STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-DXP593-101
Study Protocol Title:	A First-in-Human, Randomized, Double-Blind, Placebo-Controlled, Single Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of SARS-CoV-2 Neutralizing Antibody BGB-DXP593 in Healthy Subjects
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BGB-DXP593	Code name for monoclonal antibody BGB-DXP593, also named DXP593, BD-368-2, and WBP2281
BLQ	Below the assay quantification limit
BMI	Body mass index
CL	Clearance
C_{max}	Maximum observed concentration
CV	Coefficient of variance
ECG	Electrocardiogram
eCRF	Electronic case report form
LLOQ	Lower limit of quantitation
MedDRA®	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	Pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SMC	Safety Monitoring Committee
SOC	System organ class
SD	Standard deviation
TEAE	Treatment-emergent adverse event
$t_{1/2}$	Terminal half-life
t_{max}	Time to maximum observed concentration
V_Z	Volume of distribution
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for BGB-DXP593-101, A First-in-Human, Randomized, Double-Blind, Placebo-Controlled, Single Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of SARS-CoV-2 Neutralizing Antibody BGB-DXP593 in Healthy Subjects. The focus of this SAP is for the planned final analysis specified in the study protocol.

Reference materials for this statistical plan include the BGB-DXP593-101 Original Protocol dated on 04 August 2020.

2. STUDY OVERVIEW

This is a first-in-human, randomized, double-blind, placebo-controlled, single dose escalation study to investigate the safety, tolerability, pharmacokinetic (PK), and immunogenicity of BGB-DXP593 in healthy subjects.

Two dose levels are planned for eligible subjects to receive a single intravenous dose of study drug (ie, BGB-DXP593 or placebo) at 10 mg/kg or 30 mg/kg, respectively. Another higher dose level will be allowed for dose escalation.

Enrollment will begin at the 10 mg/kg dose level. Escalation to the next dose level will occur 7 days after the last subject at the current dose level has received the study drug, and the safety, laboratory data have been reviewed.

At each dose level, eligible subjects will be randomized at a 3:1 ratio (6 active: 2 control) to the active arm for receiving BGB-DXP593 or to the control arm for receiving the same volume of placebo (ie, normal saline), respectively.

The sentinel dosing will be adopted for each dose level. In the other words, 2 eligible subjects will be randomized at a 1:1 ratio (1 active: 1 control) to receive BGB-DXP593 or placebo on Day 1; and the remaining subjects will be randomized at a 5:1 ratio (5 active: 1 control) to receive BGB-DXP593 or placebo at least 48 hours later, provided satisfactory safety and tolerability is demonstrated for the first 2 subjects randomized and dosed at the dose level.

Subjects are expected to be available for follow-up visits until Day 113 of the study. Subjects will be replaced if they cannot complete the infusion. Subjects may be replaced if they discontinue from the study before Day 29.

Subjects will be monitored for safety, tolerability, PK and immunogenicity of BGB-DXP593 throughout the study.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To investigate the safety and tolerability of BGB-DXP593 administered intravenously as a single dose in healthy subjects

3.2. Secondary Objectives

- To characterize the pharmacokinetic (PK) profile of BGB-DXP593 administered intravenously as a single dose at each dose level in healthy subjects
- To evaluate the potential immunogenicity of BGB-DXP593 administered intravenously as a single dose at each dose level in healthy subjects

4. STUDY ENDPOINTS

4.1. Primary Endpoint

- Incidence and severity of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs)

4.2. Secondary Endpoints

- Changes in vital signs and 12-lead electrocardiogram (ECG) parameters from baseline
- Incidence and magnitude of clinical laboratory abnormalities
- Characterize PK concentration-time profile and PK parameters for BGB-DXP593: C_{max}, AUC_t, AUC_{inf}, AUC_{0-29}, t_{max}, $t_{1/2}$, CL, and V_z as appropriate
- Clinical immunogenicity of BGB-DXP593 evaluated through the detection of ADA over time

5. SAMPLE SIZE CONSIDERATIONS

A sample size of 8 subjects at each dose level (6 active and 2 control) totaling up to 30 subjects (including possible replacement) is not based on any statistical considerations. The sample size is based on the clinical consideration to provide safety and tolerability information and pharmacological considerations with the need to minimize exposure to healthy subjects at each dose level. No formal inferential statistics will be applied to the safety or PK data.

6. STATISTICAL METHODS

6.1. Analysis Sets

The Safety Analysis Set will include all the subjects who received the study drug, and subjects will be grouped by actual treatment received. The Safety Analysis Set is used for all safety analyses.

The PK Analysis Set will include all the subjects who received the study drug and had any measurable concentration of study drug. The PK Analysis Set will be used for PK analyses.

The ADA Analysis Set include all the subjects who received the study drug and in whom both baseline ADA and at least 1 postbaseline ADA results are available. The ADA Analysis Set is used for immunogenicity analyses.

6.2. Data Analysis General Considerations

6.2.1. Definitions and Computations

Study Day: study day will be calculated in reference to the date of the dose of study drug. For assessments conducted on or after the date of the dose of study drug, study day will be calculated as (assessment date – the date of the dose of study drug + 1). For assessments conducted before the date of the dose of study drug, study day will be calculated as (assessment date – the date of the dose of study drug). There is no study day 0.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in Appendix A.

Baseline: baseline is defined as the last non-missing value collected before the dose of study drug.

All calculations and analyses will be conducted using SAS® Version 9.4 or higher.

All subjects who received placebo from different cohorts will be pooled together into the placebo arm.

6.2.2. Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25.
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- For laboratory results collected as ≥ x, the value of the laboratory results will be set as x. For laboratory results collected as < x, the value of the laboratory results will be set as x divided by 2.
- For by-visit observed data analyses, percentages will be calculated based on the number of subjects with non-missing data as the denominator, unless otherwise specified.
- Unscheduled measurements and retested measurements will not be included in by-visit table summaries and graphs but will contribute to the best/worst case value

where required (e.g., shift table). Listings will include scheduled, unscheduled and retest data.

- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.2.3. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for the handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix A.

By-visit endpoints will be analyzed using observed data unless otherwise specified. For observed data analyses, missing data will not be imputed, and only the observed records will be included.

6.2.4. Multiplicity Adjustment

No multiplicity adjustments will be made in this study.

6.2.5. Data Integrity

Before pre-specified final analysis begins, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the subjects' relevant outcomes from the clinical database. All data should be complete and reviewed up to a pre-specified cutoff date as specified in the Data Extract and Snapshot Plan. Consistency checks and appropriate source data verification should be completed as specified in the Site Monitoring Plan.

6.3. Subject Characteristics

6.3.1. Subject Disposition

The number (percentage) of subjects randomized, treated, discontinued from the study drug and/or study will be counted by dose level. The primary reason for subjects randomized but not treated and study drug and/or study discontinuation will be summarized according to the categories in the eCRF. A listing of subject disposition will be provided.

6.3.2. Protocol Deviations

Important protocol deviation criteria will be established, and subjects with important protocol deviations will be identified and documented.

Important protocol deviations will be summarized and listed by category for all subjects in the Safety Analysis Set. Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.

6.3.3. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by dose level using descriptive statistics in the Safety Analysis Set. Summary statistics will be presented for continuous variables, and the number (percentage) of subjects in each category will be presented for categorical variables. Continuous variables include but are not limited to age, height, weight, and body mass index (BMI). Categorical variables include but are not limited to sex, race, and ethnicity. A listing of demographics and other baseline characteristics will be provided.

6.3.4. Prior and Concomitant Medications

Prior medications will be defined as medications that started and stopped before the dose of study drug. Concomitant medications will be defined as medications that (1) started before the dose of study drug and were continuing at the time of the dose of study drug, or (2) started on or after the date of the dose of study drug up to 30 days after the dose of study drug.

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes currently in effect at BeiGene at the time of database lock. They will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification.

The number (percentage) of subjects reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred name in the Safety Analysis Set. A listing of prior and concomitant medications will be provided.

6.3.5. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at BeiGene at the time of database lock. The number (percentage) of subjects reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class (SOC) and preferred term (PT) in the Safety Analysis Set. A listing of medical history will be provided.

6.4. Efficacy Analysis

There is no efficacy analysis planned for this study.

6.5. Safety Analyses

All safety analyses will be performed based on the Safety Analysis Set. Descriptive statistics will be used to analyze all safety data.

6.5.1. Extent of Exposure

The extent of study drug exposure will be summarized descriptively for the single dose administered by dose level. The number (percentage) of subjects with dose interruption and infusion rate decreased will be summarized with the respective reasons by dose level.

Subject data listings will be provided for all dosing records.

6.5.2. Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA lowest level term closest to the verbatim term, along with the linked MedDRA PT and primary SOC.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline on or after the administration of study drug and up to 30 days after the dose of study drug. Summary tables will generally focus on those AEs that were treatment-emergent. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

If any of the following TEAEs occurs, the administration of the study drug and the enrollment of new subjects will pause for the dose level:

- One or more ≥ Grade 4 TEAEs or treatment-emergent SAEs related to study drug as assessed by the investigator in any subject or
- Grade 3 TEAEs related to study drug as assessed by the investigator in 2 or more subjects at the same dose level.

An AE overview table, including the number of subjects with TEAEs, TEAEs with grade 3, TEAEs with grade 4 or higher, treatment-emergent SAEs, TEAEs that led to death, TEAEs that led to treatment discontinuation, TEAEs that led to treatment modification for study drug, and treatment-related TEAEs, will be provided by dose level. Treatment-related AEs include those events considered by the investigator to be related to study drug or with a missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC, PT and the worst grade. A subject will be counted only once by the highest severity grade according to NCI-CTCAE version 5.0 within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by SOC and PT.

6.5.3. Laboratory Values

Clinical laboratory values will be evaluated for each laboratory parameter as appropriate.

Descriptive summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be summarized by visit and dose level. Change from baseline will only be summarized for subjects with both baseline and postbaseline measurements.

Laboratory parameters that are graded in NCI-CTCAE v5.0 will be summarized by shifts from baseline CTCAE grades to maximum postbaseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately.

Subject data listings of each parameter will be provided. Abnormal values will be flagged and identified as those outside (above or below) the normal range.

6.5.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and changes from baseline will be summarized by visit and dose level.

Subject data listings of each parameter will be provided. Abnormal values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for vital signs parameters are defined as following:

- Respiratory rate: 10-22 bpm
- Temperature: 35.5-37.5 °C
- Systolic blood pressure: 90-140 mmHg
- Diastolic blood pressure: 40-90 mmHg
- Pulse rate: 60-100 bpm

6.5.5. Electrocardiograms (ECG)

Descriptive statistics for ECG parameters (heart rate and QTcF interval) and changes from baseline will be summarized by visit and dose level.

Subject data listings of each parameter will be provided. Abnormal values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for ECG parameters are defined as following:

- Heart rate: 60-100 bpm
- QTcF interval: ≤450 msec

6.6. Pharmacokinetic Analyses

The following analysis plan provides the framework for the summarization of the PK data. The objective is to assess BGB-DXP593 PK and characterize PK parameters following a single intravenous dose. The PK analyses will include only subjects randomized to receive BGB-DXP593 and with enough data to enable estimation of key parameters. Additional PK analyses (such as modeling and simulation using nonlinear mixed effects modelling) may be conducted if deemed necessary and will be described in a separate analysis plan.

6.6.1. Calculation of Serum Pharmacokinetic Parameters

Actual dose and blood draw times will be used to calculate the PK parameters. Parameters will be listed individually and summarized by dose level using descriptive statistics.

The following plasma PK parameters will be calculated for BGB-DXP593, as appropriate for the data collected. Other PK parameters may be calculated if supported by the data.

Calculation and presentation of PK parameters will be based on the Work Instruction: Best Practice Guidance: Non-Compartmental Pharmacokinetic Data Analysis for Clinical Studies. Version 1.0, Document Number VV-QDOC-13140.

Parameter (Units)	Definition	Method of Determination
AUC_{0-29} (μg·day/mL)	Area under the serum concentration versus time curve from Day 1 to Day 29	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{inf} (μg·day/mL)	AUC from zero to infinite time with extrapolation of the terminal phase	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{0-8} (μg·day/mL)	Area under the serum concentration versus time curve from Day 1 to Day 8	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{0-15} (μg·day/mL)	Area under the serum concentration versus time curve from Day 1 to Day 15	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{last} (μg·day/mL)	AUC from time zero to time of last quantifiable concentration	Calculated using the linear up/log down variant of the trapezoidal rule
C_{max} (μg/mL)	Maximum observed drug concentration during a dosing interval	Reported value
t_{max} (h)	Time to reach C_{max}	Actual elapsed time for reported C_{max}
$t_{1/2}$ (days)	half-life	$\ln(2)/\lambda_z$, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve
CL (L/h)	clearance	Calculated as Dose/AUC_{inf}
V_z (L)	volume of distribution during the terminal phase	Calculated as CL/λ_z, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve

6.6.2. Reporting of Pharmacokinetic Concentrations for Descriptive Statistics

The PK analyst will appropriately flag and annotate treatment of any anomalous concentrations, exclusions and any special treatment for descriptive statistics and plots. BGB-DXP593 concentration and time data will be listed individually and summarized by dose level using descriptive statistics.

The following conventions will be used for reporting descriptive statistics for concentration data.

- PK concentrations should be reported in listings at the same level of precision as that in the source data.
- If a concentration at a given time point is below the assay quantification limit (BLQ), the concentration shall be reported as the term “BLQ” with the lower limit of quantitation (LLOQ) defined in the footnotes. BLQ values shall be treated as zero for computation of descriptive statistics.
- If a concentration at a given time point is missing it shall be reported as a missing value. Missing values may be defined in a bioanalytical source as “NS” (no sample), “NR” (no result), “IS” (insufficient sample), etc. If missing data are not identified in the bioanalytical source (i.e., the record is missing), the reporting convention of “NS" shall be utilized.
- If the calculated mean concentration is BLQ, the mean value shall be reported in outputs (such as tables) as BLQ and SD and CV% shall be reported as ND (not determined). Minimum, median, and maximum may be reported.

6.6.3. Plots of Pharmacokinetic concentrations

BGB-DXP593 concentration versus time data will be plotted individually and summarized graphically using arithmetic mean (±SD) plots by dose level. Arithmetic mean concentrations that are BLQ shall be set to zero for plotting on both linear scale and log-linear scale.

6.6.4. Reporting of PK Parameters for Descriptive Statistics

The PK analyst will appropriately flag and annotate treatment of any anomalous PK parameters, exclusions and any special treatment for descriptive statistics.

- All the PK parameters except t_{max} should have at least the following summary statistics: sample size (n), mean, standard deviation (SD), coefficient of variance (CV%), median, minimum, maximum, geometric mean, geometric CV%; t_{max} should be presented as median, range (minimum, maximum) , and sample size (n) when presenting the summary statistics.
- Geometric mean (geometric CV%) will be the default method of reporting PK parameters within in-text tables.
- For any parameters that $n \leq 2$, SD should not be presented.
- The units for all PK parameters will be provided.
- It is recognized that the number of decimals in reported concentrations, for example: “9632.94401 ng/mL” or “9.963294401 ug/mL" are highly improbable and will be queried (since bioanalytical assays generally do not have this level of precision). Usually the first-in-human dose escalation trial will provide the numerical range of PK parameters e.g. AUC range from 10 to 10,000 ng.hr/mL and C_{max} range from 1 to 1000 ng/mL.

  In this scenario, for reporting PK parameters such as AUC and $C_{max,}$ the following guidance is provided for rounding:

  – If the numerical value is below 100 then one decimal place may be used e.g. 0.1 or 99.9.

  – For values ranging from >100, whole numbers should be used e.g. 100 or 9999.

  – If > 10,000 the clinical pharmacologist may decide on changing units e.g. from µg/ml to mg/ml.

  – For reporting times e.g. for t_{max} or $t_{1/2}$, if <1 hr use 2 decimals; time up to 24 hr should be reported to one decimal place e.g. 23.5 hr, time >24 hr should be rounded to nearest whole number e.g. 105 hr.

6.6.5. Software

For the calculations of PK parameters Phoenix® WinNonlin® Version 7.0 or higher (Certara, NJ. USA) will be used.

6.7. Immunogenicity Analyses

The scope of anti-drug antibodies (ADA) calculations used for characterizing clinical immunogenicity depends on the incidence and kinetics of detected (ADA). Therefore, not all parameters described below may be derived.

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of subjects who develop detectable ADAs. The incidence of positive and neutralizing ADAs will be reported for ADA-evaluable subjects according to the following definitions:

- ADA-evaluable subject: Number of subjects with reportable non-missing baseline result and at least one reportable sample taken after drug administration during the treatment or follow-up observation period with reportable result (used for computing treatment-induced ADA incidence).
- Treatment-emergent ADA: Treatment-boosted ADA subject or treatment-induced ADA subject. Synonymous with “ADA Incidence”.
- Treatment-induced ADA: ADA-evaluable subjects that were ADA-negative at baseline and ADA-positive following administration of biologic product.
- Treatment-boosted ADA: Baseline-positive ADA-evaluable subject with significant increases (4-fold or higher) in ADA titer after biologic drug administration. [Baseline-positive ADA-evaluable subject: an ADA-evaluable subject with positive ADA result].
- Persistent ADA: Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer.
- Transient ADA: Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period, or two or more time points during the treatment, where the first and last ADA-positive samples are separated by a period of less than 16 weeks, and the subject last sampling time point is ADA-negative.
- Neutralizing ADA: subjects with positive NAb.

The immunogenicity results will also be listed.

Additional ADA analyses (such as the effect of immunogenicity on PK, and safety) may be conducted if deemed necessary and will be described in a separate analysis plan.

7. INTERIM ANALYSIS

There is no formal interim analysis planned for this study.

8. CHANGES IN THE PLANNED ANALYSIS

Not applicable.

9. REFERENCES

Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Washington, DC, USA, November 27, 2017.

Work Instruction: Best Practice Guidance: Non-Compartmental Pharmacokinetic Data Analysis for Clinical Studies. Version 1.0, Document Number VV-QDOC-13140.

APPENDIX A. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

In general, missing or partial dates will not be imputed at the data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

1. Adverse Events

If AE start (onset) date or end date is missing or partial missing, the following imputation rules apply.

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > death date, then set to death date

If year of the end date is missing or end date is completely missing, do not impute.

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, then set to first of the month
- If the imputed start date > death date, then set to death date

If year of the start date is missing or start date is completely missing, do not impute.

If the imputed start date > the end date (or the imputed end date), set the imputed start date = end date (or the imputed end date).

2. Prior/Concomitant Medications/Procedures

When the start date or end date of a medication/procedure is partially missing, the date will be imputed to determine whether the medication/procedure is prior or concomitant. The following rules will be applied to impute partial dates for medication/procedure:

If start date of a medication/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed start date > death date, then set to death date

If end date of a medication/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to December 31

- If only day is missing, then set to last day of the month
- If the imputed end date > death date, then set to death date

If the year of start date or year of end date of a medication/procedure is missing, or the start date or end date is completely missing, do not impute.