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Statistical Analysis Plan

OPN-375 (fluticasone propionate delivered by exhalation delivery system)

OPN-FLU-CS-3206

A 24-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 186 and 372 µg of OPN-375 Twice a Day (BID) in Subjects with Chronic Rhinosinusitis Without the Presence of Nasal Polyps

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1 ABBREVIATIONS

Abbreviation or Term	Definition
AE	Adverse event
AM	Morning
ANCOVA	Analysis of covariance
APOV	Average percent of opacified volume
APOV-E	Average percent of opacified volume in the ethmoid sinuses
APOV-M	Average percent of opacified volume in the maxillary sinuses
BID	Two times a day
BOCF	Baseline Observation Carried Forward
CFR	Code of Federal Regulations
CRF	Case Report Form
CRS	Chronic Rhinosinusitus
CSNS	Composite score of nasal symptoms
CI	Confidence Interval
CT	Computed tomography
DB	Double-blind
DCF	Data Clarification Form
EDS	Exhalation Delivery System
EOS	End of Study
EQ-5D	EuroQol-5
EQ VAS	EQ Visual Analogue Scale
EVA	Electronic visual acuity
ET	Early termination
FAS	Full Analysis Set
GCP	Good Clinical Practice
GLM	Generalized linear model
GLMM	Generalized linear mixed model
HEOR	Health Economics & Outcomes Research
HPQ	Health and Work Performance Questionnaire
IA	Interim analysis
IE	Intercurrent Event
IASAP	Interim analysis Statistical Analysis Plan
ICH	International Conference on Harmonization
INS	Intranasal Steroid
IOP	Intraocular pressure
ITT	Intent-to-Treat
IWRS	Interactive web response system
J2C	Jump-to-Control
LS	Least Squares
LM	Lund-Mackay Staging
MAR	Missing at Random
MCS	Mental component score
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed-effect model for repeated measures
NB	Negative Binomial
PASS 15	Power Analysis and Sample Size Software
PBO	Placebo
PCS	Physical component score
PGIC	Subject Global Impression of Change
PHE	Public Health Emergency
PM	Evening
PMM	Pattern Mixture Model
POV	Percent of Opacified Volume

PRO	Patient Reported Outcome
PSQI	Pittsburgh Sleep Quality Index
QIDS	Quick Inventory of Depressive Symptomatology
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SE	Standard Error
SF-36v2	36-Item Short Form Health Survey Version 2
SF-6D	Short Form-6 dimension
SIT	Smell Identification Test
SNOT-22	22-item Sinonasal Outcomes Test
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
US	United States
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary
WPOV-E	Worst Percentage of Opacified Volume in the Ethmoid Sinuses
WPOV-M	Worst Percentage of Opacified Volume in the Maxillary Sinuses
WPOV	Worst Percentage of Opacified Volume among the Maxillary and Ethmoid Sinuses
ZLM	Zinreich Modification of Lund-Mackay Staging
WZLM	Worst ZLM score for the worst sinus among Maxillary and Ethmoid Sinuses

2 INTRODUCTION

This Statistical Analysis Plan (SAP) references Protocol OPN-FLU-CS-3206 (Amendment 4.0, dated 11 May 2022) and the corresponding electronic case report form (eCRF). There are no deviations from this amendment presented in this SAP.

Protocol OPN-FLU-CS-3206 is the second of the two pivotal randomized, controlled clinical trials intended to provide substantial evidence supporting an indication for the treatment of CRS, and this study is identical in design to Protocol OPN-FLU-CS-3205 with one important exception. Protocol OPN-FLU-CS-3205 enrolled a subject population including subjects with or without the presence of Nasal Polyps at baseline. Protocol OPN-FLU-CS-3206 included only subjects without Nasal Polyps present at baseline.

In the interest of clarity and efficiency, the OPN-FLU-CS-3205 SAP, (14 February, 2022) is the Statistical Analysis Plan of reference for this clinical program. The OPN-FLU-CS-3205 SAP encompasses the efficacy and safety endpoints, estimand, statistical methods, and data handling rules used in the CRS development program. Thus, the CS-3205 SAP is the primary reference for the statistical analyses of efficacy and safety endpoints, as well as the statistical estimands and methods, endpoint definitions, and data handling rules, unless otherwise indicated in this document.

The focus of this OPN-FLU-CS-3206 SAP is to document changes and additions to secondary endpoints, to highlight the changes to statistical models as a result of no stratification for polyp status, and to specify the hypothesis testing strategy to control the family-wise Type I error probability in study OPN-FLU-CS-3206.

If additional analyses are performed to supplement the planned analyses they will be identified as such in the Clinical Study Report (CSR).

3 STUDY OVERVIEW

3.1 General Study Design and Study Schema

This is a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy and safety of intranasal administration of OPN-375 (186 and 372 µg twice daily) in subjects with CRS without the presence of nasal polyps.

All Study Procedures and Evaluations, as well as the timing of all tests, procedures, and assessments, are identical to study OPN-FLU-CS-3205; reference the OPN-FLU-CS-3205 SAP for the study flow diagram and schedule of assessments.

3.2 Unique Secondary Objectives and Endpoints

This section describes the secondary Objectives and Endpoints which are not common to both protocols. The hypothesis testing strategy including these endpoints is described in Section 5.3.

3.2.1 Key Secondary Objectives/Endpoints added to Protocol CS-3206

- Frequency of acute exacerbations of CRS over the 24-week treatment period, defined as a worsening of symptoms that requires an escalation of treatment in subjects with CRS without NP, from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205 (pooled data)
- Change from baseline to the end of Week 4 in four separate cardinal CRS symptoms, as measured by (AM, Instantaneous) CSNS: congestion, facial pain or pressure sensation, nasal discharge (anterior and/or posterior), and sense of smell.
- Time to first acute exacerbation of CRS, defined as a worsening of symptoms that requires escalation of treatment

3.2.2 Other Secondary Endpoints

Note that the secondary endpoints in OPN-FLU-CS-3205 refer to the population of subjects without and without Nasal Polyps at baseline, and the same endpoints in OPN-FLU-CS-3206 refer to the population of subjects without Nasal Polyps at baseline.

The following change to Protocol OPN-FLU-CS-3206 is due to the addition of AM, Instantaneous DNS symptoms to key secondary endpoints.

- change from baseline to Weeks 4, 8, and 12 for the total population and in patients with and without previous sinus surgery:
  - in average AM/PM instantaneous (evaluation of symptom severity immediately preceding the time of scoring), (except Week 4 (AM) – key secondary endpoint) and AM/PM reflective (evaluation of symptom severity over the past 12 hours), averages are based on scores recorded in the diary for the 7 days before each time point for:

- nasal congestion
- sense of smell score
- nasal discharge (anterior and/or posterior) score
- facial pain or pressure sensation score

The following secondary endpoint was added to Protocol OPN-FLU-CS-3206:

- change from baseline to Week 24/ET in the percent of opacification of the combined volume of the ethmoid and maxillary sinuses

4 GENERAL CONSIDERATIONS FOR STATISTICAL ANALYSIS

Reference OPN-FLU-CS-3205 SAP for the statistical considerations common to both protocols. The following considerations are unique to Protocol OPN-FLU-CS-3206.

4.1 Sample Size Determination

Sample size assumptions were originally generated based on previous Phase 3 studies of OPN-375 in subjects with nasal polyposis and data from a study evaluating the change in maxillary and ethmoid opacification in CRS patients treated with an intramuscular dose of triamcinolone (Pallanch 2013).

Updated standard deviation estimates for both co-primary endpoints in this amendment are based on a blinded interim analysis of Protocol OPN-FLU-CS-3205. Based on the results for changes from baseline in morning symptoms among subjects with nasal polyps in the previous studies conducted with OPN-375, a sample of 70 subjects per group (210 total subjects) is sufficient to detect a 0.9 scale difference in 7-day average AM instantaneous CSNS between treatments (OPN-375 vs placebo) using a 2-sided test at the 5% significance level with 88% power, and assuming a standard deviation (SD) of 1.7.

This sample size is also adequate to detect a 9% difference between treatments in average percent opacification (APOV) using a 2-sided test at the 5% significance level with 88% power, and assuming a SD of 17%.

The sample size was estimated for the co-primary efficacy endpoints using Power Analysis and Sample Size Software (PASS 15).

4.2 Randomization and Stratification Factors

In Protocol OPN-FLU-CS-3206 there is a single stratification factor for randomization: previous sinus surgery (Yes vs No). The entry criteria for this study excluded subjects with Nasal Polyps Present at baseline.

This stratification factor is included in the analysis model as a categorical covariate. In the event that a stratification error occurs, i.e., a subject is incorrectly stratified, in the primary analyses the subject will be analyzed as randomized (stratified), consistent with the ITT principle. The error will be documented as a protocol violation; however, these subjects will be included in the per-protocol analyses.

4.3 Interim Analysis

A blinded interim analysis was planned for both co-primary endpoints in this study to evaluate the sample size assumptions as follows:

1. Co-primary endpoint change from baseline in the 7-day average instantaneous AM CSNS to assess the variance.
2. Co-primary endpoint change from baseline to Week 24/ET APOV to assess variance.

This interim analysis was planned to occur when at least 50% of subjects reached Week 24/ET endpoint for APOV, and at least 75% of subjects reached the Week 4 endpoint for CSNS. The complete details of this interim analysis are provided in the Protocol OPN-FLU-CS-3206 Interim Statistical Analysis Plan (IASAP) (23 September, 2021).

The blinded IA of both CSNS and APOV co-primary endpoints have occurred and resulted in a decision to not increase sample size. Reference the OPN-FLU-CS-3205 SAP for further detail regarding the IA of Protocol OPN-FLU-CS-3205.

5 STATISTICAL METHODS FOR EFFICICY ANALYSES

5.1 Adjustments to the Statistical Models

In Protocol OPN-FLU-CS-3205 randomization was stratified by Nasal Polyp status at baseline (Absent, Present), and Prior Nasal Surgery (Yes, No). All statistical models in the OPN-FLU-CS-3205 SAP include categorical terms for both Nasal Polyp status and Prior Nasal Surgery.

In Protocol OPN-FLU-CS-3206 randomization was stratified only by Prior Nasal Surgery (Yes, No) since the subject population consisted only of subjects without Nasal Polyps at baseline. Therefore, for all statistical models referenced in OPN-FLU-CS-3205 SAP the categorical term for Nasal Polyp status is removed for the analyses of the efficacy endpoints in Protocol OPN-FLU-CS-3206.

There are no other changes to the statistical models or methods in the efficacy analyses of Protocol OPN-FLU-CS-3206.

5.2 Estimation – Secondary Endpoints

For the secondary endpoints added to Protocol OPN-FLU-CS-3206, and described in Section 3.2, the statistical methods are described in OPN-FLU-CS-3205 SAP. However, the pooled endpoints, from both protocols, will be included in the Integrated Summary of Efficacy (ISE) SAP and fully described there.

5.3 Multiplicity – Type I Error Control

5.3.1 Co-primary Efficacy Endpoints

The primary hypothesis of this trial is that OPN-375 high dose (372 µg) group will be superior to the placebo group in both co-primary endpoints.

The familywise Type 1 error probability for the test of the primary hypothesis is α=0.05. The strategy for strong, familywise control of the Type I error is based on closed testing procedure as follows.

1. Test each co-primary endpoint for OPN-375 high dose (372 µg) vs placebo: If $p < 0.05$ for both endpoints, then proceed to key secondary endpoints; otherwise, stop. The order of the testing is as follows:

   a) OPN-375 372 µg versus placebo in the change from baseline in the 7-day average instantaneous AM CSNS at the end of Week 4

   b) OPN-375 372 µg versus placebo in the APOV in the ethmoid and maxillary sinuses change from baseline to Week 24/ET

5.3.2 Type I Error Control for Key Secondary Endpoints

The following planned comparisons are defined based on pooled data from Study OPN-FLU-CS-3205 and Study OPN-FLU-CS-3206. Testing will continue based on closed testing procedure, with α=0.05, if the primary hypothesis is met, as follows:

2. OPN-375 372 µg versus placebo in the frequency of acute exacerbations of CRS over 24 weeks

3. OPN-375 372 µg versus placebo in the frequency of acute exacerbations of CRS over 24 weeks in CRS without NP population

4. OPN-375 372 µg versus placebo in change from baseline to Week 4 on CSNS score in subjects who were symptomatic at trial entry despite reported use of an intranasal steroid for treatment of CRS within 30 days of Visit 1

The following planned comparisons are defined based on Study OPN-FLU-CS-3206. Testing will continue based on closed testing procedure, with α=0.05, if the key secondary hypotheses (2-4) are met, as follows:

5. Test each co-primary endpoint for OPN-375 low dose (186 µg) vs placebo: If $p < 0.05$ for <u>both</u> endpoints, then proceed to next endpoints; otherwise, stop. The order of the testing is as follows:

    a) OPN-375 372 µg versus placebo in the change from baseline in the 7-day average instantaneous AM CSNS at the end of Week 4

    b) OPN-375 372 µg versus placebo in the APOV in the ethmoid and maxillary sinuses change from baseline to Week 24/ET

6. OPN-375 372 µg versus placebo in change from baseline to the end of Week 4 in nasal congestion
7. OPN-375 372 µg versus placebo in change from baseline to the end of Week 4 in nasal discharge (anterior and/or posterior)

8. OPN-375 372 µg versus placebo in change from baseline to the end of Week 4 in facial pain or pressure sensation

9. OPN-375 372 µg versus placebo in change from baseline to the end of Week 4 in sense of smell

10. OPN-375 372 µg versus placebo in time to first acute exacerbation of CRS

The following planned comparisons are defined based on pooled data from Study OPN-FLU-CS-3205 and Study OPN-FLU-CS-3206. Testing will continue based on closed testing procedure, with α=0.05, if the key secondary hypotheses (5-10) are met, as follows:

11. OPN-375 186 µg versus placebo in the frequency of acute exacerbations of CRS over 24

12. OPN-375 186 µg versus placebo in the frequency of acute exacerbations of CRS over 24 weeks in CRS without NP population

13. OPN-375 186 µg versus placebo in change from baseline to Week 4 on CSNS score in subjects who were symptomatic at trial entry despite reported use of an intranasal steroid for treatment of CRS within 30 days of Visit 1

The following planned comparisons are defined based on Study OPN-FLU-CS-3206. Testing will continue based on closed testing procedure, with α=0.05, if the key secondary hypotheses (11-13) are met, as follows:

14. OPN-375 186 µg versus placebo in change from baseline to the end of Week 4 in nasal congestion in CRS without NP population
15. OPN-375 186 µg versus placebo in change from baseline to the end of Week 4 in nasal discharge (anterior and/or posterior)

16. OPN-375 186 µg versus placebo in change from baseline to the end of Week 4 in facial pain or pressure sensation

17. OPN-375 186 µg versus placebo in change from baseline to the end of Week 4 in sense of smell

18. OPN-375 186 µg versus placebo in time to first acute exacerbation of CRS

5.4 Subgroup Analyses

The following endpoints will be analyzed according to the primary estimand by subgroup: subjects with prior sinus surgery versus without prior sinus surgery at baseline.

- Co-primary endpoints (CSNS, APOV)
- All CSNS endpoints other than the primary,
- All individual daily nasal symptoms scores that are components of the CSNS (as well as sense of smell)
- SNOT-22 Total Score

The same MMRM models for used for CSNS and DNS and the same ANCOVA model for APOV will include appropriate terms for treatment-by-subgroup interaction as well as the appropriate contrasts to obtain the within-subgroup inferential statistics. The model-based, within-subgroup LS mean difference between each active treatment group and placebo (active-placebo), 95% CI, and nominal p-value will be displayed, as well as the treatment-by-subgroup interaction nominal p-value.

5.5 Additional Sensitivity Analyses – Supplementary Estimands

Several alterations of the primary estimand regarding the handling of intercurrent events are considered as sensitivity analyses (supplementary estimands) for protocols OPN-FLU-CS-3206 and OPN-FLU-CS-3205. The primary estimand is defined in Protocol OPN-FLU-CS-3206, Section 9.3.3, and is identical to the primary estimand in protocol OPN-FLU-CS-3205.

While these supplementary estimand sensitivity analyses are pre-specified in this SAP for protocol OPN-FLU-CS-3206, they will also be applied post-hoc to protocol OPN-FLU-CS-3205. These sensitivity analyses will be performed for both co-primary endpoints. The statistical methods for analyses and handling of missing data are fully described in the OPN-FLU-CS-3205 SAP.

Table 5.1 contains a summary of the primary estimand and all supplementary estimands defined based on alterations of the primary estimand in the handling of intercurrent events specifically for use of systemic steroids and nasal surgery. The imputation method for missing data for each co-primary endpoint under the treatment policy strategy for treatment discontinuation intercurrent event is fully described in the OPN-FLU-CS-3205 SAP.

Table 5.1 Summary of Primary and Supplementary Estimands and the Handling of Intercurrent Events

Estimand	Intercurrent Events		
	Systemic Corticosteroids	Nasal Surgery	Treatment/Study Discontinuation
Primary[1]	Composite Strategy for CRS[3]; Poor Score[4]	Composite Strategy; Poor Score	Treatment Policy Strategy[6]
Supplementary – S1[2]	Treatment Policy Strategy	Composite Strategy; Poor Score	Composite Strategy; Poor Score
Additional Sensitivity			
Supplementary SE-2	Treatment Policy Strategy	Composite Strategy: Worst Score[5]	Treatment Policy Strategy
Supplementary SE-3	Composite Strategy; Poor Score	Composite Strategy; Poor Score	Treatment Policy Strategy
Supplementary SE-4	Composite Strategy; Worst Score	Composite Strategy; Worst Score	Treatment Policy Strategy

1. Primary Estimand in Protocols OPN-FLU-CS-3206 and OPN-FLU-CS-3205
2. Supplementary Estimand in Protocols OPN-FLU-CS-3206 and OPN-FLU-CS-3205
3. Systemic corticosteroids use for CRS exacerbation or worsening of CRS nasal/sinus symptoms: Composite Strategy
   Systemic corticosteroid use for other indications is defined as treatment and study discontinuation event.
   Modified Treatment Policy Strategy: Subject continues in the study; if an IE for systemic steroids for CRS or nasal surgery occurs, a poor score is assigned as defined in (4); otherwise, treatment policy strategy is followed as defined in (6)
4. Poor Scores: For CSNS, a value of '9' is assigned. For APOV, a poor score is defined as follows: for a subject with a baseline APOV ≥ 75%, a value of '100%' is assigned; if baseline APOV < 75%, a poor score is defined as baseline APOV + 25%
5. Worst Scores: For CSNS, a value of '9' is assigned. For APOV, a value of '100%' is assigned
6. Treatment Policy Strategy; subjects may continue in the study until one of the following two mutually exclusive outcomes:
   a) Subject completes Week 4, use CSNS endpoint value; completes Week 24/ET CT scan, use APOV endpoint value;
   b) Subject discontinues the study. Missing data due to study discontinuation following treatment discontinuation is imputed; a full description of the imputation method for each co-primary endpoint is provided in the OPN-FLU-CS-3205 SAP.