STATISTICAL ANALYSIS PLAN

SYM004-09

AN OPEN-LABEL, MULTI-CENTER PHASE 1B/2A TRIAL INVESTIGATING DIFFERENT DOSES OF SYM004 IN COMBINATION WITH FOLFIRI IN PATIENTS WITH METASTATIC COLORECTAL CANCER PROGRESSING AFTER FIRST-LINE THERAPY

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VERSION NUMBER AND DATE: V1.1, 08JUNE2017

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.1 (Dated 07JUNE2017) for Protocol SYM004-09.

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

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	24FEB2017	[redacted]	Not Applicable – First Version
1.0	30MAR2017	[redacted]	Updates made after Symphogen's review.
1.1	07JUNE2017	[redacted]	Updates made to the SAP text and shells as follows: 1. Updated the definition of dermatologic toxicity in the SAP text. 2. Added a listing and count of TEAEs of hypomagnesaemia to the overall AE summary table. 3. Added a listing of FOLFIRI exposure variables.

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation of safety data collected up to the cut-off date of 15th May 2017, for Protocol Sym004-09. This document describes the data to be summarized and presented in the abbreviated clinical trial report (CTR).

This statistical analysis plan (SAP) is based on version V3.0 of the clinical trial protocol (CTP), dated 05AUG2016. However, based on a sponsor decision to discontinue the trial, only two doses (12 mg/kg and 9 mg/kg) of Sym004 in combination with FOLFIRI will now be investigated. No further subjects are to be recruited or enrolled in the trial and the Dose Expansion (Phase 2a) part of the trial will not be conducted. Therefore the original trial objectives detailed in Version 3.0 of the CTP will not be fully documented in this SAP.

2. TRIAL OBJECTIVES

The original primary objective for the Dose-Escalation (Phase 1b) part of this trial was to determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) of Sym004 when administered by intravenous (IV) infusion every second week in combination with a standard dosing regimen of FOLFIRI (Folinic Acid [FA; leucovorin], 5-fluorouracil (5-FU), Irinotecan) to subjects with locally advanced or metastatic colorectal cancer (CRC).

As the trial will be discontinued the objective of the trial is now to assess the safety of Sym004 when administered in combination with a standard dosing regimen of FOLFIRI.

2.1. EXPLORATORY OBJECTIVES

There will not be any exploratory objectives.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This was an open-label, multicentre, phase 1b trial with an initial dose-escalation phase followed by a dose-expansion phase.

The trial was to be conducted in the USA and countries within the EU.

Approximately 2 to 3 investigational trial sites were to participate in the dose-escalation phase to determine the MTD of Sym004 administered every second week in combination with a standard dosing regimen of FOLFIRI. Subjects were to be allocated in sequence to 1 of up to 5 dose levels of Sym004, based on tolerability.

Ten subjects at 6 investigational sites in Spain and USA were enrolled in the Dose Escalation (Phase 1b) part of the trial at the time the decision was taken to discontinue the trial. The primary statistical analysis timing and

database will be based upon a sponsor determined data cut-off, which is set up to include sufficient safety data (at least 3 months after the last subject's first dose), while allowing subjects in response or stable disease to continue benefiting from their study treatments.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 5.3 and Table 1 of the CTP.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

- The trial has been stopped early, phase 2a of this trial has been cancelled.
- Only summaries and listings required for an abbreviated CTR will be generated, based on the full analysis set (FAS) unless otherwise stated.
- No efficacy analysis will be carried out.
- The Dose Limiting Toxicity (DLT) analysis set has been renamed and the definition updated to be the Maximum Tolerable Dose (MTD) analysis set.

4. PLANNED ANALYSES

The final planned analyses identified in this SAP will be performed by [redacted] Biostatistics following the authorization of the SAP and database (DB) lock, which will include all trial data collected up to the cut-off date of the 15th May 2017. No formal statistical tests will be carried out on this trial.

5. ANALYSIS SETS

5.1. FULL ANALYSIS SET (FAS)

The Full Analysis Set (FAS) will comprise all subjects who received at least one dose of trial treatment. Subjects will be summarized according to the treatment they received.

All outputs will be presented on the FAS unless otherwise indicated.

5.2. MAXIMUM TOLERABLE DOSE (MTD) ANALYSIS SET

The Maximum Tolerable Dose (MTD) Analysis Set will be comprised of all subjects in the FAS who completed

Cycle 1 (i.e. minimum 2 infusions of Sym004 in combination with FOLFIRI [full dose]) or who have dose limiting toxicities (DLTs) in cycle 1. Subjects who discontinue study treatment for reasons other than DLT will be excluded from the MTD Analysis Set. As per the protocol, these subjects were to be replaced.

The MTD analysis set will be used for evaluation of DLTs.

6. General Considerations

6.1. Reference Start Date and Data Cut-off Date

Reference start date is defined as the first day of trial treatment (Day 1) for each subject.

The data cut-off date for the primary analysis is the 15th May 2017. Only observations with an assessment date or start date that is prior to or equal to the date of data cut-off will be included in the analysis data model (ADaM) datasets and statistical outputs. If however, there are adverse event (AE) or concomitant medication stop dates that are after the cut-off date and are available in the database at the time of DB lock (for AEs or medications that started prior/equal to the cut-off date), these will be presented in listings.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, and there is no evidence to suggest that the assessments were completed after dosing, that measurement will be considered as baseline.

6.3. Unscheduled Visits and Early Termination Data

Unscheduled measurements will not be included in by-visit summaries, but will contribute to the best/ worst case value where required.

Early termination data (End of treatment visit) will be presented as per the assigned visit labels.

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

6.4. Windowing Conventions

No visit windowing will be performed for this trial.

6.5. STATISTICAL TESTS

No statistical tests will be performed for this trial.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline (if required) will be calculated as:

- Test Value at Visit X – Baseline Value

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.2 or higher.

7. STATISTICAL CONSIDERATIONS

Not applicable for this trial.

8. OUTPUT PRESENTATIONS

Appendix 1 shows the conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this trial and therefore the format and content of the summary tables and listings to be provided by [redacted] Biostatistics.

If there are missing data in a summary table, the number of subjects with missing data will be included in brackets after the N for each treatment arm, i.e. 50 (2). Percentages will be based on the total number in the corresponding analysis set, unless otherwise indicated, hence any subject(s) with missing data are included in the denominator.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this trial.

Subject disposition and trial discontinuations will be summarized in a table which will include the following:

1. Number of subjects screened (i.e., subjects who gave informed consent).
2. Number (%) of subjects allocated to treatment
3. Number (%) of subjects treated (FAS).

4. Number of subjects evaluable for MTD.
5. Number (%) of subjects allocated to treatment but not treated.
6 Number (%) of subjects who withdrew from Sym004 treatment
7. Number (%) of subjects who withdrew from FOLFIRI treatment
8. Number (%) of subjects who withdrew from both Sym004 and FOLFIRI.
9. Number (%) of subjects ongoing Sym004 at Data Cut-off.
10. Number (%) of subjects ongoing FOLFIRI at Data Cut-off.
11. Number (%) of subjects who discontinued from trial (including reason for discontinuation).

Percentages for category 2 will be based on the 'Number of subjects screened'.

Percentages for categories 3 - 4 will be based on the 'Number of subjects allocated to treatment'.

Percentages for categories 5 - 11will be based on the 'Number of subjects treated (FAS)'.

Treatment withdrawals (subjects who have discontinued from trial treatment) for each trial treatment received will be presented overall and by reason, for the FAS.

The number of subjects in each analysis set per country will be summarized in a table also.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data will be presented for the FAS.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic characteristics will be reported for this trial:

- Age (years)
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BSA (m^2)

10.1. DERIVATIONS

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

In case of missing day or day and month, Age will be calculated using the month and/or year of informed consent minus month and/or year of birth.

11. SURGICAL, MEDICAL AND DISEASE HISTORY

Surgical, Medical and Disease History information will be presented in listings for the FAS. Surgical disease history will include prior local treatment modalities and prior cancer surgeries.

Medical history will be coded using MedDRA, Version 19.1 or higher.

12. MEDICATIONS

12.1. PRIOR ANTI-CANCER THERAPIES

Prior anti-cancer radiotherapy, prior cancer treatments and prior anti-cancer drug therapies will be listed for the FAS.

12.2. CONCOMITANT MEDICATIONS AND THERAPIES

Medications (including prophylactic treatments for skin toxicity and premedications for Sym004 and FOLFIRI) will be presented in listings for the FAS and coded using Enhanced WHODRUG Version March 2015.

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.

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

13. TRIAL TREATMENT EXPOSURE AND COMPLIANCE

Administration details of Sym004 and FOLFIRI drugs will be listed for each drug received for the FAS. The following list summarizes the compliance and exposure endpoints that are to be derived for Sym004, Irinotecan,

5-FU bolus and 5-FU infusion. Treatment was given every 2 weeks and therefore this is noted in the units for dose intensity:

- Number of infusions of trial treatment received
- Treatment duration (weeks) – including any treatment delays
- Exposure duration (weeks)
- Cumulative dose received (mg/kg or mg/m^2)
- Dose intensity (mg/kg/2 weeks or mg/m^2/2 weeks)
- Relative dose intensity (%)

The following will be derived and listed for Sym004 only:

- Number of dose reductions
- Number of dose interruptions

13.1. DERIVATIONS

13.1.1. NUMBER OF INFUSIONS OF TRIAL TREATMENT RECEIVED

Any administration of trial treatment regardless of the actual dose (any dose > 0) will be counted as one infusion of that treatment.

13.1.2. TREATMENT DURATION (WEEKS)

Treatment duration (weeks) will be calculated for Sym004, Irinotecan, calcium folinate and 5-FU bolus as:

(Last dose date prior to data cut off – first dose date + 14)/7 days

As the 5-FU infusion is given over 46 hours, treatment duration (weeks) will be calculated for 5-FU infusion as:

(Last dose date prior to data cut off – first dose date + 13)/7 days

13.1.3. EXPOSURE DURATION (WEEKS)

Exposure duration (weeks) will be calculated for Sym004, Irinotecan, calcium folinate, 5-FU bolus and 5-FU infusion as:

(Last dose date prior to data cut-off – first dose date + 1)/7 days

13.1.4. DOSE RECEIVED (MG/KG OR MG/M^2)

The dose of Sym004 received (mg) at each treatment administration visit will be calculated as follows:

$$\frac{\textit{Total dose (mg) * Total volume Infused (mL)}}{\textit{Total volume prepared (mL)}}$$

The Sym004 dose in mg/kg for a subject will be calculated as:

Dose of Sym004 received (mg) / Body weight (kg),

where weight recorded on the day of treatment administration is to be used. In case this weight is missing, the latest available weight prior to this visit will be used.

The dose received (mg) at each visit for each FOLFIRI drug (irinotecan, Calcium Folinate and 5-Fluorouracil) will be equal to the total planned dose (mg), if the total dose delivered was 100%. Otherwise, if < 100% of dose was delivered then dose received (mg) = the amount of dose delivered (mg).

The dose for each FOLFIRI drug in mg/m^2 will be calculated for a subject as:

Dose of drug received (mg) / BSA (m^2),

where weight recorded on the day of treatment administration is to be used to determine BSA. In case this weight is missing, the latest available weight prior to this visit will be used.

13.1.5. *CUMULATIVE DOSE (MG/KG OR MG/M^2)*

The cumulative dose is defined the sum of all doses received prior to data cut-off in units of mg/kg for Sym004 and mg/m^2 for each FOLFIRI drug.

13.1.6. DOSE INTENSITY (MG/KG/2 WEEKS OR MG/M^2/2 WEEKS)

The dose intensity (mg/kg/2 weeks) for Sym004 is defined as:

Cumulative dose (mg/kg) / (Treatment duration in weeks/2)

The dose intensity (mg/m^2/2 weeks) for each FOLFIRI drug is defined as:

Cumulative dose (mg/m^2) / (Treatment duration in weeks/2)

13.1.7. RELATIVE DOSE INTENSITY (%)

The relative dose intensity for Sym004 and all FOLFIRI drugs is defined as:

(Dose intensity (mg/kg/2 weeks) / Planned dose intensity (mg/kg/2 weeks) on Day 1) * 100

The relative dose intensity will be summarized using the following categories:

>110%

>100% - 110%

>90% - 100%

>80% - 90%

>70% - 80%

>60% - 70%

<= 60%

13.1.8. NUMBER OF DOSE REDUCTIONS

The number of dose reduction will only be derived for Sym004 and presented in listings. A subject will be identified as having a dose reduction if the question 'Was the treatment prescribed at a reduced dose' is ticked 'Yes' on the eCRF Sym004 administration details page and the subject received at least one dose of this newly prescribed dose. The reason for dose reduction is recorded on this page also, as either "Adverse event", "Infusion related reaction" or "Other".

The number of dose reductions per subject will by calculated as shown in the table below (the numbers in the cells are the number of dose reductions):

Received at least one dose of		*Subjects randomized to 9 mg/kg*	*Subjects randomized to 12 mg/kg*
9 mg/kg		*na*	*1*
6 mg/kg		*1*	*2*
4.5 mg/kg		*2*	*3*
3 mg/kg		*3*	*4*
1.5 mg/kg		*4*	*5*

13.1.9. NUMBER OF DOSE INTERRUPTIONS

The number of dose of interruptions will only be derived for Sym004 and presented in listings. The number of dose interruptions per subject will be derived as the number of times the question 'Was infusion interrupted?' is ticked 'Yes'.

14. ENDPOINT EVALUATION

No formal analyses are planned.

14.1. PRIMARY ENDPOINT ANALYSES

The primary endpoint is the occurrence of DLTs for each of the Sym004 dose levels given in combination with FOLFIRI. Only DLTs that occurred during Cycle 1 of trial treatment (i.e. minimum 2 infusions of Sym004 in combination with FOLFIRI [full dose]) will be summarized.

The following information relating to DLTs as per investigator opinion will be presented for the MTD analysis set:

1. Number (%) of Subjects with who experienced a DLT.
2. Number (%) of Subjects with DLTs according to SOC and PT.

Percentages here will be based on number of subjects in each of the Sym004 dose levels given in combination with a FOLFIRI regiment.

14.2. SECONDARY ENDPOINT ANALYSES

All secondary endpoints are safety endpoints, and therefore these are detailed in Section 15 of this SAP.

14.3. OTHER ENDPOINT ANALYSES

Tumor, sum of the longest diameter (SOLD) and disease assessment data will be presented in listings only.

15. SAFETY OUTCOMES

Safety and tolerability of trial treatment will be assessed by the examination of AEs, laboratory data, ECGs and vital signs. No formal statistical comparison will be made between treatment arms and some safety summaries will be presented using descriptive statistics.

All listings and summaries of safety data will be based on the FAS.

15.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 18 or higher.

Treatment emergent adverse events (TEAEs) are defined as AEs that started on or after the first dose of trial treatment and prior to the last date of trial treatment + 28 days (inclusive). If an AE started on the same date as the first administration of Sym004 and FOLFIRI, then the timing related to trial treatment as recorded on the adverse events page of the eCRF will be taken into account when determining treatment emergence.

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 table for number of subjects within each of the categories described in the sub-sections 15.1.1-15.1.9 below, will be provided as specified in the templates. In addition to the categories described in the subsections below, the number of subjects with at least one serious TEAE related to Sym004 only and the number of subjects who experience at least one TEAE of hypomagnesaemia , will be presented in the overall AE summary table.

Listings will include TEAEs and Non-TEAEs.

15.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by worst grade (maximum severity) and relationship to each trial treatment. A summary of treatment related TEAES by worst grade >= 3 will be presented also.

15.1.1.1. Severity

Severity is classified according to NCI-CTCAE criteria V4.03 (Grade 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Life-threatening or disabling), 5 (Death related AE)). If a subject reports a TEAE more than once within that SOC/ PT,

the AE with the worst grade (maximum severity) will be used in the corresponding summaries. Missing grades are not to be imputed.

15.1.1.2. Relationship to Trial treatment

Relationship, as indicated by the Investigator, is classed as "Related" or "Unrelated". TEAEs with a missing relationship to a trial treatment will be regarded as related to that particular trial treatment. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to trial treatment will be used in the corresponding relationship summaries.

15.1.2. TEAEs Leading to Dose Reduction of Trial Treatment

TEAEs leading to dose reduction of trial treatment are those events with an action taken with trial treatment of "Dose Reduced". These TEAEs will be listed only.

15.1.3. TEAEs Leading to Interruption of Trial Treatment

TEAEs leading to an interruption of trial treatment are those events with an action taken with trial treatment of "Drug Interrupted". These TEAEs will be listed only.

15.1.4. TEAEs Leading to Trial Treatment Withdrawal

TEAEs leading to trial treatment withdrawal are those events with an action taken with trial treatment of "Drug Withdrawn". These TEAEs will be listed only.

15.1.5. TEAEs Leading to Trial Termination

TEAEs leading to trial termination are those events with an action taken of "Led to study termination". These TEAEs will be listed only.

15.1.6. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF. A summary of serious TEAEs by SOC and PT will be prepared.

15.1.7. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the (e)CRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

15.1.8. INFUSION RELATED REACTIONS (IRRS)

Infusion related reactions (IRRS) are those events which have an answer of "yes" to the question, "Is this event an infusion related reaction?" on the Adverse Events page of the (e)CRF. These IRRs will be listed only.

15.1.9. DERMATOLOGIC TOXICITIES

Dermatologic toxicities include any AE terms as described in the "Dermatologic Toxicity" sections in the 2015 package inserts of cetuximab, panitumumab, or necitumumab, as well as AE terms under infectious sequelae in cetuximab package insert unless all AEs with a specific preferred term are unrelated. AEs with reported/preferred term of "Skin toxicity" will be reviewed and determine on a case-by-case basis. Symphogen will specify the AE terms that are to be classified as a dermatologic toxicity in a spreadsheet and provide this to [redacted] Biostatistics.

Investigator responses to the question "Is this adverse event skin related?" will be presented in the data listing but not used in the dermatologic toxicities classification to avoid subjectivity and inconsistency.

15.1.10. NON-SERIOUS TEAES WITH A FREQUENCY OF >= 5%

TEAEs that are non-serious and have a frequency, in any of the treatment arms of >= 5%, will be summarized separately by SOC and PT.

15.2. DEATHS

The number of deaths and primary reason for death, for all deaths and deaths within 30 days from the last dose of trial treatment will be summarized based on the Death eCRF-page for the FAS. In addition a listing of deaths including date of informed consent, dates of first and last trial treatment administration, the number of days since last administration of trial treatment, primary reason for death and whether an autopsy was performed will be provided.

15.3. LABORATORY EVALUATIONS

Hematology, serum chemistry, coagulation, urinalysis and tumor antigen biomarker data will be included in listings.

NCI-CTCAE grades will be calculated for hematology, serum chemistry, coagulation and urinalysis parameters included in Version 4.03 of the criteria. These grades will be shown in the data listings only.

Laboratory values that are outside the normal range will be presented as a separate listing.

15.4. ECG EVALUATIONS

All ECG data will be displayed in listings only.

15.5. VITAL SIGNS

All vital signs data will be displayed in listings only.

15.6. OTHER SAFETY ASSESSMENTS

15.6.1. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS (ECOG PS)

Eastern Cooperative Oncology Group (ECOG) PS is assessed on day 1 of each treatment cycle (28 ± 2 days) and prior to Sym004 administration.

All ECOG PS data will be listed for the FAS.

15.6.2. PROTOCOL DEVIATIONS

Protocol deviations collected in the [redacted] clinical trial management system (CTMS) will be presented in a listing for the FAS.

16. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not presented are:

- Pregnancy test
- Skin Examination (Yes/No and Date)
- Skin Rash
- Tumour biopsy sample dates (collect at screening only)

These domains and/or variables will not be summarized or presented, but will be available in the clinical trial database and SDTM datasets

17. REFERENCES

Not Applicable

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

[redacted] OUTPUT CONVENTIONS

Outputs will be presented as per the format/layout shown in the shells.

DATES & TIMES

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

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

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

Treatment Group	For Tables and Graphs	For Listings
Sym004 12 mg/kg in combination with FOLFIRI	Sym004 12 mg/kg + FOLFIRI	Sym004 12 mg/kg + FOLFIRI
Sym004 9 mg/kg in combination with FOLFIRI	Sym004 9 mg/kg + FOLFIRI	Sym004 9 mg/kg + FOLFIRI

LISTINGS

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

- Treatment group,
- Subject ID,
- date (where applicable),

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 < trial med start date, then not TEAE If start date >= trial med start date/ and <= trial med end date +28 days, then TEAE
	Partial	If start date < trial med start date, then not TEAE If start date >= trial med start date and <= trial med end date +28 days, then TEAE
	Missing	If start date < trial med start date, then not TEAE If start date >= trial med start date and <= trial med end date +28 days, then TEAE
Partial, but known components show that it cannot be on or after trial med start date.	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after trial med start date.	Known	If stop date < trial med start date, then not TEAE If stop date >= trial med start date and <= trial med end date +28 days, 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 < trial med start date, then not TEAE If stop date >= trial med start date and <= trial med end date +28 days, then TEAE

START DATE	STOP DATE	ACTION
	Missing	Assumed TEAE
Missing	Known	If stop date < trial med start date, then not TEAE If stop date >= trial med start date and <= trial med end date +28 days, 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 < trial med start date, then not TEAE If stop date >= trial med start date and <= trial med end date +28 days, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

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

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < trial med start date, assign as prior If stop date >= trial med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < trial med start date, assign as prior If stop date >= trial med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant