STATISTICAL ANALYSIS PLAN

IMCGP100-401

AN OPEN-LABEL, MULTI-CENTER, ROLLOVER STUDY IN PATIENTS WITH ADVANCED MELANOMA AFTER COMPLETING AN IMCGP100 CLINICAL STUDY

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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TABLE OF CONTENTS

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1. Introduction

This document describes the methods, rules and conventions to be used in the presentation and analysis of data for Protocol IMCgp100-401.

This statistical analysis plan (SAP) is based on Protocol version 3.0, dated 07NOV2016.

2. Study Objectives

2.1. Primary Objective

The primary objective is to determine the number of patients with adverse events (AEs) associated with IMCgp100 treatment.

2.2. Secondary Objectives

- To characterize the long-term safety (> 1 year dosing) and tolerability profile associated with treatment with IMCgp100
- To evaluate the incidence of anti-IMCgp100 antibody formation following multiple infusions of IMCgp100
- To estimate the overall survival (OS) in patients treated with IMCgp100.

3. Study Design

3.1. General Description

IMCgp100-401 is a rollover study that is designed to provide continued access to IMCgp100 for eligible patients with advanced melanoma who have previously participated in study IMCgp100-01 (the parent study). Parent studies that are eligible for patients to continue to receive IMCgp100 in this rollover study must have completed and satisfied their primary endpoints or have been terminated by the Sponsor for reasons other than safety.

This rollover study will enroll patients who are currently receiving IMCgp100 treatment and for whom the parent IMCgp100 clinical study completes. At the time of parent study completion, the rollover study will enroll all patients actively receiving IMCgp100 treatment in the parent study in order to continue to provide these patients access to treatment. Patients who enroll in the rollover study will, in the opinion of the investigator, continue to receive clinical benefit from treatment with IMCgp100. Patients who are receiving treatment as part of an ongoing and not yet completed study, are not eligible to participate in the rollover study until the time of study completion.

At the time of rollover study entry, each patient will be assigned to the appropriate dosing cohort based on the parent study dosing regimen, cohort and the recommendation of the Sponsor and principal investigator. Changes to the dosing cohort from the parent study to the rollover study must be approved in writing by the Sponsor prior to enrolling the patient in the rollover study. See Table 6-1 in Section 6.1 of the study protocol for details of Dose and

Treatment Schedule of this rollover study. All patients must sign the rollover study consent form and be enrolled in the new study. All assessments will commence with Rollover Cycle 1 (RC1). Safety assessments (physical examinations, clinical laboratory, and electrocardiogram (ECG) assessments, as well as continuous monitoring of AEs) will continue throughout the study at the described intervals. Patients will continue to receive IMCgp100 until loss of clinical benefit for the individual patient (as per local imaging standard of care and the appropriate response criteria, as defined by the principal investigator), unacceptable toxicity as defined by the principal investigator or Sponsor, withdrawal of consent, loss to follow-up, or death.

3.2. Schedule of Events

Schedule of events can be found in Section 7 of the protocol.

3.3. Changes to Analysis from Protocol

The following are documented changes to analysis from protocol:

- Tables/Listings for change from baseline and shift tables are removed from the analysis for vital signs and ECG data. Note that vital signs will only be collected at baseline.

4. Planned Analyses

A final analysis after database lock is planned for this study.

4.1. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this SAP, Database Lock, and Analysis Sets and associated output shells.

5. Analysis Sets

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to the final analysis of the study.

5.1. All Patients Enrolled Set [ENR]

The All Patients Enrolled (ENR) set will contain all patients who provide informed consent for this study.

5.2. Full Analysis Set

The Full Analysis Set (FAS) comprises all patients assigned to treatment, who received at least 1 full or partial dose of IMCgp100. The FAS will be used for all demography, baseline characteristics, and OS data summaries.

5.3. Safety Analysis Set [SAF]

The Safety Analysis Set (SAF) includes all patients who have received at least 1 full or partial

dose of IMCgp100. The safety analysis set will be used for the safety summary of the study.

6. General Considerations

6.1. 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 day of the first dose of rollover study drug, (Day 1).

If the date of the event is on or after the reference start date, then:

- Study Day = (date of event – reference start date) + 1.

If the date of the event is prior to the reference start date, then:

- Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day and any corresponding durations will appear as missing in the listings.

Please note for survival, the first dose of the parent study will be used as reference instead.

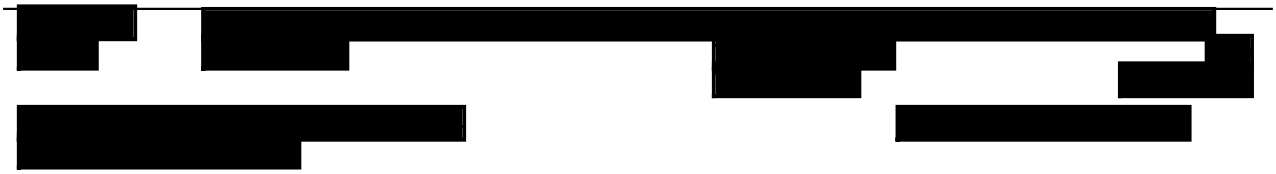
6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement (including unscheduled assessments) taken prior to the first dose of rollover treatment received (i.e.,Rollover Cycle 1 Day 1 RC1D1 pre-dose). In the case where the date of the last non-missing measurement and the first dose date of rollover treatment coincide, that measurement will be considered pre-dose and included in the baseline calculation as appropriate. This will be the rule for demography, other baseline characteristics (including disease status), laboratory data, and physical examination data. For ECGs and vital signs, where the time of assessment is recorded, if the last non-missing measurement and the reference start date coincide, then only if the time of the measurement is prior to the time of first dose will the measurement be considered pre-dose and included in the baseline calculation. Furthermore, because ECGs are supposed to be taken pre-dose on RC1D1, any RC1D1 measurements of ECGs with a time on or after the time of first dose will be queried with Data Management.

Note that baseline measurements made in the rollover study will only be used for summarizing baseline demographic information and disease characteristics. It will not be used for analyzing change from baseline, as comparisons to these baseline values cannot take into account the fact that patients were already taking IMCgp100 in their parent study.

6.3. Retests, Unscheduled Visits and End of Treatment Data

In general, for by-visit summaries, data recorded at the nominal or observed visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will



contribute to the baseline value, or best/worst case value where required.

In the case of a retest (same visit number assigned), the earliest available measurement for that visit will be used for by-visit summaries. For best/worst case, all available measurements including retest values will be used.

End of Treatment (EOT) visits will be summarized together in the by-visit summaries.

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

6.4. Windowing Conventions

There will be no post-hoc visit windowing for the analyses performed for this study. All data will be organized and analyzed according to the scheduled visit times (allowing for ± 7 days) as outlined in the Protocol Section 7-1 and by the visit denoted on the eCRF.

6.5. Statistical Tests

There will be no formal statistical hypotheses testing.

6.6. Software Version

All analyses will be conducted using SAS version 9.4 or higher.

7. Statistical Considerations

7.1. Adjustments for Covariates and Factors to be Included in Analyses

Not applicable in this study.

7.2. Multicenter Studies

This study will be conducted by multiple investigators at multiple centers internationally. However, no summaries by country or center will be completed for this study.

7.3. Missing data

Missing data will not be imputed.

7.4. Multiple Comparisons/ Multiplicity

Not applicable.

7.5. Examination of Subgroups

No subgroups will be defined for this study.

8. Output Presentations

APPENDIX 1 shows conventions for presentation of data in outputs.

The template shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by

IQVIA Biostatistics.

9. Disposition and Withdrawals

All patients who provide informed consent will be accounted for in this study. Any subjects who signed the informed consent, but never started the study treatment for any reason will be regarded as screen failures. For these patients, the eCRF data collected will not be included in summary analyses but will be reported in the CSR as part of the listings.

Patient disposition and discontinuation/withdrawals will be presented for the All Patients Enrolled (ENR) set. Important protocol violations will be listed for the Full Analysis Set (FAS).

10. Demographic and other Baseline Characteristics

Demographic data and other baseline characteristics will be presented for the FAS.

The following demographic and other baseline characteristics will be listed for this study:

1. Demography
   - Age (years)
   - Sex
   - Is the patient of child bearing potential? (females only)
   - Race
   - Ethnicity
   - Country
   - Weight (kg)
   - Height (cm)
   - BMI (kg/m^2)
2. Disease data
   - Diagnosis and extent of cancer (disease at baseline)
   - Prior anti-cancer therapy

10.1. Derivations

- Age (years) will be derived using the following SAS code:

  floor ((intck('month',&birth,&date) - (day(&date)< day(&birth))) / 12)
  - &birth= Date of birth

[redacted]

- &date = (Date of informed consent)
- Note: For countries where only the year of birth is provided due to privacy laws, impute birth month and day as June 15.

- Time since primary diagnosis (years) = (Date of informed consent – Date of Primary Diagnosis + 1) / 365.25
  - Note: Partial primary diagnosis dates are imputed using 15th day of month if only month/year present or July 02 if only year present.
- Best response on any prior anti-cancer therapy for metastatic disease = the "best" *best response* as derived from the *Prior Anti-Cancer Therapy (PAT)* eCRF page, considering all medications identified from the medical review. From best to worst, the following order will be used:
  - Complete Response
  - Partial Response
  - Stable Disease
  - Progressive Disease
  - Non-Evaluable
  - Not Applicable
- BMI (kg/m^2) = weight (kg) / (height (cm) / 100) ^{2}

11. Surgical and Medical History

Medical History information will be listed only.

- Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, using the latest version of MedDRA available at the time of coding for the reporting period.
  - Medical History conditions are defined as those conditions beginning prior to screening which stop prior to or are ongoing at Screening.
  - Presented by System Organ Class (SOC) and Preferred Term (PT).

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12. Concomitant Medications

Concomitant medications and significant non-drug therapies will be presented and coded using the World Health Organization drug dictionary (WHODD), using the latest version available at the time of coding for the reporting period.

Medications will be listed by Preferred Name (coded) and by Reported Term.

See APPENDIX 2 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant. (Refer to Protocol Section 6.2)

- 'Prior' medications are medications which started and stopped prior to the first dose of study drug of the rollover study.
- 'Concomitant' medications are medications which:
    - started prior to, on or after the first dose of study drug of the rollover study and started no later than the last dose of study drug of this rollover study,
    - AND ended on or after the date of first dose of study drug of the rollover study or were ongoing at the end of the rollover study.
- 'Post' medications are medications which started after the last dose of study drug of this rollover study.

12.1. Prohibited Concomitant Medications/Therapies

During the 'concomitant' period of the study (as above), patients may not receive other additional investigational drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. While systemic corticosteroid therapy will interfere with the mechanism of action of the study drugs, its use is recommended in some settings. See Protocol Section 6.2.3 for further details.

Medications/therapies that are prohibited will be flagged in the listing of concomitant medications. These will be identified using a medically-approved list of Preferred Names provided by the Sponsor. See APPENDIX 2 for handling of partial dates for concomitant alternative cancer therapies under Algorithm for Prior / Concomitant Medications.

13. Study Drug Exposure

All information relevant to exposure will be calculated from Rollover Cycle 1 Dose 1 (RC1D1), unless otherwise noted. Number of cycles, duration of dose on rollover study in days, duration of dose from first parent study in days, total actual dose received in rollover, dose intensity in rollover, relative dose intensity will be summarized for IMCgp100. Tolerability of study treatment will be assessed by summarizing the number of treatment dose interruptions. Reasons for dose interruptions will be listed.

The SAF analysis set will be used for presenting all exposure and tolerability variables.

13.1. Study Drug Exposure Derivations

A cycle is defined as 28 days = 4 weeks, and at least 1 dose administration visit per cycle for each of the treatment regimen for IMCgp100 (doses are given every week).

The following will be derived:

- *Number of cycles started* = total number of cycles of study drug received (including partial cycles), during the rollover study
- *Number of cycles completed* = total number of complete cycles of study drug received without any interruption, during the rollover study
- *Total planned dose* = sum of the total dose levels that a patient planned to receive during the rollover study, up to the date of last study drug administration
- *Duration of treatment* (days) = (date of last study drug administration – date of first study drug administration in the rollover study + 1). Note that this calculation does not include any post dose rest period. *Duration of treatment from first parent study dose* (days) = (date of last study drug administration – date of first parent study dose of IMCgp100 + 1). Note that this calculation does not include any post dose rest period
- *Duration of interruption (days)* = (start date of next study drug administration following interruption - date of visit in which interruption started). Note that this is calculated for each interruption a given patient has and is only calculated where study drug administration restarts following interruption.
    - "Date of visit in which interruption started" = 'date of visit' from the *Date of Visit* eCRF pages, where the visit may also be a visit classified as "not done". If it is clear that an interruption to dosing has occurred, but no *Date of Visit* eCRF page nor *Administration of Study Drug* eCRF page is entered at least 14 days (i.e. at least 7 days ± 7 day visit window) following the previous dosing visit, where dosing would have been expected, then the date of the *expected* next dose following last administered dose, may be used instead (=previous 'start date of study drug administration' + 14 days). See the definition of a *dose interruption* below.
    - If a patient does not have a "start date of *next* study drug administration following interruption" then a dose interruption is <u>not</u> counted because either:
        - The Date of study drug discontinuation from the *End of Treatment* page of the eCRF is filled out, in which case the study drug was discontinued rather than interrupted, or
        - The outcome (interruption or discontinued) is unknown at the time of data cut off, where the study drug discontinuation from the *End of Treatment* page is missing and study drug administration remains skipped or omitted. In this case, it is assumed there was no interruption, until there

[redacted]

is evidence of the study drug administration restarting.

- *Total actual dose received* = sum of the total dose levels that a patient received during the rollover study, up to the date of last study drug administration. The same considerations as for *Total planned dose* above apply here.
- Dose intensity (dose per week) = [Total actual dose received / Duration of treatment (days)] × 7
- Planned dose intensity (dose per week) = [Total planned dose / Duration of treatment (days)] × 7
- Relative dose intensity (%) = (Dose intensity / Planned dose intensity) × 100

Additional Notes on Derivations:

a. The *Administration of Study Drug* eCRF page will be used for these calculations, unless otherwise noted.

b. The *number of cycles started* is counted for all cycles of dosing in which study drug was actually administered. Any administration of study drug received, regardless of the 'Actual dose administered' on the eCRF (any dose > 0 units), that occurs in a given cycle (as indicated by the visit) will be counted as one cycle of that study drug.

    a. Note: Multiple doses within a Cycle do not count multiple times towards the *number of cycles*. For example, four doses (> 0 units) of IMCgp100 during visits in Cycle 1 count as one cycle of study drug since all these dose administrations occurred during a single Cycle (i.e. Cycle 1).

c. The number of cycles completed is counted for all cycles of dosing in which study drug was actually administered, and furthermore where no interruption occurs. Therefore, in a 4-week cycle, all doses each week must be administered for the entirety of the cycle, in order to count. Reduced doses are allowed, as per number of cycles started above.

d. The *total planned dose* is based on either the 'Parent Study Dose IMCgp100', or if applicable, the dose entered in 'Was dose changed from parent study' item, on the *Parent Study Details -IMCgp100* eCRF page. This planned dose is summed up over all visits where a patient planned to receive study drug, even if the said dose is actually missed during the visit, up until the cut-off as described above. This calculation is necessary for the planned dose intensity, which is used to calculate the relative dose intensity.

e. The *total actual dose received* is based on the 'Actual dose administered' entered on the *Administration of Study Drug* eCRF for each visit administration of study drug. The actual dose administered is summed up over all visits where a patient actually received study drug, up until the cut-off as described above.

f. The date of first study drug administration is taken from the earliest 'Dose start date' entered on the eCRF.

g. The date of last study drug administration is taken from the latest 'Dose end date'

[redacted]

entered on the eCRF.

Definitions of Dose Interruption:

Dose interruption – an entire dosing visit is skipped or entered as omitted in the eCRF. To clarify, if a dose on a single day is restarted and partial or entire dose is still taken, then this is not a dose interruption. Dose interruptions will be flagged on the *Administration of Study Drug* eCRF page where the response to '*Did the patient receive investigational product at this visit?'* is equal to *'No, reason for dose omission'.* Also, dose interruptions are counted in cases where a patient misses an entire study visit, where dosing is expected.

A single interruption is defined as any length of time a patient misses dosing visits. For example, for IMCgp100 which is administered weekly, then a single dose interruption would be defined regardless of whether only 1 week was missed or 2 consecutive weeks dosing were missed.

13.1.1. Missing Data Methods For Study Exposure Variables

Missing data for elements of certain study exposure variables will be handled as follows:

- The date of first study drug administration is not expected to be missing for any patients.
- If the date of last study drug administration is missing or partial, then the date will be taken instead from the Date of discontinuation on the *End of Treatment* page of the eCRF.

14. Efficacy Outcomes

14.1. Overall Survival (OS)

Overall Survival (OS) is defined as the time from the date of first dose of study drug in the parent study until death due to any cause. Any patient not known to have died at the time of analysis will be right-censored based on the last recorded date on which the patient was - known to be alive, i.e. the latest of (i) the "Date of death or Last contact" (for those patients still alive) on the End of Study eCRF page and (ii) "Date patient last known to be alive" on the Survival Follow Up eCRF page. Also, to make sure that the last date patient was known to be alive is as accurate as possible, any date from the eCRF that indicates the patient is still alive will also be considered. The eCRF pages to be included in this check are: *AE/SAE*, *Prior and Concomitant Medication,* any page relating to patient Disposition*, Administration of Study Drug, Vital Signs, Electrocardiogram,* all Laboratory pages*,* and *Physical Examination.* The eCRF page dates that are not included in this check are: visit dates or signature dates or any other module that is not a true assessment date, e.g., sample processing dates. Date of death will be collected to assess OS only and will be listed according to treatment regimen.

OS will be calculated in number of months, calculated in two steps as:

- Time in days = (date of event – date of first dose in the parent study) + 1

- Therefore, time in months = time in days/ (365.25/12). In other words, 1 month = 30.4375 days.

Note here that time is calculated from the first dose of the treatment in the parent study.

15. Safety Outcomes

All summary outputs for safety outcomes will be based on the SAF analysis set. All safety tables and listings will be presented according to the Appendix 1.

Unless otherwise stated, the overall observation period will be divided into 3 mutually exclusive segments as follows:

- Pre-treatment period: any time point prior to the first dose of IMCgp100 in the rollover study
- On-treatment period: from immediately after the first dose of study medication of the rollover study to 90 days after last dose of study medication in the rollover study.
- Post-treatment period: starting at Day 91 after last dose of study medication of this rollover study (including the 90-day Safety Follow-up period defined in Protocol Section 3.2)

For domains such as concomitant medications and adverse events, definitions of concomitance and treatment emergence are included in the associated sections of this SAP section 12 and 15.1, respectively.

15.1. Adverse Events

Patients with multiple adverse events in the same category are counted only once in that category and those with adverse events in more than 1 category are counted once in each of those categories. Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, using the latest version of MedDRA available at the time of coding for the reporting period.

Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity from the date of first dose of the rollover study (regardless of time) up until 90 days after the last dose of study drug of this rollover study.

See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the templates.

An AE Listing will include TEAEs and Non-TEAEs, including those from before the first dose in the parent study and post-treatment periods which will be flagged as such. Only TEAEs will be summarized.

AE Structure as Recorded in the eCRF:

AEs will be recorded in the eCRF such that any change in severity over the course of their duration will be recorded as a single record. The AE/SAE eCRF page collects 'Initial Grade' and 'Most Extreme Grade' but not the date of the severity grade change. No further manipulation post collection is required, and the AE/SAE data will be listed as recorded.

The definition of a treatment-emergent AE will be handled for AEs that change in severity over the course of their duration, by assuming that any AE that *might have* **worsened** in severity within the timeframe from the date of first dose of the rollover study (regardless of time) up until 90 days after the last dose of study drug, will be defined as treatment-emergent. A worsening severity is defined as changing from a less severe (lower) CTCAE grade to a more severe (higher) CTCAE grade. For example, if an AE started prior to date of first dose of the parent study but ended on or after date of first dose of the parent study (regardless of time), and the 'Most Extreme Grade' is more severe (higher) than the 'Initial Grade', then the AE is assumed to be treatment-emergent.

15.1.1. All TEAEs

Incidence of TEAEs by subject count, in addition to number of total TEAEs, will be presented by System Organ Class (SOC) and Preferred Term and also broken down further by maximum severity of the NCI CTCAE grade (Grade ≥3).

15.1.1.1. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade

Severity is based on NCI CTCAE v.4.03 grades and classed as mild, moderate, severe, life threatening, or death related to AE (increasing severity), as represented by Grades 1-5, respectively. TEAEs starting after the first dose of study drug with a missing severity will be classified as 'missing'. If a patient reports the same AE more than once within that SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries. In determining maximum severity, response values will be ranked in order from minimum severity to maximum severity as Missing, Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5 (as values: 'missing', 'mild', 'moderate', 'severe', 'life threatening', and 'death related to AE').

A summary table will present TEAEs, showing number of subjects (%) for all grades and grades ≥ 3 for each SOC/PT. This summary table will also be repeated for TEAEs related to IMCgp100.

15.1.1.2. Relationship to Study Drug (IMCgp100)

Relationship, as indicated by the investigator, is classed as unrelated or related. The categories 'possibly' related or 'related' will be pooled to create the 'related' category. TEAEs with a missing relationship to study drug will be regarded as 'missing'.

15.1.2. TEAEs Leading to Discontinuation of Study Drug

TEAEs leading to permanent discontinuation of study drug will be identified by using the "Action taken with the study drug" variable collected on the eCRF, where the variable is equal to 'Drug permanently discontinued'. These will be flagged in the listing.

[redacted]

15.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as 'Yes' in response to the "Does the Adverse Event meet seriousness criteria?" question on the Adverse Event/ Serious Adverse Event (*AE/SAE)* page of the eCRF.

A listing of SAEs (including deaths reported as SAEs) will be created.

15.1.4. Adverse Events Leading to Death

TEAEs leading to death are those events which have a 'Most Extreme Grade' recorded as 'Grade 5 - Death related to AE', or Seriousness Criteria has 'Death' ticked. Any AE leading to death will be also listed in a separate data listing from SAEs.

15.2. Deaths

If any patients die during the study as recorded on the *Death* page of the eCRF, the information will be presented in a data listing.

15.3. Laboratory Evaluations

Results from local laboratory data will be included in the reporting of this study for Hematology, Chemistry, and Cytokines. All laboratory parameters assessed for safety purposes will be evaluated locally. A list of laboratory assessments to be included in the outputs is included in Table 7-3 of the Protocol, Section 7.3.4. The treatment periods to be used for reporting laboratory data are defined in Section 15.

Presentations will use SI Units (International System of Units).

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.

Handling of retests and unscheduled measurements for laboratory results is included in Section 6.3.

Hematology laboratory values will be summarized in a table. These summaries will be repeated for biochemistry (chemistry and cytokines). Furthermore, a listing of all laboratory data with values flagged as clinically significant will be presented with their corresponding NCI CTCAE grades and the classifications relative to the laboratory normal ranges will be presented for both hematology and biochemistry laboratory tests.

15.3.1. Laboratory Specific Derivations

The following laboratory parameters will be derived as follows:

- Corrected Calcium [mmol/L]* = (0.02 * (Normal Albumin [g/L] – Serum Albumin [g/L])) + Serum Calcium [mmol/L]
    - * This correction will only be applied for records at the patient/visit level where albumin is less than the lower limit of normal. For records where albumin is greater than or equal to the lower limit of normal, no correction will be applied,

and the Corrected Calcium value will equal the calcium (uncorrected) value, as collected on the eCRF.

- Normal albumin is assumed to be 40 g/L.
- Note: The reference ranges for Corrected Calcium will be derived on a patient by patient, visit by visit level, as the same reference ranges collected locally for calcium (uncorrected), which is a parameter collected directly from eCRF.

All other laboratory parameters are available from the data collected on the eCRF. Local laboratory results will be converted into SI units (International System of Units) and presentations will use SI Units.

15.3.2. Laboratory Reference Ranges and Markedly Abnormal Criteria

The following laboratory tests do not have grades defined by NCI CTCAE:

Hematology:

- Hematocrit
- Absolute basophils
- Absolute eosinophils
- Absolute monocytes

Biochemistry:

- Bicarbonate
- Calcium (uncorrected) – as collected directly from eCRF
- Chloride
- Blood urea nitrogen
- Urea
- Gamma-interferon
- Interleukein-6
- Interleukein-10
- Tumor necrosis factor-α

For these laboratory tests, results will be graded by the low/normal/high classifications based on laboratory normal ranges. In this case, quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units 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.

[redacted]

The lower and upper limit will be referred to in outputs as LLN = Lower Limit Normal and ULN = Upper Limit Normal, respectively.

15.3.3. NCI CTCAE Grading for Laboratory Data

Laboratory measurements will be graded by the study team using NCI CTCAE version 4.03 as defined by National Cancer Institute.

Laboratory tests covered by NCI CTCAE are as follows (found under 'Investigations' in the link above unless otherwise specified):

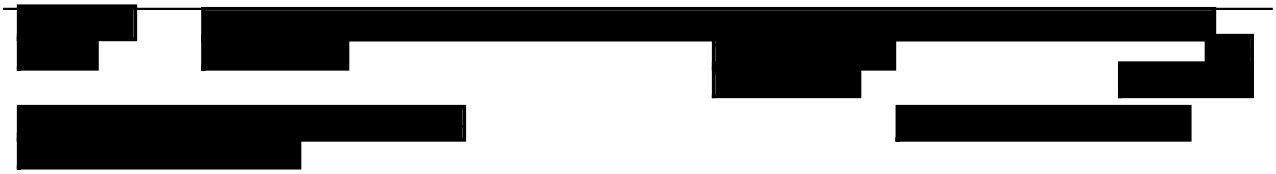
Hematology:

- Hemoglobin
- White blood cell count (Leukocytes)
- Platelet count
- Absolute neutrophils count
- Absolute lymphocyte count

Biochemistry:

- Creatinine
- Sodium (see hypernatremia/hyponatremia)
- Potassium (see hyperkalemia/hypokalemia)
- Albumin (see hypoalbuminemia)
- Total bilirubin (and direct/indirect)
- Alkaline phosphatase
- ALT
- AST
- Magnesium (see hypermagnesemia/ hypomagnesemia)
- Corrected Calcium (see hypercalcemia/hypocalcemia) – see Section 15.3.1
- Glucose (see hyperglycemia/hypoglycemia)
- Amylase
- Inorganic phosphate (see hypophosphatemia)
- Lipase

For laboratory tests covered by NCI CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. Any missing laboratory value will consequently have a missing CTCAE Grade.



If CTCAE Grade 1, specified in the NCI CTCAE version 4.03 documentation, requires LLN/ ULN follow the rules below.

For LLN:

- If LLN is above or equal to the lower value of the range for the Grade 1, then continue with the process as specified in the documentation.
- If LLN is below the lower value of the range for the Grade 1 then check if the laboratory test value is equal to the lower value, if yes set this to Grade 1. If the laboratory test value is above the lower value of the range for the Grade 1, then set to Grade 0. Else grade as per the rules for Grade 2 onwards.

For ULN:

- If ULN is below or equal to the higher value of the range for the Grade 1, then continue with the process as specified in the documentation.
- If ULN is above the higher value of the range for the Grade 1 then check if the laboratory test value is equal to the higher value, if yes set this to Grade 1. If the laboratory test value is below the higher value of the range for the Grade 1, then set to Grade 0. Else grade as per the rules for Grade 2 onwards.

15.4. ECG Evaluations

Results from the ECG (Electrocardiogram) as recorded by the Investigator on the eCRF at Screening and at End of Treatment will be included in the reporting of this study. The treatment periods to be used for reporting ECG data are defined in Section 15. No change from baseline values for ECG will be reported for this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcB Interval (msec)
- QTcF Interval (msec)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)

The observed ECG values will be shown through a listing. Values meeting markedly abnormal criteria will be flagged in the listing.

15.4.1. ECG Specific Derivations

No extra ECG derivations are necessary, as all parameters are collected from eCRF page.

15.4.2. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined criteria for varying degrees of abnormality for prolonged QTc (based on ICH – E14 standard ranges)

- Absolute values for QTcB interval and QTcF will be classified as:
  - Missing result
  - ≤450 msec (i.e. 'Normal')
  - >450-480 msec
  - >480-500 msec
  - >500 msec

15.5. Vital Signs

The treatment periods will not be used for reporting vital signs data, as defined in Section 15. Vital signs, excluding weight, are only recorded up to and at baseline. Weight is collected throughout the study period. The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Respiratory Rate (breaths/min)
- Pulse Rate (bpm)
- Temperature (^{0}C)
- Weight (kg)

All measurements apart from weight are taken in a sitting position after at least 5 minutes of rest.

All vital sign evaluations performed will be listed with their classifications relative to the vital signs markedly abnormal criteria given in Section 15.5.2 below.

15.5.1. Vital Signs Specific Derivations

Weight can be entered on the eCRF in kg or lbs. Any weight assessments entered in lbs will be converted to kg by dividing by 2.205.

15.5.2. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements observed values will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg	Grade 1: 120 to 139 mmHg Grade 2: 140 to 159 mmHg Grade 3: ≥ 160 mmHg
DBP	mmHg	≤ 60 mmHg	Grade 1: 80 to 89 mmHg Grade 2: 90 to 99 mmHg Grade 3: ≥ 100 mmHg
Respiratory Rate	breaths/ min	< 10 breaths/min	≥ 20 breaths/min
Heart rate	bpm	≤ 60 bpm	≥ 100 bpm
Body temperature	˚C	NA	Grade 1: 38.0 – 39.0 ˚C Grade 2: >39.0 – 40.0 ˚C Grade 3/4: >40.0 ˚C
Weight	kg	NA	NA

Since weight has no Low or High markedly abnormal criteria in this rollover study, it will have "NA" in lieu of "Low", "Normal" or "High" in listings. For other vital sign, a value that is not Low nor High will be represented as "Normal".

15.6. Physical Examination

Physical Examination results will be listed, and abnormalities will be flagged.

16. Exploratory Objectives

16.1. Immunogenicity

Data pertaining to the Immunogenicity exploratory endpoints will be listed and will be based on the SAF analysis set.

17. Other Data Not Summarized or Presented

The CRF pages

not summarized or presented are:

- Principal Investigator Signatures
- Subsequent Cycle Status
- Safety Follow-up D90

[redacted]

18. References

ICH Steering Committee. (2005). *ICH Harmonised Tripartite Guideline: The clinical evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs E14.* Retrieved from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf

Parent X, S. C. (2009). ["Corrected" calcium: calcium status underestimation in non-hypoalbuminemic patients and in hypercalcemic patients]. *PubMed*, 1. doi:10.1684/abc.2009.0348

Services, U. D. (2010, June 14). *National Institute of Health.* Retrieved April 2, 2019, from CTCAE: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX 1. **Programming Conventions for Outputs**

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the following IQVIA output conventions.

1. ABBREVIATIONS

- ASCII American standard code for information interchange file format
- CGM Computer graphics metafile
- ODS Output Delivery System
- RTF Rich text file format

2. INTRODUCTION

This document applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures. These standards should be used in the absence of customer specific standards.

3. OUTPUT FILE NAMING CONVENTIONS

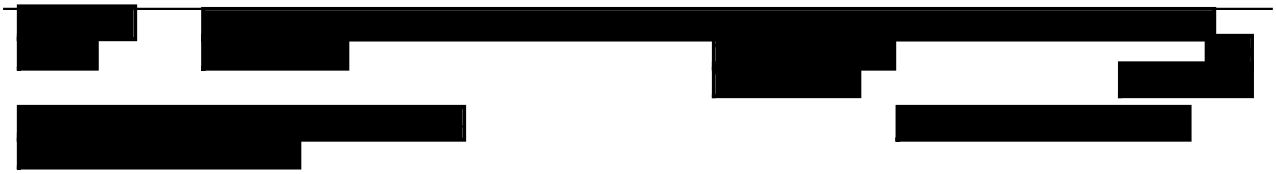
File names should only consist of lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

Output files should be in RTF format.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('t' for table, 'l' for listing and 'f' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (e.g. T14_3_01_1.RTF)

4. PAPER SIZE, ORIENTATION AND MARGINS

- The size of paper will be A4.
- The page orientation should preferably be landscape, but portrait is also permitted.
- Margins should provide at least 3 centimeters of white space all around the page, regardless of the paper size.



- The number of columns per page (linesize) should be 132 for A4.
- The number of rows per page (pagesize) should be 46 for A4.

5. FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No bolding, underlining italics or subscripting should be permitted. Try to avoid using super-scripts, unless absolutely necessary. Single spacing should be used for all text.
Figures should have a default font of "Times Roman", "Arial", or "Courier New".
This can be achieved by using the following options in SAS for figures created using SG Procedures or GTL:

```
proc template;
 define style newfont;
 parent = styles.rtf;
 style GraphFonts from GraphFonts /
 'GraphDataFont' = ("Courier New", 10pt)
 'GraphLabelFont' = ("Courier New", 10pt)
 'GraphValueFont' = ("Courier New", 10pt)
 'GraphFootnoteFont' = ("Courier New", 10pt);
 end;
run;
ods rtf style=newfont;
```

6. HEADER INFORMATION

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
- The sponsor name and protocol number should appear in rows 1 and 2, left-aligned
- The output identification number should appear in row 4, centered after a blank line in row 3
- The output title should start in row 5, centered
- The output population should appear in row 6, centered. The population should be spelled out in full, e.g. Full Analysis Set in preference to FAS.
- Row 7 should be a blank line
- Row 8 should be a continuous row of underscores ('_') (the number of underscores should equal the linesize)
- Sentence case should be used for titles

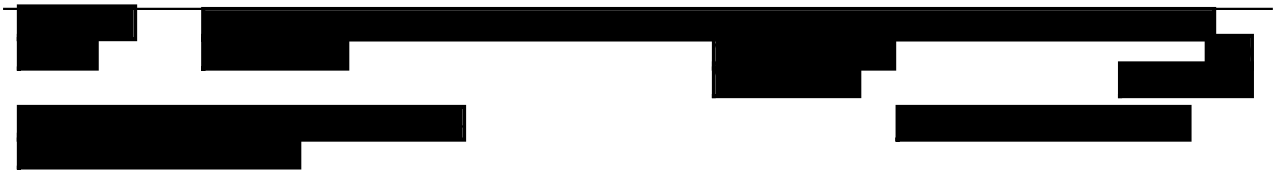
[redacted]

- The output titles should be designed so that they are arranged consistently through all outputs. For example, content (e.g. Vital signs) followed by metric (e.g. observed values) e.g. Vital signs – observed values.
- Titles should not contain quotation marks or footnote references
- The column headings should be underlined with a row of underscores ('_')
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered
- Column headings containing numbers should be centered
- Column headings should be in proper case or sentence case
- In general, the population count should appear in the column header in the form "(N=XXX)"
- "Statistic" should be the column header over n, Mean, SE, n (%) etc.
- As a rule, all columns should have column headings if possible.

7. TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank
- The left hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned, where possible.
- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized
- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- The study drug should appear first in tables with treatments as columns
- All listing outputs should be sorted (preferably by Treatment, Patient Identifier [Site Number + Patient Number]).



- Do not use superscripts and subscripts
- Exponentiation will be expressed without superscripts, i.e., m^2 will be displayed as m2.
- The width of the entire output should match the linesize

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, Std, Median, Minimum, Maximum)
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
- Minimum and maximum: N
- Mean, median and CV%: N + 1
- Std: N + 2

Note: An exception to this rule is for demography and other baseline characteristics summaries, in which the precision of the original data can be ignored, if less decimal places suit the statistical summary better. The full decimal precision (places) will be shown in Listings in these cases.

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

77 (100.0%)

50 (64.9%)

1 (1.3%)

- Percentages will be reported to one decimal place, except percent <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percent < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.

E.g. (<0.1%)

(6.8%)

(>99.9%)

[redacted]

- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- Where counts are zero, percentages will not appear in the output.

Confidence Intervals:

- As a rule, confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up". However, parentheses do not have to be used.
- Boundary values of confidence intervals should be separated by a comma.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:

-0.12, -0.10
9.54, 12.91

Ratios:

- Ratios should be reported to one more decimal place than the original data.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values:

- A "0" should be used to indicate a zero frequency.
- A blank or '-' will be used to indicate missing data in an end-of-text table or patient listing.
- In the case that only a single value is used in the creation of summary statistics (i.e. n=1) then only n and the mean will be presented.

8. FIGURE OUTPUT CONVENTIONS

- Figures should be provided in RTF files using the SAS Output Delivery System (ODS). Formats such as Computer Graphics Metafile (CGM), PNG (Portable Network

[redacted]

Graphic), etc. should be used for the formatted graphical output generated by SAS.

- The CGM/PNG/etc. graphical file itself may or may not contain the title or footer.
- The image should be clear and of high quality when viewed in the Word document, and when printed.
- In general, boxes around the figures should be used.

9. FOOTNOTE INFORMATION

Footers should be defined as follows:

- A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page
- Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table
- The program path and name and version number (if applicable) should appear as the last footnote at the bottom of the page
- The date/time stamp should appear directly after the program path and name
- Footnotes should be left-aligned.
- Footnotes should be in sentence case.
- Only "typewriter" symbols are permitted – e.g. "*", "$", "#", "@", "&" and "+".
- The choice of footnote symbols should be consistent. E.g. if you have the footnote "# indicates last observation carried forward" for one table, the same symbol and footnote should indicate LOCF for all tables.
- If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line (if possible)
- The page identification in the format Page X of Y (where Y is the total number of pages for the output) will appear at the bottom of the page, right aligned

Ordering of footnotes should be as follows:

1.) Abbreviations and definitions
2.) Formulae
3.) Symbols
4.) Specific notes
5.) Source data listing reference, if necessary

[redacted]

Common notes from table to table should appear in the same order.

The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

10. PROGRAMMING INSTRUCTIONS

Programming instructions must appear in blue font at the end of each table or listing shell. Programming instructions, where necessary, should follow the table or listing shells in blue font, beginning with the words "Programming Note" followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYYY HH:MM.

SPELLING FORMAT

English US

PRESENTATION OF TREATMENT GROUPS

For all Tables and Figures, treatment groups will be based on pooling as follows. For Listings, each cohort of patients will be listed separately with screen failures appearing last:

Treatment Group	For Tables and Figures	For Listings
IMCgp100 xx mcg	Patient or Overall for Regimen 1.	Regimen 1, Parent Study = xxx: IMCgp100 xx mcg
	Shells to provide more information	

Regimen 1 = treatment on a weekly basis

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scr
Baseline	BL

[redacted]

Long Name (default)	Short Name
Treatment Period	
Rollover Cycle 1 Day 1	RC1D1
Rollover Cycle 1 Day 8	RC1D8
Rollover Cycle 1 Day 15	RC1D15
Rollover Cycle 1 Day 22	RC1D22
Rollover Cycle 2 Day 1	RC2D1
…	…
End of Treatment record	
End of Treatment	EOT

LISTINGS

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

Parent study by ascending numeric order,

Within a Regimen and Parent study, dose cohorts (patients on same assigned dose) should be presented in ascending dose order,

center-patient ID,

visit (where applicable),

date and time (where applicable),

For listings where Screen Failures are included, these will appear in a category after the randomized/actual treatment groups labelled as 'Screen Failures'.

[redacted]

APPENDIX 2. **Partial 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 drug start date, then not TEAE If start date ≥study drug start date and start date ≤ study drug end date + 90, then TEAE If start date > study drug end date + 90, then not TEAE Note: If study drug end date is missing, then as long as start date ≥ study drug start date, then TEAE
	Partial	If start date < study drug start date, then not TEAE If start date ≥ study drug start date and start date ≤study drug end date + 90, then TEAE If start date > study drug end date + 90, then not TEAE Note: If study drug end date is missing, then as long as start date ≥study drug start date, then TEAE
	Missing	If start date < study drug start date, then not TEAE If start date ≥study drug start date and start date ≤ study drug end date + 90, then TEAE If start date > study drug end date + 90, then not TEAE Note: If study drug end date is missing, then as long as start date ≥ study drug start date, then TEAE
Partial, but known	Known	Not TEAE

[redacted]

START DATE	STOP DATE	ACTION
components (month/year or year) show that start date cannot be on or after study drug start date		
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study drug start date (i.e. same month/year or after, or year after)	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then 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, consider the following: -If start date ≤ study drug end date + 90, then TEAE -If start date > study drug end date + 90, then not TEAE Note: If study drug end date is missing, then as long as the imputed start date ≥ study drug 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 drug start date, then not TEAE If stop date ≥ study drug start date, then 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, consider the following: -If start date ≤ study drug end date + 90, then TEAE

[redacted]

START DATE	STOP DATE	ACTION
		-If start date > study drug end date + 90, then not TEAE Note: If study drug end date is missing, then as long as the imputed start date ≥ study drug start date, then TEAE.
	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, consider the following: -If start date ≤ study drug end date + 90, then TEAE -If start date > study drug end date + 90, then not TEAE Note: If study drug end date is missing, then as long as the imputed start date ≥ study drug start date, then TEAE.
Missing	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug 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 drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing	Assumed TEAE

Note: Study drug start date is the parent study first drug date.

[redacted]

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug 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 drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug 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 drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥study drug 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 drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment
	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

[redacted]

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study drug start date, assign as prior If stop date ≥ study drug 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 drug start date, assign as prior If stop date ≥ study drug start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

Note: Study drug start date is the parent study first drug date.

Document Approval Signature(s)

This document has been signed electronically in compliance with IQVIA and IQVIA Companies' electronic signature policies and procedures. This page is a manifestation of the electronic signatures, which may be confirmed within the IQVIA and IQVIA Companies' source system in accordance with IQVIA and IQVIA Companies' records retention policies. Note: the Title field in the signature block has been intentionally left blank.

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