PPS.

10.5.2.2 Average Rescue Medication Score (RMS)

The average RMS during the primary evaluation period will be analyzed as per the average TCS using the corresponding baseline score (including non-parametric analysis but excluding the sensitivity and subgroup analyses). As RMS is a component of the primary efficacy variable, its analysis will be repeated in the PPS.

The average RMS will be summarized descriptively during each evaluation period in the FAS and in the PPS.

10.5.2.3 Average Adjusted Symptom Score (ASS)

The average ASS during the primary evaluation period will be analyzed as per the average TCS using the corresponding baseline scores (including non-parametric analysis but excluding the PPS, sensitivity and subgroup analyses). It will be summarized descriptively during each evaluation period.

10.5.2.4 Average Combined Symptom and Medication Score (CSMS)

The average CSMS during the primary evaluation period will be analyzed as per the average TCS using the corresponding baseline scores (including non-parametric analysis but excluding the PPS, sensitivity and subgroup analyses). It will be summarized descriptively during each evaluation period.

10.5.2.5 Average Total Ocular Symptom Score (TOSS)

The average TOSS during the primary evaluation period will be analyzed as per the average TCS using the corresponding baseline scores (including non-parametric analysis but excluding the PPS, sensitivity and subgroup analyses). It will be summarized descriptively during each evaluation period.

10.5.2.6 Average Rhinoconjunctivitis Total Symptom Score (RCTSS)

The average RCTSS during the primary evaluation period will be analyzed as per the average TCS using the corresponding baseline score (including non-parametric analysis but excluding sensitivity and subgroup analyses).

Average RCTSS will be summarized descriptively during each evaluation period in the FAS and in the PPS.

10.5.2.7 Six Average Individual Rhinoconjunctivitis Symptom Scores (RSSs)

Each of the six average individual RSSs during the primary evaluation period will be analyzed as per the average TCS using the corresponding baseline score (including non-parametric analysis but excluding the PPS, sensitivity and subgroup analyses). They will be summarized descriptively during each evaluation period.

10.5.2.8 Rhinoconjunctivitis Rescue Medication Use

The proportions of days with rescue medication use, overall and for each rescue medication category, will be summarized descriptively during each evaluation period and compared between treatment groups using a Wilcoxon rank-sum test for the primary evaluation period.

The proportions of patients with at least one day of rescue medication use, overall and for each category of rescue medication, will be summarized descriptively during each evaluation period and compared between treatment groups using a χ^2 test or a Fisher exact test for the primary evaluation period.

10.5.2.9 Visual Analogue Scale (VAS)

The average VAS score during the primary evaluation period will be analyzed as per the average TCS (without transformation of the original variable) using the corresponding baseline scores (but excluding the supportive, sensitivity and subgroup analyses). It will be summarized descriptively during each evaluation period.

10.5.2.10 Proportion of Symptom-Controlled Days (PSCD)

The $PSCD_{2\text{-}0}$ will be summarized descriptively during each evaluation period and compared between treatment groups using a Wilcoxon rank-sum test for the primary evaluation period.

10.5.2.11 Proportion of Not-Controlled Days (PNCD)

The PNCD will be summarized descriptively during each evaluation period and compared between treatment groups using a Wilcoxon rank-sum test for the primary evaluation period.

10.5.2.12 Controlled Patients (CP)

The $CP75_{2\text{-}0}$ will be summarized descriptively during each evaluation period and compared between treatment groups using a χ^2 test or a Fisher exact test for the primary evaluation period.

10.5.2.13 Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12) Scores

The overall score and the seven domain scores at baseline and endpoint, and changes from baseline will be summarized descriptively. The scores at endpoint will be analyzed as per the average TCS (without transformation of the original variable) using the corresponding baseline scores (but excluding the supportive, sensitivity and subgroup analyses).

10.5.2.14 EQ-5D-5L Generic Health-Related Quality of Life Questionnaire

The 5 dimensions of EQ-5D-5L health profile and the 5 EQ-5D-5L variables levels ('no problem' vs. 'mild to extreme problem') at baseline and endpoint will be summarized descriptively.

The EQ-5D-5L VAS and EQ-5D-5L Index at baseline and endpoint, and the changes from baseline will be will be summarized descriptively. At endpoint, those variables will be analyzed as per the average TCS (without transformation of the original variable) using the corresponding baseline scores (but excluding the supportive, sensitivity and subgroup analyses).

10.5.2.15 Global Rating of Change Score (GRCS)

The GRCS will be presented in a frequency table and compared between treatment groups using a Cochran Mantel-Haenszel (CMH) test (row mean score statistic) with pooled centers as a stratification variable.

The proportions of improved patients will be compared between groups using a χ^2 test or a Fisher exact test.

10.6. Exploratory Analyses

Unless otherwise specified, exploratory analyses will be performed in the FAS.

[redacted]

10.6.2. Rhinitis Exacerbations

The proportions of days with a rhinitis exacerbation will be summarized descriptively during each evaluation period and compared between treatment groups using a Wilcoxon rank-sum test for the primary evaluation period.

10.6.3. Asthma Events

The proportion of patients experiencing at least one asthma event over the treatment period will be presented in a frequency table and compared between treatment groups using a χ^2 test or a Fisher exact test.

This table will be presented overall and per patient with concomitant asthma.

The asthma events will be detailed in the patient data listing including age group (adult/adolescent) and asthma status of the patients.

[redacted]

10.7. Other Analyses

Unless otherwise specified, all other analyses will be performed in the FAS.

10.7.1. Number of Valid Days

The number of valid days, the proportion of valid days (%) and the number of days between the date of the first administration of IP and the date of start of each evaluation period will be described for each evaluation period for the Randomized Set, the FAS and the PPS.

The distribution of the number of valid days during each evaluation period will also be graphically displayed for the Randomized Set, the FAS and the PPS.

10.7.2. Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI + CIQ: AS) Scores

The WPAI + CIQ: AS scores at baseline and endpoint, and changes from baseline will be summarized descriptively.

10.7.3. HDM Avoidance Questionnaire

The incidence of patients with at least one of the 8 items of HDM avoidance questionnaire ticked as ‘Yes’ at the end of the study in overall and by item will be summarized descriptively.

10.7.4. Immunological Markers

Due to the distribution shape expected to be close to log-normal, *D. pte*- and *D. far*-specific serum IgE and IgG_4 before and after treatment as well as the fold-changes will be summarized descriptively using number of patients, number of missing values, geometric mean, 95% confidence interval of the geometric mean, minimum, lower quartile, median, upper quartile, and maximum.

Graphs showing geometric means and 95% CI at baseline and endpoint will be displayed.

10.8. Safety Analysis

The safety analyses of events occurring during the Placebo run-in period will be performed for all patients entering the run-in period and receiving at least one dose of Placebo.

All other safety analyses will be performed in the Safety Set.

10.8.1. Adverse Events (AEs)

10.8.1.1 All Placebo Run-In Emergent AEs in Patients Entering the Run-In Period

An overview of all Placebo run-in Emergent AEs will be presented, indicating the number of events [m], number and percentage of patients (n, %) (percentages based on the number of patients entering the Placebo run-in period) with at least one:

- Placebo run-in Emergent AE
- Placebo run-in Emergent AE suspected to be drug-related (i.e., related to IP of the run-in period: Placebo)
- Serious Placebo run-in Emergent AE
- Serious Placebo run-in Emergent AE suspected to be drug-related (i.e., related to IP of the run-in period: Placebo)
- Placebo run-in Emergent AE leading to premature IP discontinuation (i.e., IP of the run-in period: Placebo)
- Placebo run-in Emergent AE leading to premature study withdrawal (i.e., run-in failures)
- Placebo run-in Emergent AE leading to death

The incidence (number of events [m], number and percentage of patients (n, %)) of the Placebo run-in Emergent AEs will be presented by MedDRA SOC and PT. AEs will be sorted by descending frequency of SOC, and by descending frequency of each PT within each SOC in all patients entering the run-in period.

Both tables will be provided by groups of non-randomized and randomized patients at the end of the run-in period, and, overall.

A detailed patient data listing of all Placebo run-in Emergent AEs and their characteristics including the onset day and the duration (days) will be provided.

10.8.1.2 All AEs in Patients Entering the Treatment Period

All tables will be provided by treatment groups according to the treatment actually received by the patient during the treatment period whether the adverse event occurred during that period or not, and, overall.

An overview of the AEs will be presented, indicating the number of events [m], number and percentage of patients (n, %) (percentages based on the number of patients included in the Safety Set for the specified group) with at least one:

- AE
- AESI
- Serious AE (SAE)
- AE leading to premature IP discontinuation
- AE leading to premature study withdrawal
- AE leading to death

- Pre-TEAE
- Serious Pre-TEAE
- Pre-TEAE leading to premature study withdrawal
- Pre-TEAE leading to death

- Placebo run-in Emergent AE
- Placebo run-in Emergent AESI
- Placebo run-in Emergent AE suspected to be drug-related (i.e., related to IP of the run-in period: Placebo)
- Serious Placebo run-in Emergent AE
- Serious Placebo run-in Emergent AE suspected to be drug-related (i.e., related to IP of the run-in period: Placebo)
- Placebo run-in Emergent AE leading to premature IP discontinuation (i.e., IP of the run-in period: Placebo)
- Placebo run-in Emergent AE leading to premature study withdrawal (i.e., run-in failures)
- Placebo run-in Emergent AE leading to death

- TEAE
- TEAE suspected to be drug-related (i.e., related to IP of the treatment period)

- TEAE AESI
- Serious TEAE
- Serious TEAE suspected to be drug-related (i.e., related to IP of the treatment period)
- TEAE leading to premature IP discontinuation (i.e., IP of the treatment period)
- TEAE leading to premature study withdrawal
- TEAE leading to premature study withdrawal suspected to be drug-related
- TEAE leading to death

- Post-TEAE
- Serious Post-TEAE
- Post-TEAE leading to premature study withdrawal
- Post-TEAE leading to death

The overview of the AEs will be also presented by age group.

A summary of the following TEAE characteristics indicating the number of events (m), the number and percentage of patients (n, %) will be presented:

- Severity
- Action taken with IP of the treatment period
- Other action taken
- Outcome
- Relationship to IP of the treatment period
- Occurrence

The incidence (number of events [m], number and percentage of patients (n, %)) of the following AEs will be presented by MedDRA SOC and PT:

- Pre-TEAEs
- Placebo run-in Emergent AEs
- TEAEs
- Most common TEAEs (with an incidence ≥ 5% in any treatment group)
- TEAEs suspected to be drug-related (i.e., related to IP of the treatment period)
- Most common TEAEs suspected to be drug-related (with an incidence ≥5% in any treatment group)
- Serious TEAEs

- Serious TEAEs suspected to be drug-related (i.e., related to IP of the treatment period)
- TEAEs leading to premature IP discontinuation
- TEAEs leading to premature study withdrawal
- TEAE leading to premature study withdrawal suspected to be drug-related

- TEAEs by severity
- TEAEs by relationship to IP ('Suspected to be drug-related' vs. 'Not suspected')
- TEAEs by severity and relationship
- Post-TEAEs

For each table, AEs will be sorted by descending frequency of SOC, and by descending frequency of each PT within each SOC in the active group.

For the analysis by severity and relationship, patients with different occurrences of the same TEAE will be counted once within each category, and multiple times across categories. That is, if a patient had the same TEAE three times, twice 'mild' and once 'moderate', then he/she will be counted once under the 'mild' category and once under the 'moderate' category. The number of events [m] will include all occurrences of TEAEs.

Each incidence table (except those by severity and relationship) will also be provided by age group.

In addition to the above tables, the following by-patient listings (including all AEs) will be presented:

- All AEs for patients who died
- All SAEs (other than those leading to death)
- All AESIs (for each patient having an AESI, patient's data listing of all AEs data will be provided): severe anaphylactic reactions, severe laryngo-pharyngeal disorders, autoimmune disorders.
- All AEs leading to premature IP discontinuation
- All AEs leading to premature study withdrawal

A detailed patient data listing of all AEs and their characteristics, including the category of each AE (Pre-TEAE, Placebo run-in Emergent AE, TEAE, Post-TEAE), if the AE is an AESI, the onset day and the duration (days) will be provided in the Safety Set.

Another detailed data patient listing for use of epinephrine from panels AE, CM and Use of Epinephrine Auto-Injection will be displayed.

10.8.2. Laboratory Parameters

Laboratory values (hematology and biochemistry) will be summarized descriptively at baseline and at endpoint.

Frequency distributions in categories relative to the normal reference ranges ('Low', 'Normal' and 'High' as defined in *Section 8.8.2*) will be also summarized at baseline and at endpoint as well as the corresponding shifts from baseline.

A by-patient listing for all patients with at least one abnormal laboratory value (hematology and biochemistry) will be presented. For each patient, the listing will display the complete profile of all parameters with at least one abnormal value.

A detailed patient data listing of all laboratory values (hematology and biochemistry) including re-tested values, flag for values outside the normal reference ranges and clinical significance according to the Investigator will be provided.

A separate patient data listing will also be provided for positive pregnancy test results.

10.8.3. Vital Signs

Vital signs will be summarized at baseline and at endpoint along with the corresponding changes from baseline.

Frequency distribution of the clinical interpretation will also be presented at baseline and endpoint.

10.8.4. Spirometry for Asthmatic Patients

FEV_1 (L and percentage of predicted value) for asthmatic patients will be summarized at baseline and at endpoint along with the change from baseline.

10.8.5. Physical Examination

All abnormal physical examination findings will be presented in a patient data listing indicating if they are clinically significant or not.

11. Presentation of Results

The analyses described in this SAP will be presented using tables, figures and patient data listings.

11.1. List of Tables

The following list includes, but is not limited to, the tables that will be provided.

Number	Title	Analysis Set
Table 14.1.1.1	Study Key Dates	Screened Patients
Table 14.1.1.2	Countries and Centers	Screened Patients
Table 14.1.1.3	Pooled Centers and Centers	Screened Patients
Table 14.1.1.4	Screen Failures	Screened Patients
Table 14.1.1.5	Patient Disposition	Randomized Patients
Table 14.1.1.6	Patient Treatment Completion Status	Randomized Patients
Table 14.1.1.7	Patient Study Completion Status	Randomized Patients
Table 14.1.1.8	Analysis Set Allocation	Screened Patients
Table 14.1.1.9	Major Protocol Deviations	Randomized Patients
Table 14.1.2.1-1	Socio-Demographics Characteristics	Patients Entering the Run-in Period
Table 14.1.2.1-2	Socio-Demographics Characteristics	Safety Set
Table 14.1.2.1-3	Socio-Demographics Characteristics	Full Analysis Set
Table 14.1.2.1-4	Socio-Demographics Characteristics	Per Protocol Set
Table 14.1.2.2-1	Allergy Medical History	Safety Set
Table 14.1.2.2-2	Allergy Medical History	Full Analysis Set
Table 14.1.2.2-3	Allergy Medical History	Per Protocol Set
Table 14.1.2.3-1	Positive Skin Prick Test (SPT) Result to at Least One Allergen	Safety Set
Table 14.1.2.3-2	Skin Prick Test (SPT) Results	Full Analysis Set
Table 14.1.2.3-3	Skin Prick Test (SPT) Results	Per Protocol Set
Table 14.1.2.4.1	Previous Medical Conditions	Safety Set
Table 14.1.2.4.2	Concomitant Medical Conditions	Safety Set
Table 14.1.3.1.1	Prior Medications	Safety Set
Table 14.1.3.1.2	Concomitant Medications	Safety Set
Table 14.1.3.2.1	Prior Procedures	Safety Set
Table 14.1.3.2.2	Concomitant Procedures	Safety Set
Table 14.1.4.1-1	Overall Treatment Exposure and Treatment Compliance During the Treatment Period	Safety Set
Table 14.1.4.1-2	Overall Treatment Exposure and Treatment Compliance During the Treatment Period	Full Analysis Set
Table 14.1.4.1-3	Overall Treatment Exposure and Treatment Compliance During the Treatment Period	Per Protocol Set
Table 14.2.1.1.1	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline]	Full Analysis Set
Table 14.2.1.1.2	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVA) during the Primary Evaluation Period (Primary Analysis)	Full Analysis Set
Table 14.2.1.2.1	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] (Supportive Analysis)	Per Protocol Set

Number	Title	Analysis Set
Table 14.2.1.2.2	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVA) during the Primary Evaluation Period (Supportive Analysis)	Per Protocol Set
Table 14.2.1.2.3	Average Total Combined Score (TCS): Non-Parametric Method (Wilcoxon Rank-Sum Test) during the Primary Evaluation Period (Supportive Analysis)	Full Analysis Set
Table 14.2.1.2.4	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVA) during the Primary Evaluation Period with no SQRT-Transformation (Supportive Analysis)	Full Analysis Set
Table 14.2.1.3.1	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVA) during the Primary Evaluation Period after Multiple Imputation of Missing Data using Missing At Random Assumptions (Sensitivity Analysis)	Randomized Patients
Table 14.2.1.3.2	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVA) during the Primary Evaluation Period afterMultiple Imputation of Missing Data using Missing Not at Random Assumption (Copy Reference Method) (Sensitivity Analysis)	Randomized Patients
Table 14.2.1.3.3	Average Total Combined Score (TCS): Mixed Model with Repeated Measures (MMRM) (Sensitivity Analysis)	Full Analysis Set
Table 14.2.1.3.4.1	Average Total Combined Score (TCS): Descriptive Statistics at Baseline and during the Primary Evaluation Period (LOCF) [Values and Changes from Baseline] (Sensitivity Analysis)	Randomized Patients
Table 14.2.1.3.4.2	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVA) during the Primary Evaluation Period (LOCF) (Sensitivity Analysis)	Randomized Patients
Table 14.2.1.3.5.1	Average Total Combined Score (TCS): Descriptive Statistics at Baseline and during the Sensitivity Primary Evaluation Period (as Initially Defined in the Protocol) [Values and Changes from Baseline] (Sensitivity Analysis)	Full Analysis Set
Table 14.2.1.3.5.2	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVA) during the Sensitivity Primary Evaluation Period (as Initially Defined in the Protocol) (Sensitivity Analysis)	Full Analysis Set
Table 14.2.1.3.6.1	Descriptive Statistics at Baseline [Including Values Used by the Investigator to Randomize the Patient] (Sensitivity Analysis)	Full Analysis Set
Table 14.2.1.3.6.2	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVA) during the Primary Evaluation Period Using the Baseline Value Used by the Investigator to Randomize the Patient (Sensitivity Analysis)	Full Analysis Set
Table 14.2.1.4.1	Average Total Combined Score (TCS): Analyses of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and each of the Covariate or the Subgroup	Full Analysis Set

Number	Title	Analysis Set
Table 14.2.1.4.2-1	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Gender	Full Analysis Set
Table 14.2.1.4.2-2	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Age Class	Full Analysis Set
Table 14.2.1.4.2-3	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Sensitization Status	Full Analysis Set
Table 14.2.1.4.2-4	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Asthma Status	Full Analysis Set
Table 14.2.1.4.2-5	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Pooled Center	Full Analysis Set
Table 14.2.1.4.2-6	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Baseline Average TCS Class	Full Analysis Set
Table 14.2.1.4.2-7	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Enrollment Period	Full Analysis Set
Table 14.2.1.4.2-8	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] -	Full Analysis Set
Table 14.2.1.4.2-9	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Race	Full Analysis Set
Table 14.2.1.4.2-10	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Geographical Region	Full Analysis Set
Table 14.2.1.4.2-11	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Baseline D.pte- and/or D.far-Specific Serum IgE Levels	Full Analysis Set
Table 14.2.1.4.2-12	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Subgroup At Least One HDM Avoidance Measure Implemented since the Start of the Study	Full Analysis Set
Table 14.2.1.4.2-13	Average Total Combined Score (TCS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline] - By Subgroup Without/With Potentially Confounding Sensitizations	Full Analysis Set
Table 14.2.1.4.3-1	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Covariate Gender	Full Analysis Set
Table 14.2.1.4.3-2	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Covariate Age Class	Full Analysis Set
Table 14.2.1.4.3-3	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between	Full Analysis Set

Number	Title	Analysis Set
	Treatment Group and the Covariate Sensitization Status	
Table 14.2.1.4.3-4	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Covariate Asthma Status	Full Analysis Set
Table 14.2.1.4.3-5	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Covariate Pooled Center	Full Analysis Set
Table 14.2.1.4.3-6	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Covariate Baseline Average TCS Class	Full Analysis Set
Table 14.2.1.4.3-7	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Subgroup By Enrollment Period	Full Analysis Set
Table 14.2.1.4.3-8	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group [redacted]	Full Analysis Set
Table 14.2.1.4.3-9	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Subgroup Race	Full Analysis Set
Table 14.2.1.4.3-10	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Subgroup Geographical Region	Full Analysis Set
Table 14.2.1.4.3-11	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Subgroup Baseline D.pte- and/or D.far- Specific Serum IgE Levels	Full Analysis Set
Table 14.2.1.4.3-12	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Subgroup At Least One HDM Avoidance Measure Implemented since the Start of the Study	Full Analysis Set
Table 14.2.1.4.3-13	Average Total Combined Score (TCS): Analysis of Covariance (ANCOVAs) during the Primary Evaluation Period by Adding Interaction between Treatment Group and the Subgroup Without/With Potentially Confounding Sensitizations	Full Analysis Set
Table 14.2.2.1.1-1	Average Rhinitis Total Symptom Score (RTSS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline]	Full Analysis Set

Number	Title	Analysis Set
Table 14.2.2.1.1-2	Average Rhinitis Total Symptom Score (RTSS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline]	Per Protocol Set
Table 14.2.2.1.2-1	Average Rhinitis Total Symptom Score (RTSS): Analysis of Covariance (ANCOVA) during the Primary Evaluation Period	Full Analysis Set
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Table 14.2.2.5.2	Average Total Ocular Symptom Score (TOSS): Analysis of Covariance (ANCOVA) during the Primary Evaluation Period	Full Analysis Set
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Number	Title	Analysis Set
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Table 14.2.2.6.1-2	Average Rhinoconjunctivitis Total Symptom Score (RCTSS): Descriptive Statistics by Evaluation Periods [Values and Changes from Baseline]	Per Protocol Set
Table 14.2.2.6.2-1	Average Rhinoconjunctivitis Total Symptom Score (RCTSS): Analysis of Covariance (ANCOVA) during the Primary Evaluation Period	Full Analysis Set
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Table 14.2.2.12	Controlled Patients (CP): Descriptive Statistics by Evaluation Periods [Proportion of Patients]	Full Analysis Set
Table 14.2.2.13.1	Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12 Scores): Descriptive Statistics over Time [Values and Changes from Baseline]	Full Analysis Set
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Table 14.2.2.14.1	EQ-5D-5L Generic Health Related Quality of Life Questionnaire: Descriptive Statistics over Time [Values and Changes from Baseline]	Full Analysis Set

Number	Title	Analysis Set
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Table 14.2.2.15	Global Rating of Change Score (GRCS): Descriptive Statistics at Endpoint	Full Analysis Set
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Table 14.2.3.3	Asthma Events: Descriptive Statistics over the Treatment Period [Proportion of Patients]	Full Analysis Set
Table 14.2.4.1-1	Number of Valid Days by Evaluation Period	Randomised Set
Table 14.2.4.1-2	Number of Valid Days by Evaluation Period	Full Analysis Set
Table 14.2.4.1-3	Number of Valid Days by Evaluation Period	Per Protocol Set
Table 14.2.4.2	WPAI + CIQ AS Scores: Descriptive Statistics over Time [Values and Changes from Baseline]	Full Analysis Set
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Table 14.2.4.4	Immunological Markers: Descriptive Statistics over Time [Values and Fold-Changes from Baseline]	Full Analysis Set
Table 14.3.1.1.1	Overview of Placebo Run-In Emergent AEs	Patients Entering the Run-In Period
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Number	Title	Analysis Set
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11.2. List of Figures

The following list includes, but is not limited to, the figures that will be provided.

- Probability of Remaining in the Study from Randomization (Kaplan-Meier Plot) – Overall and By Enrollment Period - Randomized Patients
- Average Total Combined Score (TCS) by Evaluation Periods - Full Analysis Set
- Baseline Average TCS against Average TCS during the Primary Evaluation Period (Scatter Plot) – Full Analysis Set
- Treatment Effects of the Average TCS during the Primary Evaluation Period across Covariates and Subgroups (Forest Plots) - Full Analysis Set
- Distribution of the Number of Valid Days by Evaluation Periods - Safety Set
- Distribution of the Number of Valid Days by Evaluation Periods - Full Analysis Set
- Distribution of the Number of Valid Days by Evaluation Periods - Per Protocol Set

- Immunological Markers at Baseline and Endpoint - Safety Set

11.3. List of Listings

The following list includes, but is not limited to, the patient data listings that will be provided.

- Patient Disposition - Screened Patients
- Screen Failure Patients - Screened Patients
- Withdrawn Patients after Randomization - Randomized Patients
- Analysis Set Allocation and Reason for Exclusion - Randomized Patients
- All Protocol Deviations - Randomized Patients
- Demographic Characteristics - Randomized Patients
- Allergy Medical History - Randomized Patients
- Skin Prick Tests and Sensitization Status - Randomized Patients
- Medical History: Previous and Concomitant Medical Conditions - Randomized Patients
- Childbearing Potential and Urinary Pregnancy Test - Randomized Patients
- Urinary Pregnancy Test - Randomized Patients
- Previous and Concomitant Medications - Randomized Patients
- Previous and Concomitant Procedures - Randomized Patients
- Treatment Exposure and Compliance - Safety Set
- Treatment Interruptions - Safety Set
- Daily Rhinoconjunctivitis Symptom Scores, Rescue Medication Use and Rhinitis Exacerbations - Randomized Patients
- Average Rhinoconjunctivitis Symptom Scores and Rescue Medication Scores - Randomized Patients
- Visual Analogue Scale (Weekly and Average Scores) - Randomized Patients
- Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(s)>=12) - Randomized Patients
- EQ-5D-5L Generic Heath-Related Quality of Life Questionnaire - Randomized Patients
- Global Rating of Change Score (GRCS) - Randomized Patients

- Asthma Events - Randomized Patients
- Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI + CIQ: AS) Scores - Randomized Set
- HDM Avoidance Questionnaire - Randomized Patients

- Immunological Markers - Randomized Patients
- Placebo Run-In Emergent AEs - Patients Entering the Run-In Period
- All AEs - Safety Set
- Use of Epinephrine - Safety Set
- Laboratory Values: All Haematology Parameters - Safety Set
- Laboratory Values: All Biochemistry Parameters - Safety Set
- Vital Signs – Safety Set
- Spirometry for Asthmatic Patients over the Study – Safety Set
- Abnormal Physical Examination Findings – Safety Set

12. References

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13. Appendices

The appendices 2 to 5 will be available with the final version of the SAP.

13.1. Appendix 1 – Additional Information on the Sample Size

Appendix 1 provides additional information on the rationale for the sample size determination.

Reminder: the primary endpoint is the average TCS defined, for each patient, as the average of the non-missing daily TCSs over the last four weeks prior to the end of the treatment period.

[redacted] the clinical relevance of the efficacy results on the primary endpoint is pre-defined as follows:

- the relative difference of the TCS *versus* placebo should be ≤-15%, and
- the upper bound of the 95% CI of the TCS relative difference *versus* placebo should be ≤-10%

Assuming a two-sided nominal level of significance of 5%, a relative mean difference versus placebo of -20%, a placebo mean of 3.65, and a CV of 75%, simulations showed that 739 evaluable patients per treatment group were sufficient to achieve a power of around 80% so [redacted] (estimated mean relative difference versus placebo ≤-15% and upper bound of the 95% CI ≤-10%).

[redacted]

Simulations with relative mean difference values ranging from -15% to -25% were implemented and are presented in Table 2:

Table 2: Simulations for power calculations with a sample size of 739 patients per treatment group considering various true relative mean differences vs placebo

Number of samples	Relative Mean Difference (%)	Placebo Mean	Active Mean	Common SD	Power for a statistically significant difference between groups (t-test)	Power for estimated Rel Diff ≤ -15% and UCL ≤ -10%
5,000	-15	3.65	3.10	2.531	98.64	27.30
5,000	-16	3.65	3.07	2.520	99.4	35.72
5,000	-17	3.65	3.03	2.505	99.76	48.22
5,000	-18	3.65	2.99	2.490	99.92	62.54
5,000	-19	3.65	2.96	2.479	99.96	72.08
5,000	-20	3.65	2.92	2.464	100	82.08
5,000	-21	3.65	2.88	2.449	100	89.60
5,000	-22	3.65	2.85	2.438	100	93.74
5,000	-23	3.65	2.81	2.423	100	97.00
5,000	-24	3.65	2.77	2.408	100	98.82
5,000	-25	3.65	2.74	2.396	100	99.48

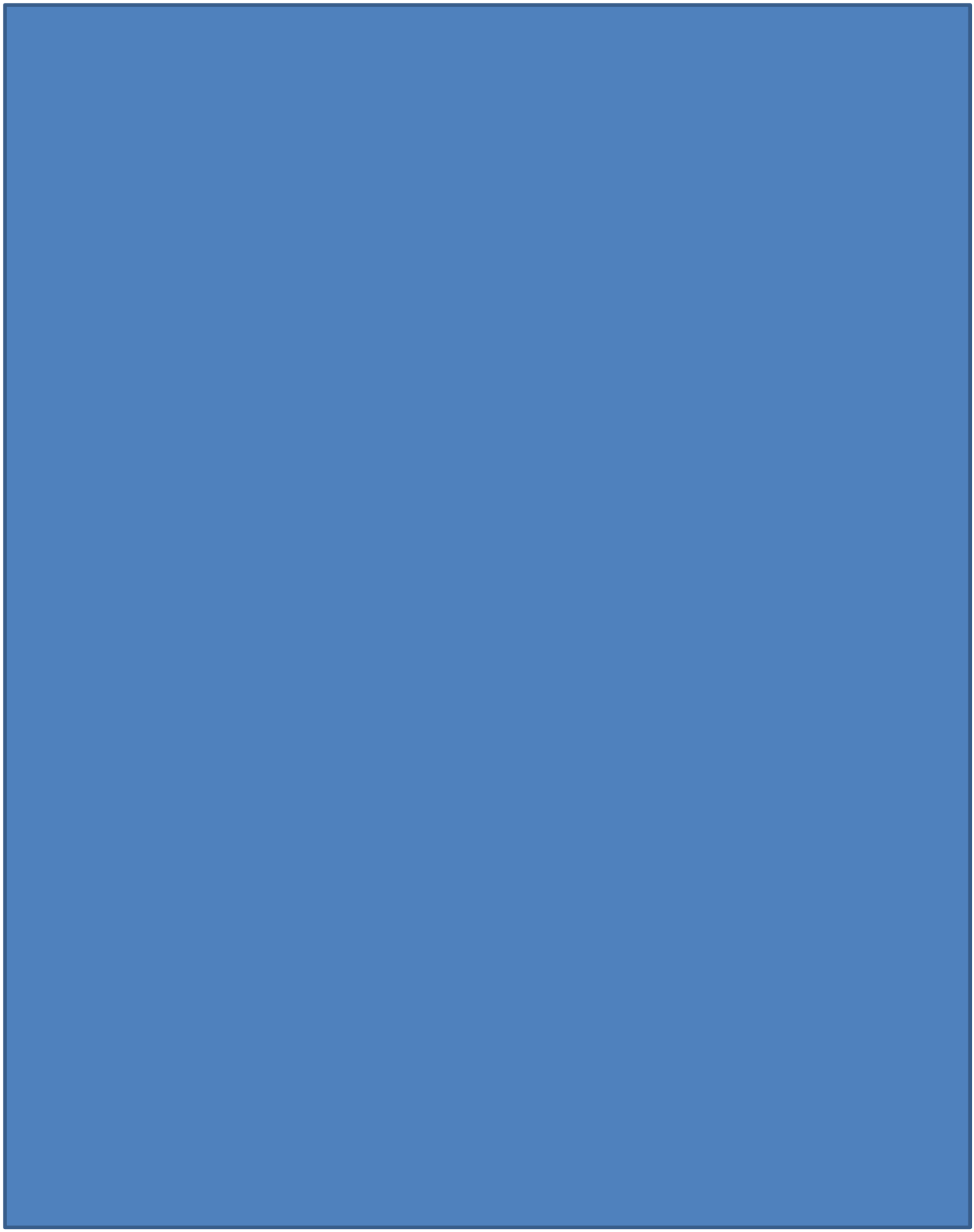
Hence, with 739 evaluable patients per arm and a true relative mean difference of -20%, the power [redacted] requirements was found to be 82.08%, which is higher than an acceptable power of 80%.

Nota:

- With a sample size of 2 x 739 patients, considering an expected difference of -17%, as initially considered in version 4.0 of the protocol, would have resulted in a 48.2% power [redacted] This is why a more optimistic but still plausible (i.e., when considering the range of possible values for the true difference as provided by the 95% CI [-30%; -3%]) expected difference of -20% was considered in the determination of the sample size.

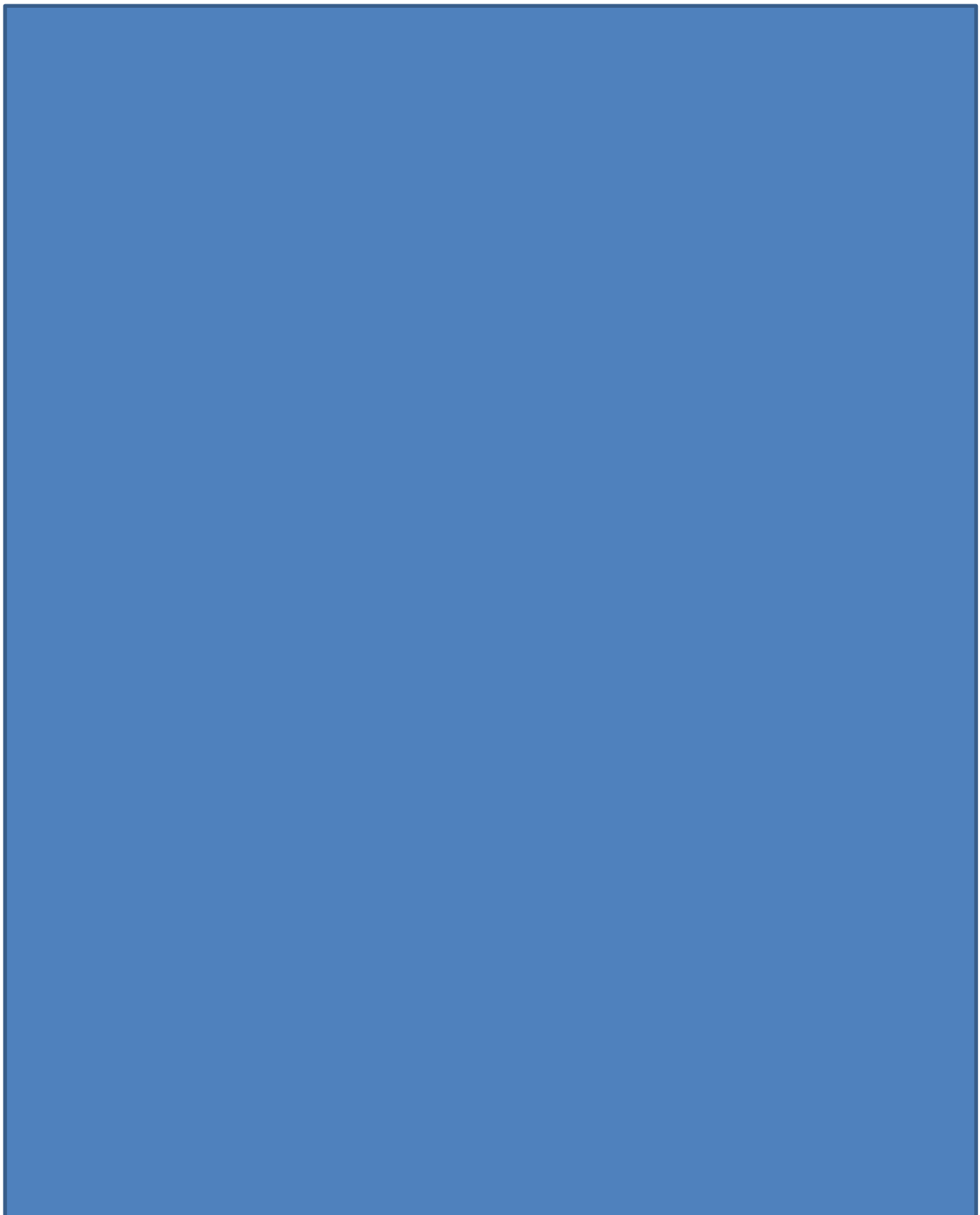
- When considering a relative mean difference of -17% and the same assumptions, simulations show that approximately 1,600 patients per arm would have been needed to achieve a power of 80% [redacted] A trial of such a size was considered as not feasible.

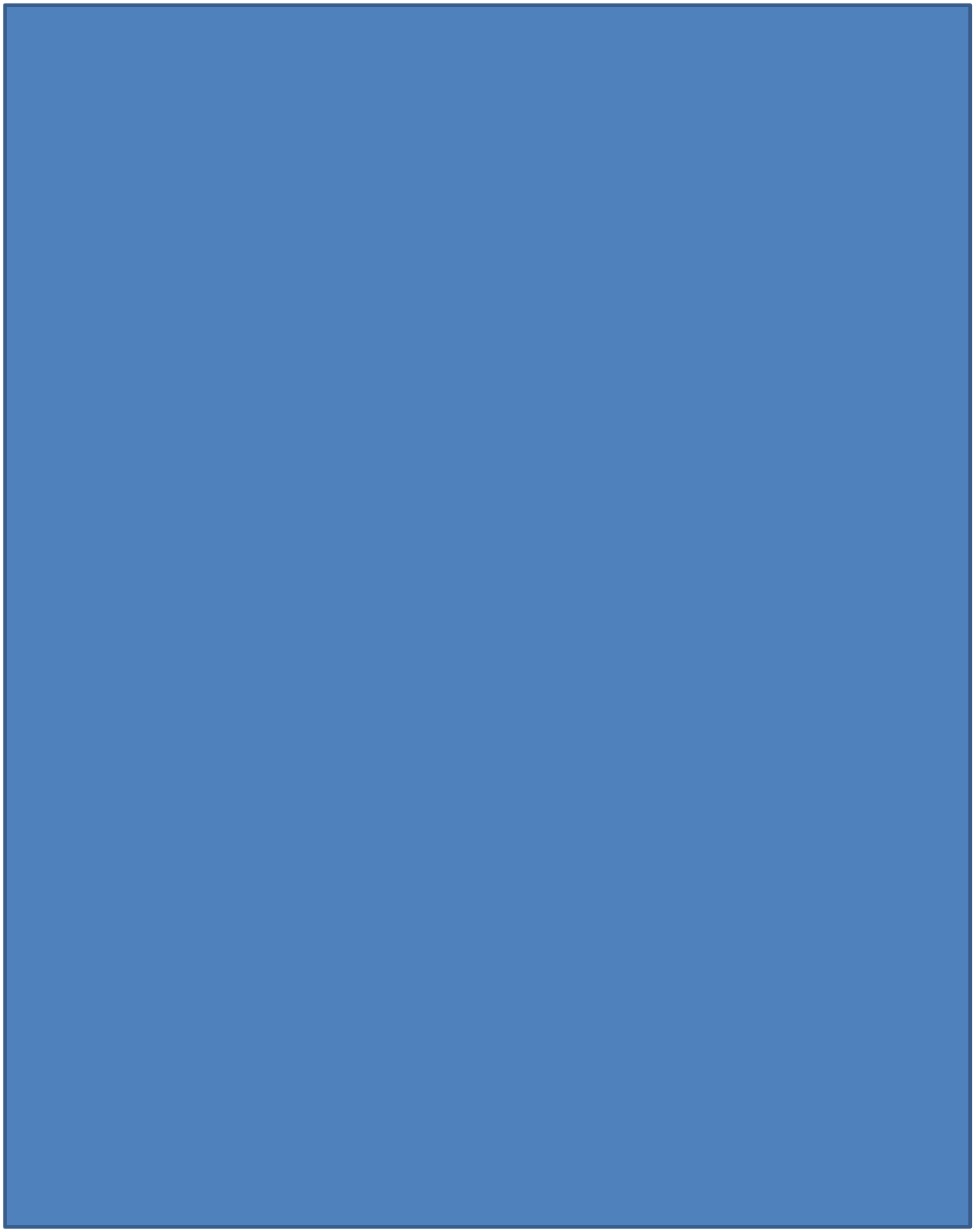
- With 2 x 739 patients the trial is highly powered (> 99%) to show a significant difference between the active and placebo groups.



```
data TTests2;
      set TTests1;
      if Method="Pooled";
      keep SampleID Probt;
   run;

   data Placebo_m;
      set Statistics1;
```





13.2. Appendix 2 – SAS Codes for Inferential Analyses

Appendix 2 provides the generic SAS codes to be used during the programming of the primary analysis (ANCOVA model).

The following abbreviations are used for the variables in the SAS Code:

- aTCS: Average TCS during the primary period
- BASE: Baseline average TCS

- TRTP: Planned treatment group
- SITEGR1: Pooled center
- BASE: Baseline average TCS
- AGEGR1: Age class (adolescent, adult)
- SEX: Gender (male, female)
- ASTHMA: Asthma status (asthma, no asthma)
- SENSTAT: Sensitization status (mono-/poly-sensitized)

```
Proc Mixed data = <DATA> method = REML;
   class TRTP SITEGR1 AGEGR1 SEX ASTHMA SENSTAT;
   model aTCS = TRTP SITEGR1 AGEGR1 SEX ASTHMA SENSTAT BASE;
   lsmeans TRTP / pdiff cl;
run;
```

aTCS and BASE will be firstly SQRT-transformed in the model.

The 95% CIs of the difference of LS Means and relative difference will be assessed using bootstrap on back-transformed LS Means issued from the SAS proc mixed.

13.3. Appendix 3 – Table Shells

Appendix 3 provides the templates to be used during the programming of the tables used in the presentation of results.