# Statistical Analysis Plan

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|---|---|
| **Protocol Title:** | An Open-label, Single-arm, Multicenter Phase 4 Study to Evaluate Safety and Tolerability of Romosozumab (EVENITY®) in Postmenopausal Women in India with Osteoporosis and a High Risk of Fracture |
| **Short Protocol Title:** | A Study of Romosozumab (EVENITY®) in Postmenopausal Women in India with Osteoporosis at a High Risk of Fracture |
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| **Authors:** | PPD |
| **Sponsor:** | Amgen Inc.<br>One Amgen Center Drive<br>Thousand Oaks, CA 91320<br>USA |
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| Version Number | Date (DDMMMYYYY) | Summary of Changes, including rationale for changes |
|---|---|---|
| Original (v1.0) | 26SEP2023 | |
| Amendment 1 | 27OCT2025 | 1. Section 2.2: added clarifying explanation for secondary endpoint hypothesis.<br>2. Section 6.1: modified the definition of full analysis set to exclude screen-failed subjects. |

| | | |
|---|---|---|
| | | 3. Section 8.4: updated incomplete sentence.<br>4. Section 9.4: combined all laboratory analytes into single bullet point.<br>5. Section 9.6.2.1: correction of EOI terminology.<br>6. Section 9.6.3: rephrased laboratory analysis to focus on post-baseline toxicity grading summaries and specified laboratory analytes for graphical representation.<br>7. Appendix A: updated analysis window for physical examination, BMD scans, and laboratory assessments. |

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## List of Abbreviations

| Abbreviation | Explanation |
|---|---|
| AE | Adverse Event |
| AMQ | Amgen-defined MedDRA Search Strategies |
| BMD | Bone Mineral Density |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CPMS | Clinical Pharmacology Modeling & Simulation |
| CRF | Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DXA | Dual-energy x-ray Absorptiometry |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| eGFR | Estimated Glomerular Filtration Rate |
| EOI | Events of Interest |
| EOS | End of Study |
| FAS | Full Analysis Set |
| GSO-DM | Global Study Operations-Data Management |
| ICF | Informed Consent Form |
| IP | Investigational Product |
| IPD | Important Protocol Deviation |
| NCT | National Clinical Trials |
| NIH | National Institutes of Health |
| PK | Pharmacokinetics |
| PT | Preferred Term |
| QTc | QT Interval Corrected |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SMQ | Standardized MedDRA Queries |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| TEAE | Treatment-emergent Adverse Event |
| US | United States |

# 1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20210025, Romosozumab, dated 19 September 2022. The scope of this plan includes the primary analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

# 2. Objectives, Endpoints and Hypotheses

## 2.1 Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To characterize safety and tolerability of romosozumab in Postmenopausal women with osteoporosis and a high risk of fracture in India. | • Subject incidence of treatment-emergent adverse events within 12 months.<br>• Subject incidence of treatment-emergent serious adverse events within 12 months.<br>• Change from baseline in laboratory assessments and vital signs at month 12. |
| **Secondary** | |
| • To characterize the efficacy of romosozumab on lumbar spine, total hip, and/or femoral neck BMD in Postmenopausal women with osteoporosis and a high risk of fracture in India. | • Percent change from baseline in BMD (measured by DXA) of the lumbar spine at 6 and 12 months.<br>• Percent change from baseline in BMD (measured by DXA) of the total hip at 6 and 12 months.<br>• Percent change from baseline in BMD (measured by DXA) of the femoral neck at 6 and 12 months. |
| **Exploratory** | |
| CCI [redacted] | |

BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry

### 2.2 Hypotheses and/or Estimations

There is no statistical hypothesis for the primary endpoint. **The hypothesis of the secondary endpoint is that the percent change from baseline in lumbar spine BMD at month 12 will be greater than a pre-specified value of 10%.**

## 3. Study Overview

### 3.1 Study Design

This multicenter, open-label, single-arm, phase 4 study of romosozumab is part of Amgen's post-marketing requirement to the Central Drugs Standard Control Organization (India Regulatory Authority). The study population consists of approximately 100 Postmenopausal Women subjects in India with Osteoporosis and a High Risk of Fracture for whom romosozumab is indicated in accordance with the approved prescribing information in India. If subject signs the informed consent, then meets the eligibility criteria to receive romosozumab per label and successfully passes the screening process (up to 35 days from the date of informed consent), they will be enrolled at the baseline visit (day 1) and given the first dose of romosozumab. The enrollment period shall stop once 100 enrolled subjects have received their first dose of romosozumab. Each subject will be followed from the first dose of romosozumab until the end of the 12-month period, death, withdrawal of consent, early discontinuation for any reason, or loss to follow-up (eg, subject transferring to another clinic), whichever occurs first. Treatment-emergent adverse events, and treatment-emergent serious adverse events will be collected and reported during the treatment/observation period for any subject who has received at least 1 dose of romosozumab. Subject incidence of treatment-emergent adverse events and treatment-emergent serious adverse events will be reported and summarized. Treatment efficacy will be determined by percent change from baseline in dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) of the lumbar spine, total hip, and femoral neck taken at 6 months, and 12 months for any subject who has a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement at the lumbar spine and received at least 1 dose of romosozumab. All data collected for the purpose of this study will be entered into the electronic case report form (eCRF).

### 3.2 Sample Size

With 100 subjects, there is a 95% chance of observing ≥ 1 adverse event if the actual event rate is 3% or more.

Also, this study has a 99% power to detect a mean BMD percentage change from baseline of 10% or more in the lumbar spine at month 12 assuming the percent change from baseline of lumbar spine BMD at month 12 has mean 13.1% and standard deviation 5.5% (National Library of Medicine, NCT01575834).

### 3.3 Adaptive Design

Not Applicable

## 4. Covariates and Subgroups

### 4.1 Planned Covariates

No covariates are involved.

### 4.2 Subgroups

No subgroup analysis is planned.

## 5. Definitions

### 5.1 Basic Definition

**Investigational Product (IP)**

Romosozumab 210 mg QM.

**Treatment-emergent Adverse Events (TEAE)**

Adverse Events (AEs) starting on or after the first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events eCRF and up to the end of study date.

**Treatment-emergent Serious Adverse Event (TESAE)**

Treatment-emergent adverse events indicated as serious on the Events eCRF.

### 5.2 Study Point of Reference

**Baseline**

The baseline measurement is defined as the last measurement prior to the first dose of investigational product. If the measurement is taken on the same day as the first dose and the exact measurement time relative to the first dose is unknown, it will be assumed to have been taken prior to the first dose of investigational product. If a subject does not receive investigational product, baseline is the closest recorded measurement on or prior to the randomization date. For baseline duplicate BMD, the baseline is obtained as the average of the measurements taken prior to the first dose of investigational product.

**Study Day 1**

Day 1 is defined as the first day that investigational product is administered to the subject.

**Study Day**

The number of days from Study Day 1, inclusive:

Study Day = (Date of Interest – Date of Study Day 1) + 1

**Analysis Visit**

To allow for variations in scheduling study visits, the analysis visit windows defined in Appendix A will be used to assign evaluations to the most appropriate nominal visit for analysis and summarization.

## 5.3 Study Date

**Informed Consent Date**

The date on which a subject signed the informed consent.

**Screening Date**

The screening date is defined as the date the ICF is signed.

**Enrollment Date**

The date of enrollment in electronic case report form (eCRF).

**First Dose Date**

The date of administration of the first dose of IP.

**Last Dose Date**

The date of administration of last dose of IP.

**End of Study Date**

The date recorded on the End of Study eCRF.

## 5.4 Study Time Interval

**Screening Period**

The period between the date of informed consent and first dose of IP.

**On-Study Period**

The time from the first dose date to the end of study date.

## 5.5 Subject Disposition

### Enrolled

Individuals are considered enrolled into the study when their enrollment date is documented in the Subject Enrollment eCRF. Enrolled individuals are referred to as "subjects".

### Exposed to IP

Subjects are considered exposed to IP if they have a value for the sum of IP volume that exceeds zero.

## 5.6 Arithmetic Calculations

### Body Mass Index (BMI)

Body Mass Index will be calculated using the following formula:

BMI ($kg/m^2$) = weight (kg) / [height (cm)/100]$^2$

### Change from Baseline

The arithmetic difference between a post-baseline value of interest and the baseline value:

Change (absolute) from Baseline = (post-baseline value – baseline value)

Change (percent) from Baseline = [(post-baseline value – baseline value) / baseline value] x 100

### Subject Incidence Rate for Adverse Events

The subject incidence rate for a given event in a specified period is defined as the number of subjects with at least one reported occurrence of the event divided by the number of subjects who are at risk for having the event in the beginning of the given period. For subjects with multiple occurrences of the same event in the given period, the event will only be counted once per subject.

### Estimated Glomerular Filtration Rate (eGFR) (mL/min) Using Modification of Diet in Renal Disease (MDRD) for Females

Conventional units (creatinine as mg/dL; age in years):
eGFR (mL/min/1.73 m2) = 175 × (Serum creatinine)$^{-1.154}$ × [Age]$^{-0.203}$ × (0.742 if female) × (1.212 if African American)

SI units (creatinine as µmol/L; age in years):

eGFR (mL/min/1.73 m2) = 175 × (Serum creatinine/88.4)$^{-1.154}$ × [Age]$^{-0.203}$ × (0.742 if female) × (1.212 if African American)

## 6. Analysis Sets

### 6.1 Full Analysis Set

The full analysis set (FAS) is defined as all subjects who **enrolled in the study**.

### 6.2 Safety Analysis Set

The safety analysis set includes all subjects in the FAS who received at least 1 dose of romosozumab.

### 6.3 Efficacy Analysis Set

The efficacy analysis set is defined as all subjects in the FAS with a baseline and at least 1 postbaseline BMD measurement, and who have received at least 1 dose of romosozumab. The efficacy analysis set may vary for different endpoints due to missing data.

### 6.4 Interim Analyses Set(s)

Not applicable.

## 7. Planned Analyses

### 7.1 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned.

### 7.2 Primary Analysis

The primary analysis will be conducted after all subjects have completed the study. The data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan. The data supporting the primary analysis will be locked. It is expected that outstanding data issues are resolved ahead of the lock to the extent possible.

### 7.3 Final Analysis

The final analysis will be the same as the primary analysis.

## 8. Data Screening and Acceptance

### 8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

### 8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will receive and store all data to be used in the planned analyses. This study will use the RAVE database.

### 8.3 Handling of Missing and Incomplete Data

Missing and incomplete dates of an adverse event or concomitant medication taken will be imputed as outlined in Appendix B.

No imputation will be done on incomplete stop date of an AE or a concomitant medication.

### 8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in the cohort. Other factors that may bias the results of the study include:

- Important protocol deviations **(IPDs)** likely to impact the analysis and interpretation of the endpoints.
- Detection of adverse events and/or serious adverse events likely to impact the safety analysis.
- The timing of and reasons for early withdrawal from treatment and from study.

**The incidence of these factors will be assessed. IPDs likely to impact the analysis and interpretation of the efficacy endpoints will be listed and/or tabulated**.

### 8.5 Outliers

Outliers due to data entry errors will be corrected by the study team before final database lock. The validity of any questionable values or outliers will be examined. Outliers or any questionable values with confirmed validity shall be included in the analyses unless there is sufficient scientific justification (e.g., important protocol deviation leading to invalid data) to exclude them.

### 8.6 Distributional Characteristics

Not applicable.

### 8.7 Validation of Statistical Analyses

Programs development and maintenance as well as output verification will be executed in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced and validated in accordance with SOP-430399. Standard macro will be used when available.

The production environment for statistical analyses will be Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

## 9. Statistical Methods of Analysis

### 9.1 General Considerations

For computation of change from baseline endpoints, baseline will be taken as the observation recorded just prior to first dose of investigational product. Descriptive statistics will be provided for selected demographics, efficacy, and safety endpoints. Continuous variables will be summarized descriptively using mean, median, standard deviation, 25th percentile, 75th percentile, minimum, maximum, and the number of non-missing observations. Frequencies and percentages will be presented for nominal and ordinal categorical variables.

### 9.2 Subject Accountability

The disposition of all subjects will be tabulated. The subjects who received investigational product, completed investigational product, discontinued investigational product and reasons for discontinuing, completed study and discontinued study and reasons for discontinuing will be summarized in number and percentage. Key study dates for the first subject enrolled, last subject enrolled, last subject end of investigational product and the last subject end of study will be presented.

### 9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used throughout the study period. Eligibility deviations are defined in the protocol.

### 9.4 Demographic and Baseline Characteristics

The following demographic and baseline disease characteristics will be summarized for all subjects using descriptive statistics based on the Full Analysis Set defined in Section 6.1.

- Age (years)
- Age groups (<65, <75 and ≥ 75 years)

- Race (If multiple races have been reported for a subject, the subject will be categorized as multiple race) and ethnicity.
- Body composition (height [cm], weight [kg], BMI [kg/$m^2$])
- BMD value (g/$cm^2$) and BMD T-score of lumbar spine, total hip, and femoral neck.
- Selected laboratory analytes (calcium corrected by albumin, phosphorus, creatinine**, 25 (OH) vitamin D**, eGFR)
- Vital signs include blood pressure, heart rate, respiratory rate and temperature.
- Prior use of any osteoporosis medication (yes, no)
- Baseline use of calcium and vitamin D (yes, no)
- Tobacco use (never, former, and currently)

## 9.5 Efficacy Analyses

**Table 9-1. Efficacy Endpoint Summary Table**

| Endpoint | Summary and Analysis Method (Specify Analysis Set if FAS is Not Used) | Sensitivity Analysis |
|---|---|---|
| Secondary endpoint | The mean percent change from baseline of lumbar spine BMD at month 12 will be compared with a pre-specified value of 10% using one-sample t-test at 5% two-sided significance level. The mean and 95% CI for percentage change from baseline of lumbar spine, total hip and femoral neck BMD (respectively) at month 6 and 12 will be presented based on t-distribution. The efficacy analysis set will be used for this analysis. | N/A |

### 9.5.1 Analyses of Efficacy Endpoint

The mean percent change from baseline of lumbar spine BMD at month 12 will be compared with a pre-specified value of 10% using one-sample t-test at 5% two-sided significance level.

The mean and 95% CI for percentage change from baseline of lumbar spine, total hip and femoral neck BMD, respectively, at month 6 and 12 will be presented based on t-distribution. The efficacy analysis set will be used for the analysis.

## 9.6 Safety Analyses

### 9.6.1 Analyses of Safety Endpoint(s)

**Table 9-2. Safety Endpoint Summary Table**

| Endpoint | Summary and Analysis Method (Specify Analysis Set if Safety Analysis Set is Not Used) | Sensitivity Analysis |
|---|---|---|
| Primary endpoint | Statistical analyses for safety endpoints are descriptive in nature. Subject incidence of treatment emergent adverse events, treatment emergent serious adverse events, fatal adverse events, and adverse events leading to discontinuation from investigational product will be provided. Changes from baseline in vital signs and laboratory assessments (serum chemistry and hematology) at month 12 will be summarized. The safety analysis set will be used for these analyses. | N/A |

### 9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or later will be used to code all events categorized as adverse events to a system organ class (SOC) and a preferred term (PT).

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events leading to discontinuation of investigational product, fatal adverse events, treatment-related adverse events, treatment-related serious adverse events, treatment-related fatal AEs and treatment-related adverse events leading to withdraw of IP.

Subject incidence of all TEAEs, SAEs and AEs leading to withdrawal of investigational product will also be summarized by SOC and PT in descending order of frequency.

In addition, summaries of TEAEs occurring in at least 5% of the subjects by preferred term will be provided in descending order of frequency.

#### 9.6.2.1 Events of Interest

The following selected events of interest (EOIs) will be summarized according to their categories and preferred term. Subject incidence rates of these events will be provided.

- Serious cardiovascular events of myocardial infarction (narrow search/scope in standardized MedDRA queries (SMQ))

- Serious cardiovascular events of stroke (narrow search/scope in Amgen-defined MedDRA search strategies (AMQ))
- **Hypocalcemia Narrow – romosozumab** (narrow search/scope in AMQ)
- Hypersensitivity (narrow search/scope in SMQ)
- Injection site reactions (narrow search/scope in AMQ)
- Osteonecrosis of the jaw (narrow search/scope in AMQ)
- Atypical **femur** fracture (narrow search/scope in AMQ)

#### 9.6.3 Laboratory Test Results

Actual value by visit and change from baseline by visit will be summarized descriptively for each laboratory parameter. **Laboratory toxicity summary based on Common Terminology Criteria for Adverse Events v5.0 (CTCAE) will be provided to compare baseline laboratory values with the most extreme post-baseline values. The percentages of subjects with post-baseline laboratory toxicities of grade 3 or higher based on CTCAE v5.0 will also be summarized.**

Graphical representation showing central tendency and dispersion of the actual values and changes from baseline **for the following** laboratory parameters over time will be provided: **calcium corrected by albumin, alkaline phosphatase, magnesium, phosphorus, white blood cell, and hemoglobin**.

#### 9.6.4 Vital Signs

Actual value and value changes from baseline of each vital sign parameter will be summarized descriptively by visit.

#### 9.6.5 Physical Measurements

Not applicable.

#### 9.6.6 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

### 9.6.7 Antibody Formation

Not applicable.

### 9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product.

### 9.6.9 Exposure to Non-investigational Product

Not applicable.

### 9.6.10 Exposure to Other Protocol-required Therapy

Not applicable.

### 9.6.11 Exposure to Concomitant Medication

Concomitant medications will not be summarized.

## 9.7 Other Analyses

Not applicable.

### 9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

CCI [redacted]

### 9.7.2 Analyses of Clinical Outcome Assessments

Not applicable.

### 9.7.3 Analyses of Health Economic Endpoints

Not applicable.

### 9.7.4 Analyses of Biomarker Endpoints

Not applicable.

## 10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

## 11. Literature Citations / References

EVENITY® (romosozumab) Package Insert. Thousand Oaks, CA. Amgen Inc.

International Council for Harmonisation, Good Clinical Practice guidelines: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf.

National Library of Medicine (US). Efficacy and Safety of Romosozumab Treatment in Postmenopausal Women With Osteoporosis (FRAME). Identifier NCT01575834. https://clinicaltrials.gov/ct2/show/NCT01575834.

## 12. Prioritization of Analyses

Not Applicable

## 13. Data Not Covered by This Plan

Not Applicable

## 14. Appendices

### Appendix A. Analytical Windows

For the baseline assessment (excluding DXA), regardless of the length of the visit window, if there are multiple records within a Baseline window, the record that is the closest to and on or prior to Study Day 1 will be considered as the baseline value.

For the post-baseline assessment, if more than 1 visit falls within the defined window, the result from the visit closest to the target day will be used. If 2 evaluations are of the same distance from the target day, the result from the later visit will be used. If more than one evaluation on the same date, the average of the results will be used. Only laboratory results collected from the central laboratory will be averaged in the case of duplicate results.

To allow for variations in scheduling, the following visit windows will be used to assign evaluations to the most appropriate nominal visit for analysis and summarization. Furthermore, there will be no gaps between visit windows in order to include as many data points as possible for summarization.

**Physical Examination**

| Nominal Visit | Target Day | Window Definition (Study Day) |
|---|---|---|
| Baseline | 1 | Last evaluation prior to or on Study Day 1 |
| EOS | 360 | Study Day 2 to End of Study |

**DXA Scans**

| Nominal Visit | Target Day | Window Definition (Study Day) |
|---|---|---|
| Baseline[a] | 1 | Last evaluation prior to or on Study Day 1 |
| Month 6 | 180 | Study Day 2 to 270 |
| EOS | 360 | Study Day 271 to End of Study **+ 90** |

[a]If results from baseline DXA are not available, the results from scans taken on or before Study Day 14 will be considered baseline values and not the Month 6 values**.**

**Vital Signs**

| Nominal Visit | Target Day | Window Definition (Study Day) |
|---|---|---|
| Baseline[a] | 1 | Last evaluation prior to or on Study Day 1 |
| Month 6 | 180 | Study Day 2 to 270 |
| EOS | 360 | Study Day 271 to End of Study |

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Month 6.

### Laboratory Assessments (Chemistry and Hematology)

| Nominal Visit | Target Day | Window Definition (Study Day) |
|---|---|---|
| Baseline[a] | 1 | Last evaluation prior to or on Study Day 1 |
| Month 1 | 30 | Study Day 2 to 60 |
| Month 3 | 90 | Study Day 61 to 135 |
| Month 6 | 180 | Study Day 136 to 225 |
| Month 9 | 270 | Study Day 226 to 315 |
| EOS | 360 | Study Day 316 to End of Study **+ 60** |

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Month 1.

### Serum PK

| Nominal Visit | Target Day | Window Definition (Study Day) |
|---|---|---|
| Baseline[a] | 1 | Last evaluation prior to or on Study Day 1 |
| Month 1 | 30 | Study Day 2 to 60 |
| Month 3 | 90 | Study Day 61 to 135 |
| Month 6 | 180 | Study Day 136 to 225 |
| Month 9 | 270 | Study Day 226 to 315 |
| EOS | 360 | Study Day 316 to End of Study |

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Month 1.

## Appendix B. Handling of Dates, Incomplete Dates and Missing Dates

### Imputation Rules for Partial or Missing Start Dates

**The reference date for the following rules is the date of first dose of study drug.**

| Start Date | | Stop Date | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Complete: *yyyymmdd*** | | **Partial: *yyyymm*** | | **Partial: *yyyy*** | | **Missing** |
| | | **< 1st dose** | **≥ 1st dose** | **< 1st dose *yyyymm*** | **≥ 1st dose *yyyymm*** | **< 1st dose *yyyy*** | **≥ 1st dose *yyyy*** | |
| **Partial: *yyyymm*** | **= 1st dose *yyyymm*** | 2 | 1 | n/a | 1 | n/a | 1 | 1 |
| | **≠ 1st dose *yyyymm*** | | 2 | 2 | 2 | 2 | 2 | 2 |
| **Partial: *yyyy*** | **= 1st dose *yyyy*** | 3 | 1 | 3 | 1 | n/a | 1 | 1 |
| | **≠ 1st dose *yyyy*** | | 3 | | 3 | 3 | 3 | 3 |
| **Missing** | | 4 | 1 | 4 | 1 | 4 | 1 | 1 |

1=Impute the date of first dose; 2=Impute the first of the month; 3=Impute January 1 of the year; 4=Impute January 1 of the stop year
Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.

### Imputation Rules for Partial or Missing Death Dates

When a death date is incomplete and missing only the day field:

- If the latest date from any of the other assessment data is prior to the month of the death, impute the day as the first day of the month.
- If the latest date from other assessment data is in the same month as the death month, the partial death date will be imputed using the latest date.