Study Title	EVALUATION OF SAFETY OF REPEATED DOSES OF OP0201 METERED DOSE INHALER COMPARED TO PLACEBO IN HEALTHY ADULT VOLUNTEERS
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STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: OP0201-C-002

EVALUATION OF SAFETY OF REPEATED DOSES OF OP0201 METERED DOSE INHALER COMPARED TO PLACEBO IN HEALTHY ADULT VOLUNTEERS

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V2.0, 03APR2019

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - APPROVAL

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
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MODIFICATION HISTORY

Listed below are modifications made to the SAP after the signed approval(s).

Unique Identifier for this Version	**Date of the Document Version**	**Author**	**Significant Changes from Previous Authorized Version**
[redacted]	[redacted]	[redacted]	[redacted]
2.0	03APR2019	[redacted]	[redacted] 2. [redacted]

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety and pharmacokinetic (PK) data for Protocol OP0201-C-002. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.
This statistical analysis plan (SAP) is based on the protocol Amendment 1 dated 09OCT2018.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

- To evaluate the safety and tolerability of OP0201 30 mg per day (given as 2 sprays per nostril 3 times a day [TID] for 14 consecutive days) and OP0201 60 mg per day (given as 4 sprays per nostril TID for 14 consecutive days) compared to 0 mg placebo (HFA-134a only) administered in a similar parallel-group fashion TID for 14 consecutive days in healthy adult volunteers.

2.2. SECONDARY OBJECTIVES

- To evaluate if any systemic exposure of dipalmitoylphosphatidylcholine (DPPC) can be detected in serum at levels higher than endogenous DPPC levels in serum in up to 15 healthy adult volunteers who will be evaluated in the Cohort B dose (OP0210 60 mg per day) versus placebo.

- To evaluate if any systemic exposure of cholesteryl palmitate (CP) can be detected in serum at levels higher than endogenous CP levels in serum in up to 15 healthy adult volunteers who will be evaluated in the Cohort B dose (OP0210 60 mg per day) versus placebo (if feasible).

3. STUDY ENDPOINTS

3.1. PRIMARY ENDPOINTS

- Adverse events (AEs), otoscopy, tympanometry, nasal and epipharynx endoscopy, University of Pennsylvania Smell Inventory Test (UPSIT) olfactory test, audiology pure tone hearing test, triplicate 12-lead electrocardiogram (ECG), physical examination, vital signs, and clinical laboratory tests.

3.2. SECONDARY ENDPOINTS

- Maximum baseline adjusted serum concentration (C_{max}) of DPPC on Day 14.
- Time to maximum concentration (t_{max}) of DPPC on Day 14.
- Maximum baseline adjusted serum concentration (C_{max}) of CP on Day 14 (if feasible).
- Time to maximum concentration (t_{max}) of CP on Day 14 (if feasible).
- Additional parameters may be calculated, if appropriate.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

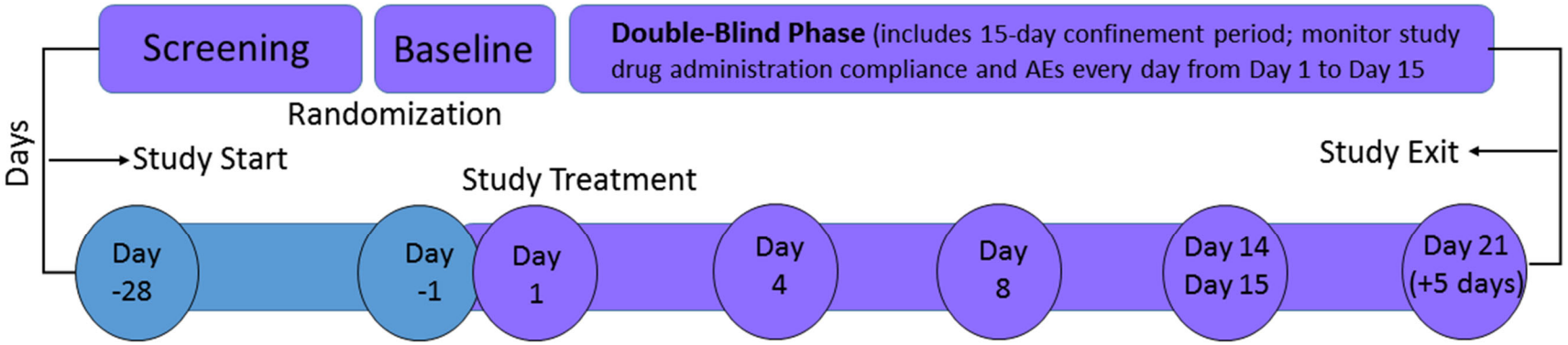
This is a randomized, double-blind, placebo-controlled, parallel-group, dose-escalation study in healthy volunteers to evaluate the safety and tolerability of OP0201 administered intranasally 3 times a day (TID) using a metered dose inhaler (MDI) compared to a matching placebo (HFA-134a minus active ingredients) administered intranasally TID using a MDI for 14 consecutive days (see Figure 1 for the study schematic). The plan is to enroll up to 30 subjects at 1 study center in the US. Two dose cohorts are planned (Cohort A and Cohort B; N=15 per cohort, see Cohort Dosing below, Table 1). Within each cohort, subjects will be randomized in a 4:1 ratio to receive either OP0201 or placebo. After all subjects in Cohort A have completed the Day 14 visit, a Safety Review Committee (SRC) will review all the blinded safety data to determine whether the doses administered are safe and well tolerated. The SRC will make a recommendation to escalate to the next cohort (Cohort B) or not.

Table 1 Dose Cohorts and Dose Regimen

Cohort	Dose Regimen	Cohort Dose Allocation		Total Subjects in Each Cohort	Total Subjects Per Dose Group
		Per Day Total Dose (mg)	Cumulative Total Dose (mg)		
A	**2 sprays per nostril TID x 14 days**	OP0201 (30 mg)[a] Placebo (0 mg)	OP0201 (420 mg)[a] Placebo (0 mg)	15	N=12 (OP0201) N=3 (Placebo)
B	**4 sprays per nostril TID x 14 days**	OP0201 (60 mg)[a] Placebo (0 mg)	OP0201 (840 mg)[a] Placebo (0 mg)	15	N=12 (OP0201) N=3 (Placebo)

a 2.5 mg per spray
N = number of subjects; TID = three times a day

Figure 1 Study Schema



4.2. SCHEDULE OF EVENTS

Table 2 Schedule of Activities

Study Period (with Visit Windows)	Screening Period	Confinement Period[a] (In-Clinic)						Study Exit	
	Days -28 to -1 (Screening) In-Clinic	Day -1 (Admission)	Day 1 (Enrollment)	Day 4	Day 8	Day 14	Day 15	Day 21 (+5 Day) In-Clinic	EaT[b]
Informed Consent/Authorization	X								
Demographics	X								
Inclusion/Exclusion	X	X							
Pregnancy Test (Urine)[c]	X	X						X	X
Follicle Stimulating Hormone Test[d]	X								
Urine Drug Screen[e]	X	X							
Viral Serology[f]	X								
Medical, Surgical, Ear History	X								
Physical Examination[g]	X							X	X
Vital Signs[h]	X	X	X	X	X	X	X	X	X
12-Lead ECG[i]	X		X			X		X	X
Ear History	X								
Otoscopy[j]	X	X		X	X	X			
Tympanometry	X	X		X	X	X		X[o]	X[p]

Study Period (with Visit Windows)	Screening Period	Confinement Period[a] (In-Clinic)						Study Exit	
	Days -28 to -1 (Screening) In-Clinic	Day -1 (Admission)	Day 1 (Enrollment)	Day 4	Day 8	Day 14	Day 15	Day 21 (+5 Day) In-Clinic	EaT[b]
Nasal and Epipharynx Endoscopy[k]	X	X			X	X			
Clinical Laboratory Tests[l]	X					X			X
UPSIT Olfactory Test[m]	X				X	X		X[n]	X
Audiology Pure Tone Hearing Test	X					X		X[o]	X[p]
Admission		X							
Train Participant on Study Product Administration[q]		X	X						
Randomization		X							
Study Treatment[r]			X	X	X	X			
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
PK Sample Collection			X[r]			X[s]			
Device Experience Questionnaire – Subject[t]							X		X[u]
Device Experience Questionnaire – Study Center Staff Administering the Treatment[t]							X		X[u]

EaT = Early termination; ECG = Electrocardiogram; IP = Investigational Product; PK = pharmacokinetic; UPSIT = University of Pennsylvania Smell Inventory Test.

a Eligible healthy volunteers will be admitted to the study center on Day -1 and be randomized on Day -1. Subjects will remain resident at the study center until after all the Day 15 assessments have been completed.
b EaT: To be performed if the subject was treated but early discontinue from the study.
c For all females, urine pregnancy test must be negative to meet study enrollment criteria.
d To be performed on postmenopausal women at Screening to confirm menopausal status (see Protocol Appendix 6).
e Specific tests to be conducted are listed in Protocol Table 8, Appendix 3.
f To be performed at Screening only (see Protocol Table 8, Appendix 3).
g Includes general appearance, overall status of the skin, head, neck, trunk, eyes, heart and lungs (eg, breathing sounds), abdomen, extremities, lymph nodes. Height and weight are recorded only at the Screening visit.
h Vital signs include blood pressure, respiratory rate, pulse rate, and body temperature.
i A single 12-lead ECG will be collected for screening purposes. For subjects in Cohort A, a single 12-lead ECG will be collected on Day 1 prior to the first dose and on the study exit visit (Day 21). For subjects in Cohort B, triplicate ECGs will be collected on Day 1: 30 and 60 minutes prior to the first dose, Day 14: 30 minutes prior to the last dose and 5, 20, 35, 50 minutes following the last dose on Day 14. In cases where ECG and PK sampling overlap, ECGs should be collected first, to ensure that PK samples are collected at the scheduled time point.
j Otoscopy involves ear endoscopy, taking a picture of the tympanic membrane and assessing if there are any abnormal findings.
k Nasal endoscopy will include a measurement of nasal cavity length (in mm) at the Screening visit only. For all other scheduled assessments, the nasal and epipharynx endoscopy assessment should be done prior to the first dose of the day.
l Includes hematology, clinical chemistry, coagulation and urinalysis (see Protocol Table 8, Appendix 3).
m At Screening, a total UPSIT score of ≥35 (for females) and a total UPSIT score of ≥34 (for males) is required to meet study enrollment criteria.
n To be collected at the Day 21 study exit visit only if abnormal at the Day 14 visit. Abnormal is defined as UPSIT score <35 (for females) and <34 (for males) (see Protocol Section 8.2.8).
o Audiology pure tone hearing test if abnormal in either ear at Day 14 visit. Abnormal defined as >20 dB worsening from baseline at Day 14 visit (See Protocol reference Rosenfeld et al, 2004). Typanometry is performed along with the Audiology pure tone hearing test so if the subject requires a hearing test at this visit, tympanometry will also be performed.
p Audiology pure tone hearing test and tympanometry not required if subjects drops out before Day 14, but if they drop out after Day 14 and had an abnormal test result at Day 14 visit, then every effort should be made to have the patient complete these assessments at the EaT visit.
q Study subjects need to be trained on study treatment administration on Day -1 or on Day 1, prior to the first dose.
r Study treatment dosing recommendation: the first dose at 9:00 am, second dose at 16:00 pm and the third dose at 23:00 pm.

s PK sample timing Cohort B only: Day 1: 30 and 60 minutes prior to the first dose, Day 14: 30 minutes prior to the last dose and 5, 20, 35, 50 minutes following the last dose on Day 14. The 5-minute PK sample should be collected within ±2 minutes of the scheduled time and the 20-minute PK sample should be collected within +5 minutes of the scheduled time. All other PK samples should be collected within ±5 minutes of the scheduled time.

t To be completed before discharge from the study center on the morning of Day 15 (See Protocol Appendix 7 for an example).

u This assessment is needed only if subjects discontinue the study prior to completing the questionnaire on Day 15.

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

Pharmacokinetic analysis of CP will not be completed because the quantitative method for the determination of CP is not feasible. This resulted in the below changes from the protocol to the SAP:

Protocol	SAP
Secondary Objective: To evaluate if any systemic exposure of cholesteryl palmitate (CP) can be detected in serum at levels higher than endogenous CP levels in serum in up to 15 healthy adult volunteers who will be evaluated in the Cohort B dose (OP0210 60 mg per day) versus placebo.	To evaluate if any systemic exposure of cholesteryl palmitate (CP) can be detected in serum at levels higher than endogenous CP levels in serum in up to 15 healthy adult volunteers who will be evaluated in the Cohort B dose (OP0210 60 mg per day) versus placebo **(if feasible)**.
• Secondary Endpoint: Maximum baseline adjusted serum concentration (C_{max}) of CP on Day 14.	• Maximum baseline adjusted serum concentration (C_{max}) of CP on Day 14 **(if feasible)**.
Secondary Endpoint: Time to maximum concentration (t_{max}) of CP on Day 14.	Time to maximum concentration (t_{max}) of CP on Day 14 **(if feasible)**.

5. PLANNED ANALYSES

5.1. SAFETY REVIEW COMMITTEE (SRC)

After all subjects in Cohort A have completed the Day 14 visit, a SRC will review all the blinded safety data to determine whether the doses administered are safe and well tolerated. The SRC will make a recommendation to escalate to the next cohort (Cohort B) or not.
[redacted] Data Management will entirely support the provision of blinded data for the SRC meeting including creating the SRC plan and will deliver required material directly to the SRC committee for this purpose.
[redacted] Biostatistics will not be in involved in this blinded review.

5.2. INTERIM ANALYSIS

There are no formal interim analyses planned for this study.

5.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by [redacted] Biostatistics following sponsor authorization of this SAP, identification of major protocol deviations requiring analysis exclusions, database lock, determination of analysis sets, and unblinding of treatment.

6. ANALYSIS SETS

6.1. ENTERED ANALYSIS SET

The entered analysis set will contain all screened subjects who provide informed consent for this study, including screen failure subjects. Subjects in this population will be used for pre-treatment adverse events listing including serious adverse events (SAE), disposition listing and summary. Demographics and eligibility criteria will be presented separately for screen failure subjects.

6.2. SAFETY ANALYSIS SET

The safety analysis set will contain all subjects who are assigned to study treatment and receive at least one dose of any study medication (OP0201 or Placebo) and will be analyzed according to treatment received. Subjects in this population will be used for all safety, dosing, and demographic summaries.

6.3. PHARMACOKINETIC ANALYSIS SET

The pharmacokinetic analysis set will include all subjects in Cohort B who receive at least 1 dose of study drug, OP0201 or placebo, and have at least 1 quantifiable serum DPPC concentration collected post-dose without any important protocol deviations/violations or events thought to significantly affect the PK of DPPC. Subjects in this population will be used for all PK analyses and summaries.

7. GENERAL CONSIDERATIONS

Derivation of the PK parameters for DPPC in serum will be the responsibility of the clinical pharmacokineticist at [redacted]. The PK and safety summaries and data listings as well as the statistical analysis of the PK variables will be the responsibility of the study biostatistician at [redacted].
Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

7.1. SUMMARY STATISTICS

For qualitative or categorical variables, the population size (N for sample size and n for number of non-missing values) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables, including PK variables (serum concentrations and PK parameters for DPPC) will be summarized using descriptive statistics, including N, n, mean, standard deviation (SD), coefficient of variation (CV%) as appropriate, median, minimum, and maximum values. Geometric mean (GMean) and geometric coefficient of variation (GCV%) will be included for PK parameters, where applicable. For t_{max}, only N, n, median, minimum, and maximum will be reported. Coefficient of variation will not be presented for change-from–baseline results. A minimum of 3 valid data values (n=3) is required for all descriptive statistics to be generated. If n is less than 3, only N, n, minimum, and maximum will be reported.

7.2. TREATMENT SUMMARIZATION

In general, unless otherwise stated for specific endpoints in the respective sections of this document, data will be presented for each treatment group, with placebo subjects from both cohorts combined into a single, overall placebo group. Data for all active treated subjects and for all treated subjects combined will also be presented when appropriate.

7.3. PRECISION

Safety variables (i.e., otoscopy, tympanometry, nasal and epipharynx endoscopy, UPSIT olfactory test, audiology pure tone hearing test, clinical laboratory values, vital signs, and ECG intervals), including derivations thereof, will be reported to the same precision as the source data.

For all PK, and quantitative safety lab data, the precision of the descriptive statistics will be based upon the interpreted number of decimal places or significant figures (according to whichever precision method is applicable for that statistic) of the respective source dataset, defined as the precision of the non-excluded value with the most common precision in the entire source dataset (across all time points and treatment periods, within the subgroup as applicable).

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimal places the data carry. Elapsed time variables for PK will be analyzed and reported with 2 decimal places with units of hours. Pharmacokinetic parameters derived by the clinical pharmacokineticist will be considered equivalent to raw data and will be mapped to the CDISC SDTM (Clinical Data Interchange Standards Consortium Study Data Tabulation Model) database using Implementation Guide Version 3.2 without any rounding applied to parameter estimates. All PK parameters will be rounded for reporting purposes in CDISC ADaM (Analysis Dataset Model) datasets and in by-subject listings. The rounded PK parameter

data will be used for the calculation of descriptive statistics and in all statistical analyses. The precision for each PK parameter will be indicated by the clinical pharmacokineticist in the form Pharmacokinetic Review of WinNonlin Analysis (PI_FM_PK0203). Parameters directly derived from source data (e.g., C_{max}) will be analyzed and reported with the same precision as the source data. Actual elapsed sample collection times and parameters derived from them (e.g., t_{max}) will be reported to 2 decimal places with units of hours.

For the reporting of descriptive statistics of Safety, and PK data, the arithmetic mean, GMean (for PK parameters only), SD, median, and confidence intervals (CIs) will be presented to 1 decimal place or significant figure more than the precision of the source data, according to whichever precision method is applicable to the source data provided by the study database, safety laboratory, or bioanalytical laboratory regardless of how many significant figures or decimal places the data carry. The minimum and maximum will be presented to the same decimal place or significant figure precision as the source data, according to whichever precision method is applicable to the source data. All the above statistics for PK concentrations and C_{max} will have precision based on the same precision method interpreted to have been used in the source data. Coefficient of variation, GCV%, and other percentages will always be reported to 1 decimal place.

7.4. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.
Reference start date is defined as the date of the first dose of study medication (Day 1 is the day of the first dose of study medication). Study Day will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:
  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:
  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the corresponding SDTM domains and listings. Study Day and any corresponding durations will be imputed in the corresponding ADaM domains as described in APPENDIX 2, Partial Date Conventions. The imputed values will be used for data summarizations as needed.

7.5. BASELINE

Baseline is defined as the last scheduled non-missing measurement taken prior to dosing and will

correspond to: Screening assessment for clinical laboratory; Day -1 assessment for Vital Signs; Day 1 pre-dose assessment for ECG in Cohort A, and the average of the mean triplicate ECG assessments at Day 1, 60 minutes pre-dose and Day 1, 30 minutes pre-dose for ECG in Cohort B; Screening assessment for Physical Examination; Day -1 assessment for Otoscopy, Tympanometry, and Nasal and Epipharynx Endoscopy ; and Screening assessment for University of Pennsylvania Smell Inventory Test (UPSIT) Olfactory test, and Audiology Pure Tone hearing test. However, if a subject is missing the planned baseline collection then the last non-missing evaluation prior to dosing (scheduled or unscheduled), if available, will become the baseline value.

For PK assessments, baseline serum concentration is defined as the mean of the two predose serum concentrations observed in samples collected on Day 1 prior to the first dose. If one predose sample is missing, the other Day 1 predose concentration will be used for baseline correction.

7.6. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

Unscheduled measurements will not be included in summary statistics but will contribute to the best/worst case value where required (e.g. shift tables) and assessment of clinical outliers. Early termination results will be recorded as such and included with the Study Exit visit summaries.
In the case of a retest of a scheduled assessment, results from that scheduled time (i.e., the original assessment) will be used for summaries unless flagged as invalid. If results from a scheduled assessment are flagged as invalid, then results from retest assessment will be used for summary.

Listings will include all scheduled, unscheduled, retest, and early discontinuation data.

7.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Post-baseline Value – Baseline Value

Body Mass Index (BMI) will be calculated as:

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

Age will be calculated as:

- Age (years) = Integer value of [(Date of informed consent – date of birth + 1)/365.25]

7.8. SOFTWARE VERSIONS

All derivations, statistical analyses, summaries, plots, and listings will be generated using SAS Version 9.4

or higher (SAS Institute, Inc., Cary, North Carolina). Noncompartmental analysis for PK parameter estimation will be performed using Phoenix® WinNonlin® 6.4 or higher (Certara, L.P., Princeton, New Jersey). Compliance of SDTM and ADaM datasets to CDISC standards will be verified by using the Open CDISC Community tool version 2.0.1 (Pinnacle 21, Plymouth Meeting, Pennsylvania).

8. STATISTICAL CONSIDERATIONS

8.1. SAMPLE SIZE DETERMINATION

The sample size is not based on statistical considerations, but is typical for studies of this nature, and is considered adequate to characterize the distribution of the planned endpoints.

There will be a total of 30 subjects; 2 dose cohorts of 15 subjects each. Subjects will be randomized in 4:1 (OP0201:placebo) ratio to receive either OP0201 or placebo within each dose cohort.

8.2. MISSING DATA

Missing safety data will not be imputed unless otherwise noted in the corresponding sections of this document (e.g., dates, AE severity, AE relationship). Imputed values will be included in the corresponding ADaM but not in the SDTM datasets.

Missing PK concentrations will be handled as described in Section 16.

9. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The shells provided with this SAP describe the presentations for this study and therefore are the format and content of the summary tables, listings, and figures to be provided by [redacted] Biostatistics.

10. DISPOSITION AND WITHDRAWALS

All entered subjects as defined in the Entered Analysis Set will be accounted for in this study. Subject disposition will be tabulated by cohort and treatment for number of subjects entered, randomized, treated, prematurely withdrew, completed study, and for each reason of premature withdrawal from the study along with the associated percentages. The percentages for the reason of withdrawal for screen failure subjects will be based on the entered set, whereas it will be based on safety set for treated subjects. The tabulation will also be presented for all active treated subjects, all placebo treated

subjects, and for all subjects combined from both cohorts, irrespective of treatment received, as Overall.

A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each subject. Screen failure subjects will be listed indicating the primary reason of screen failure and will be included in disposition summary tabulations.

Listings of inclusion/exclusion criteria responses, study eligibility during screening and Day -1, and study treatment administration date and times will be provided.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Individual subject demographics and baseline characteristics (medical, surgical, and ear history) will be presented in listings.

For the safety analysis set, demographic characteristics such as age, height, weight, and body mass index (BMI) will be summarized by cohort and overall using descriptive statistics. Frequency counts and percentages will be presented for sex, race, and ethnicity. No statistical testing will be carried out for demographic or other baseline characteristics.

12. PROTOCOL DEVIATIONS

12.1. DEVIATIONS RELATED TO STUDY CONDUCT

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedure requirements. The noncompliance may be either on the part of the subject, the site PI, or the study site staff. Protocol deviations will be listed including a classification of minor or major, as determined by clinical staff and sponsor.

12.2. DEVIATIONS RELATED TO PK ANALYSIS

Changes to the procedures or events, which may impact the quality of the PK data in Cohort B, will be considered important protocol deviations/events for PK and will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples of important protocol deviation or event include, but are not limited to, administration of prohibited medication, sample processing errors that lead to inaccurate bioanalytical results, inaccurate dosing on the day of PK sampling, and/or non-compliance with dosing to the extent that it is expected to affect the PK objectives of the study. In the case of a significant protocol deviation or event, PK data collected during the affected treatment period will be excluded from the study results. Other changes to the procedures or events which do not impact the quality of the PK data will not be

considered significant protocol deviations. A common example of a non-significant protocol deviation is a missed blood sample or deviation from the scheduled time of blood collection at a time unlikely to affect the PK objectives. In contrast, a scheduled pre-dose sample which is erroneously collected postdose would be considered an important deviation leading to exclusion of this data point (and derived PK parameters, if appropriate) from the PK analysis.

Non-compliance with dose administration will be reviewed on a case-by-case basis to determine whether the deviation is expected to affect the PK objectives of the study.

13. MEDICAL, SURGICAL, AND EAR HISTORY

Any relevant medical, surgical, and ear history recorded will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. All medical history, including surgical, and ear history will be listed and summarized by System Organ Class and Preferred term for all subjects in the safety analysis set.

14. MEDICATIONS

All medication usage will be coded using the World Health Organization Drug Dictionary (WHO-DD) version 01MAR2018E Format B-2 and listed.

- Prior medications are medications which stopped prior to the first dose of study medication.
- Concomitant medications are medications which were taken during the treatment period, or specifically:
    - started on or after the date and time of first dose of study medication or
    - started prior to the first dose of study medication and were continued after the first dose of study medication

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e., concomitant.

15. STUDY MEDICATION EXPOSURE

Study drug administration number within the day (first, second, or third), date and time of administration as well as the total number of sprays administered successfully for each nostril (left and right) will be listed for each administration. Dose administered at each administration will be calculated based on the total number of successful sprays from both nostrils and Overdose Quantity recorded on the CRF using the equation below:

Dose administered = (Number of successful sprays in both nostrils x 2.5 mg) + Overdose Quantity

Any protocol deviation or adverse event related to study drug administration will also be included in the listing. Mean daily dose as well as total dose administered over the dosing period of the study will be summarized using descriptive statistics for both cohorts.

Overall compliance will be calculated as:

$$Total\ Compliance = 100\ x \frac{actual\ total\ number\ of\ sprays}{expected\ total\ number\ of\ sprays}$$

where expected total number of sprays is 168 for Cohort A and 336 for Cohort B.
Daily compliance will be calculated as

$$Day_i\ Compliance = 100\ x \frac{actual\ number\ of\ sprays\ on\ Day_i}{expected\ number\ of\ sprays\ on\ Day_i}$$

where i = 1 to 14 and expected number of sprays on Day_i = 12 for Cohort A and 24 for Cohort B.

Compliance for each study day, mean daily compliance, and overall compliance will be listed. Mean daily and overall compliance will be summarized.

16. PHARMACOKINETIC ANALYSIS

16.1. SERUM CONCENTRATION DATA

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters. If a subject is missing both predose sample collections, their observed concentrations will be listed and summarized but not included in baseline-corrected listings or summaries.

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. Baseline-corrected DPPC serum levels will be derived by subtracting the observed levels at sample time on Day 14 from the mean baseline on Day 1 predose, if possible. If the resulting value is negative, the estimated baseline-corrected level will be set to zero (0) for purposes of reporting and subsequent analysis.

Observed and baseline-corrected serum concentrations will be summarized by treatment using

descriptive statistics. Predose and postdose concentrations of DPPC that are below the limit of quantification (BLQ) will be treated as zero for the computation of descriptive statistics.

A subject listing of all observed and baseline-corrected concentration-time data will be presented by treatment. Figures of arithmetic mean of observed and baseline-corrected concentration-time data (±SD, as appropriate) will be presented by treatment on linear and semi-logarithmic scales. Individual subject observed concentration-time data will be graphically presented on linear and semi-logarithmic scales.

16.2. PHARMACOKINETIC PARAMETERS

For PK parameter calculations, if both Day 1 predose samples are missing, no PK parameters will be estimated for this subject. If any predose sample is BLQ, it will be assigned a numerical value of zero for PK parameter calculations and baseline calculations.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile on Day 14. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as zero when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero.

The following PK parameters will be estimated for serum DPPC by non-compartmental methods using actual elapsed time from dosing.

C_{max}	Maximum baseline-corrected serum concentration (µg/mL) obtained directly from the baseline-concentration versus time data.
t_{max}	Time of maximum baseline-corrected serum concentration (h), obtained directly from the observed baseline-concentration versus time data.

A subject listing of individual PK parameters will be provided. Pharmacokinetic parameters will be summarized by treatment using descriptive statistics.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

17.1. ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment. All AEs will be coded to appropriate System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 21.0.

Pre-treatment AEs are defined as AEs that begin before the initiation of the first dose of study drug administration on Day 1 but after obtaining informed consent and will be recorded as pre-treatment AEs. These events will be presented in the listings only and will not be included in the tabular summary of AEs.

Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred after the initiation of the first dose of study drug administration on Day 1 or a pre-treatment AE that worsened in severity. See APPENDIX 2 for handling of partial dates for AEs. In the rare case where it is not possible to assess treatment emergence, the AE will be classified as treatment emergent (i.e., the worst case).

Severity
AE severity will be classified as Mild, Moderate, or Severe as per protocol Appendix 4. TEAEs with missing severity will be classified as Severe. If subject reports a TEAE more than once within the same SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

Relationship to Study Medication
Relationship to study medication will be completed by the Investigator as per Protocol Appendix 4, classified as “Related” or “Not Related”. A TEAE is assessed as “Related” if there is reasonable/plausible possibility that the TEAE may have been caused by the study medication. A TEAE is assessed as “Not Related” if no causal relationship exists between the study medication and the TEAE, but an obvious alternative cause exists, e.g. the subject’s underlying medical condition or concomitant therapy. TEAEs with missing relationship to study medication will be regarded as “Related” to study medication. If a subject reports the same TEAE more than once within the same SOC/ PT, the AE with the worst-case relationship, i.e., “Related” to study medication, will be used in the corresponding relationship summaries.

All AE tabulations will be performed by treatment and with all active treated subjects combined overall as well as all placebo treated subjects combined from both cohorts displaying the number and percentage of subjects. Incidence of TEAEs will be tabulated as follows:

- Across System Organ Class (SOC) and Preferred Term (PT): serious TEAEs and those leading to death or study discontinuation, related TEAEs and serious related TEAEs, by severity, and related TEAEs by severity.
- By System Organ Class (SOC) and Preferred Term (PT).

- By System Organ Class (SOC), Preferred Term (PT) for TEAEs related to study medication.
- By System Organ Class (SOC), Preferred Term (PT) and maximum severity.
- By System Organ Class (SOC), Preferred Term (PT) and maximum severity for TEAEs related to study medication.

17.1.1. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the variable pertaining to Action Taken with Study Treatment on the Adverse Events page of the (e)CRF and will also be included in the Adverse Events listing.

17.1.2. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF. SAEs will be collected for all entered subjects and identified as such in the listings. An SAE is defined as any untoward medical occurrence that, at any dose results in 1 or more of the following outcomes: death, is life-threatening, requires in-patient hospitalization or prolongs existing hospitalization, persistent disability/ incapacity, is a congenital anomaly or birth defect, or other medically important event as detailed in the Appendix 4 of the study Protocol.

If any subject dies during the study as recorded on the adverse events page of the (e)CRF, the information will be presented in the SAE data listing.

17.2. Otoscopy

Individual results of all Otoscopy assessments will be listed including the result of overall assessment (Normal or Abnormal) as recorded on the (e)CRF. The frequencies of overall assessment results as well as the categorical response to each Otoscopy variable will be tabulated along with the corresponding percentages by ear (left and right) and treatment.

Each Otoscopy variable will be derived programmatically as Normal or Abnormal according to the following criteria description:

- Contour has the following categories: normal, retracted, full, bulging, perforated, or not assessable. Normal response will be interpreted as Normal whereas any other response will be interpreted as Abnormal.

- Color has the following categories: normal, partly red, completely red, or not assessable. Normal response will be interpreted as Normal whereas any other response will be interpreted as Abnormal.

- Fluid has the following categories: No or Yes. The interpretation of normal/abnormal will be as follows: response of No will be interpreted as Normal; whereas a response of Yes will be interpreted as Abnormal. If the response is Yes indicating the presence of fluid behind the tympanic membrane, then the color of fluid is also recorded (yellow, translucent, red, blue, black, or clear).

- Translucency has the following categories: translucent, semi-opaque, opaque, or not assessable. The response of translucent will be interpreted as Normal whereas other responses will be interpreted as Abnormal.

Shifts from baseline to each post-baseline visit will be tabulated by ear and treatment for the results of assessments derived above as Normal or Abnormal. The shift tables will present the frequency and the corresponding incidences along with the 95% CI for the incidences.

17.3. TYMPANOMETERY

Tympanometery assessments will be listed and tabulated for the right and left ear by treatment based on the Normal or Abnormal Tympanograms assessments. Tympanogram overall result will be derived programmatically as Normal for Type A assessments and will be derived as Abnormal for Type B or Type C assessments. The frequency of tympanogram results as Normal and Abnormal will be presented with the corresponding percentages for each ear, left and right, by treatment.

A shift table will be provided presenting the incidence of changes from baseline assessment to postbaseline assessments for the Tympanogram assessment as Normal or Abnormal for each ear by treatment along with the corresponding 95% CIs.

17.4. NASAL AND EPIPHARYNX ENDOSCOPY

All results from Nasal and Epipharynx Endoscopy for Normal or Abnormal appearance will be listed including the length of nasal cavity (defined as the distance from the tip of the nose to the entry point of the Eustachian tube) for both the left and right nare. The frequency of results (Normal or Abnormal) for each assessment will be tabulated by treatment and will be presented along with the corresponding percentages.

A shift table presenting the incidence of changes in overall result from baseline to each post-baseline assessment will be tabulated by treatment and for each ear (left and right), including the corresponding 95% CIs.

Results from Epipharynx Endoscopy (Normal and Abnormal) will be listed and tabulated similarly as described above for the right and left ear.

17.5. OLFACTORY TEST (UPSIT)

The date and time of administration of the UPSIT test will be listed along with the test scores. A total UPSIT score of <35 is abnormal for females and a total score <34 is abnormal for males. Based on this criterion the Olfactory diagnosis, recorded on the CRF as Normal or Abnormal, will be included in the listing. A shift table indicating change in diagnosis from baseline to all postbaseline assessments will include the incidence as well as the corresponding 95% CI. Changes from Normal to Abnormal will also be recorded as Adverse Events and will be presented in the corresponding listings and summaries as described in Section 17.1.

17.6. AUDIOLOGY PURE TONE HEARING TEST

The date and time of Audiology Pure Tone hearing test will be listed including the results from each assessment at all tested frequencies. Results from Speech Audiometry and Screening Reflex Threshold for both ears will be listed. The interpretation of the results indicating the extent of hearing loss will also be indicated. Frequency counts and percentages for each category of hearing loss will be tabulated by treatment for all visits.

A shift table indicating change in overall hearing loss from baseline to all postbaseline assessments will include the incidences as well as the corresponding 95% CI.

17.7. LABORATORY EVALUATIONS

Central laboratory results will be included in the reporting of this study for Hematology, Clinical Chemistry, Coagulation, and Urinalysis. Viral serology, urine drug and alcohol screening, pregnancy and FSH levels will be assessed as part of subject screening to determine eligibility. A list of laboratory assessments to be included in the outputs is included in Appendix 3 of the protocol, Table 6. Presentations will be in SI Units, as provided by the labs.

Protocol-specified clinical laboratory tests will be summarized using descriptive statistics. Clinical laboratory data collected during study conduct, which were not required per protocol, such as for special testing to further evaluate an AE, will be listed separately and not summarized.

Quantitative laboratory measurements reported as “< X”, i.e. below the lower limit of quantification (BLQ), or “> X”, i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as “< X” or “> X” in the listings.

The following summaries will be provided for laboratory data:

- Observed and change from baseline to Day 14 (for quantitative measurements).

- Incidence of abnormal values according to normal range criteria
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements) for Day 14.

17.7.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges by the lab vendors and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

Clinical laboratory reference/normal ranges will be provided separately and results outside the normal range criteria will be flagged as such in the listings.

17.8. ECG EVALUATIONS

Results of the ECG assessments will be included in the reporting of this study. For Cohort A the results of 12-lead ECG results will be listed; whereas for triplicate ECG measurements taken for Cohort B the average over the triplicate readings will also be presented in addition to the individual triplicate assessment results.

The following ECG parameters will be reported for this study (ms): PR, QRS, QT, QTc, QTcF, QTcB, and HR (bpm). The average of triplicate readings in Cohort B will be used for all analysis purposes.

Overall assessment of ECG (Investigator's judgment) will be recorded as following:

- Normal
- Abnormal, Not Clinically Significant (ANCS)
- Abnormal, Clinically Significant (ACS)

The following summaries will be provided for ECG data:

- Actual and change from baseline (for quantitative measurements and all post-baseline assessments) by study day as well as for the screening visit.
- Shift from baseline according to overall assessment of ECG, as judged by the Investigator, by study day for all post-baseline assessments.

17.8.1. CLINICALLY NOTEWORTHY ECG CRITERIA

Clinically noteworthy quantitative ECG measurements will be identified in accordance with the following criteria:

- Observed values for QTcF will be classified as:
  - > 450 msec
  - > 480 msec
  - > 500 msec
- Change from QTcF will be classified as:
  - >30 msec increase from baseline
  - >60 msec increase from baseline

17.9. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Sitting Systolic and Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{o}C)

The following summaries will be provided by treatment for vital signs data:

- Observed and change from baseline for all post-baseline assessments.

17.10. PHYSICAL EXAMINATION

Physical exam results will be listed including the date and time of assessment, specification of any abnormalities, and any changes noted from baseline to post-baseline assessment.

18. DATA NOT SUMMARIZED OR PRESENTED

The details of the telephone call on Day 30 (Study Exit) will not be mapped to the SDTM/ADaM databases except for subject reported adverse events or concomitant medications. These details will be available in the clinical database.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

This appendix (including the example layout) is optional, depending on the customer. Include if no customer guidelines, otherwise reference customer guidelines

OUTPUT CONVENTIONS

Outputs will be presented according to the [redacted] Global Biostatistics Standard Output Conventions, which is available upon request.

DATES & TIMES

Depending on data available, dates and times will take the format yyyy-mm-dd; times will take the format hh:mm:ss; combined dates and times will take the format yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US

PRESENTATION OF TREATMENT GROUPS

For most safety outputs, data will be summarized by treatment groups and will be represented as follows and in that order:

Treatment Group	For Tables
OP0201 30 mg	OP0201 30 mg administered intranasally (2 sprays per nostril) TID for 14 consecutive days
OP0201 60 mg	OP0201 60 mg administered intranasally (4 sprays per nostril) TID for 14 consecutive days
All Active	All Active Treated Subjects
All Placebo	All Placebo Treated Subjects
All Subjects	All Treated Subjects

Some safety outputs will summarize data by cohorts and treatment groups, they will be represented as follows and in that order:

Treatment Group	For Tables
Cohort A, Overall	OP0201 30 mg or Placebo administered intranasally (2 sprays per nostril) TID for 14 consecutive days
Cohort A, OP0201 30 mg	OP0201 30 mg administered intranasally (2 sprays per nostril) TID for 14 consecutive days

Treatment Group	For Tables
Cohort A, Placebo	Placebo administered intranasally (2 sprays per nostril) TID for 14 consecutive days
Cohort B, Overall	OP0201 60 mg or Placebo administered intranasally (4 sprays per nostril) TID for 14 consecutive days
Cohort B, OP0201 60 mg	OP0201 60 mg administered intranasally (4 sprays per nostril) TID for 14 consecutive days
Cohort B, Placebo	Placebo administered intranasally (4 sprays per nostril) TID for 14 consecutive days
All Active	All Active Treated Subjects
All Placebo	All Placebo Treated Subjects
All Subjects	All Treated Subjects

PRESENTATION OF VISITS

For safety outputs, except those related to AEs, visits will be represented as follows and in that order:

Treatment Period	Visit Name(s)
Screening Day -28 to -1	Screening
Confinement Period	Day -1, Day 1, Day 4, Day 8, Day 14, Day 15
Study Exit	ET, Day 21 Follow-up

ET=Early Termination

PRESENTATION OF NOMINAL TIMES

For PK outputs, nominal times will be represented as follows and in that order:

Analyte	Cohort	Nominal Timepoints
DPPC	B	Day 1: 60 mins Predose, and 30 mins Predose; Day 14: 30 mins Predose, 5 mins, 20 mins, 35 mins, 50 mins

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Cohort
- Unique Subject ID

- Study Day
- Assessment date and time

APPENDIX 2. PARTIAL AND MISSING DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

MISSING DATES FOR CERTAIN ECG / PK ASSESSMENTS:

The dates on certain triplicate ECG assessments and pre-dose PK sample collections were not recorded in source data as per the CRF design resulting in missing date values in the corresponding source datasets. However, in both cases the external file with the results from the Bio-analytical lab for PK and from the Cardiac Safety Services group for ECG will contain all dates including those that are missing in the source datasets. The external files will be merged in with the source data files to create the corresponding SDTM domains, thereby allowing all dates to be populated.