NOVARTIS

Clinical Development

INC424/Ruxolitinib/Jakavi®

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An open-label, multi-center, Expanded Treatment Protocol (ETP) of ruxolitinib in patients with Polycythemia Vera who are Hydroxyurea resistant or intolerant and for whom no treatment alternatives are available

RAP Module 3 – Detailed Statistical Methodology

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Version	Date	Changes
First Version	18-Feb-2015	NA
Amendment 1	13-Mar-2018	Table of Contents: 2.5.2 and 2.5.3 are included by changing the heading style from 4 to 3. Section 2.4.1, “Listings will be provided for disposition, informed consent, inclusion/exclusion criteria and the screening logs” was changed to “Listings will be provided for disposition, inclusion/exclusion criteria and the screening logs” since informed consent listing is deleted from TFL shells Amendment 1. Section 2.4.7, “Concomitant medications and significant non-drug therapies after the start of the study treatment and up to 30 days after the last dose date will be summarized by WHO drug class and WHO drug term for the Safety Set” was changed to “Concomitant medications and significant non-drug therapies after the start of the study treatment and up to 30 days after the last dose date will be summarized by ATC code the Safety Set”. In “These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment”, “and continuing after the start of study treatment” was removed. Both sentences are changed to be consistent with Protocol Section 10.3. Sectin 2.8, “three mutually exclusive segments” was changed to “mutually exclusive segments” and “post-treatment period” was changed to “If applicable, post-treatment period” to keep consistent with protocol Section 10.5.3.1. Section 2.8.1, “SAEs adjusted for patient-year exposure, regardless of study drug relationship” was added as the last bullet point as this is newly added in TFL shells Amendment1 Table 14.3.1-1.11: Serious adverse events adjusted for patient-year exposure, regardless of study drug relationship, by primary system organ class, preferred term, maximum grade and treatment group (Safety Set) Section 2.8,2, “Boxplots will be presented for selected hematology and biochemistry parameters over time using Safety set” was changed to “Boxplots will be presented for selected hematology parameters over time using Safety set” since biochemistry parameters are not collected. Section 2.9.1, sample size was changed from 1,500 to 500 to keep consistent with Protocol Amendment 1 Section 10.8.

Table of contents

1 Introduction

1.1 Document content

This RAP module describes the planned statistical methods for all safety and efficacy analyses. It is structured as

- a draft of Section 9.7 (Statistical methods planned in the protocol and determination of sample size).
- a draft of Appendix 16.1.7 (Randomization scheme and codes) of the clinical study report (CSR).
- a draft of Appendix 16.1.9 (Documentation of statistical methods) of the CSR.

It is written in future tense. It will be reviewed and updated (including conversion to past tense) for entry into the clinical study report after the analysis has taken place.

1.2 References

Please refer to the following documents:

- CSR template (Full Clinical Study Report)
- Guidelines for content of Statistical Appendices of the Clinical Study Report

2 CSR Section 9.7 - Statistical methods planned in the protocol and determination of sample size

2.1 CSR Section 9.7.1 Statistical and analytical plans

The statistical analysis of these data will be performed by Novartis personnel in accordance with the data analysis section, Section 10, of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR. SAS version 9.4 will be used in all analyses.

This is a global, single arm, open-label, multi-center trial designed to provide early access and evaluate the safety of ruxolitinib in patients with polycythemia vera who are HU resistant or intolerant and who have no other standard treatment options. Efficacy and patient reported outcomes will also be assessed.

Final analyses will be performed when all patients have been followed for 30 days after they have either prematurely discontinued or been discontinued from the study after completing treatment as per protocol (i.e., until the drug is commercially available for this indication in each participating country).

It is planned that the data from all centers that participate in this trial will be pooled and analyzed. Unless otherwise specified, qualitative data will be described using frequency and percentages, while quantitative data, will be described using descriptive statistics: n, mean, standard deviation, median, minimum, and maximum.

No interim analysis is planned, and the final analysis will be performed after all patients have either completed the study or have been prematurely discontinued from the study.

2.2 Data included in the analysis

All data reported in the database (scheduled, repeat and unscheduled visits) up to the cut-off date will be included in the analyses.

2.3 Analysis sets

The following analysis sets, or populations, will be considered in the data analyses:

Full analysis set (FAS) comprises all patients to whom study treatment has been assigned. Demographics, baseline characteristics, and patient disposition will be presented using the FAS. Furthermore, all efficacy data will be analyzed using the FAS.

The Safety set includes all patients who received at least one dose of study treatment. All safety data will be analyzed using the Safety Set.

2.4 Patients and treatments

2.4.1 Patient disposition

Patient disposition will be summarized using the Full analysis set (FAS).The following will be tabulated:

- Number (%) of patients screened;
- Number (%) of patients enrolled;
- Number (%) of patients, who remained in the trial at the time of data cut-off;
- Number (%) of patients who discontinued the treatment;
- Number (%) of patients with primary reason for end of treatment (based on patient status entered in the 'END OF TREATMENT DISPOSITION' page);
- Number (%) of patients with primary reason for end of study (based on completion of 'STUDY EVALUATION COMPLETION' page);

Listings will be provided for disposition, inclusion/exclusion criteria and the screening logs.

2.4.2 Patient demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively using the FAS. Demographic data will include age, age categories (≤60, >60 years), sex, race, ethnicity, weight, and height. Baseline characteristics will include polycythemia vera history including bone marrow biopsy, any prior medication for PV (yes/no), frequency of phlebotomy within 52 weeks prior to screening (1, 2, >2), frequency of patients with thromboembolic events; frequency of patients with pre-malignant or non-melanoma malignant skin lesion (NMSC), HU resistance or intolerance, Hct (<45%, ≥45-≤50%, >50%), WBC counts [(≤10, >10-≤15, >15) $x10^9$/L] and platelet counts at baseline [(<100, ≥100-<400, ≥400-<600, ≥600) x 10^9/L]. Baseline characteristics will also include

splenectomy history due to PV (yes/ no); previously treated with ruxolitinib (yes/no) and patient received ruxolitinib on a clinical trial (yes/no), palpable spleen at screening (yes/no and Eastern Cooperative Oncology Group (ECOG) Performance Status (0, 1, 2).

Listings including smoking history will be provided using FAS.

2.4.3 Protocol deviations

Protocol deviations will be categorized into the following categories per ICH guidelines for CSR-reportable protocol deviations:

- Patient developed study/treatment withdrawal criteria during the study, but was not withdrawn
- Patient received the wrong treatment or incorrect dose
- Patient took an excluded concomitant medication
- Patient did not satisfy the entry criteria

Other important deviations may also be identified and summarized, as necessary, which may impact the scientific value of the trial.

All protocol deviations, including protocol deviations leading to exclusion from any analysis population will be specified in the study Validation and Planning (VAP) document.

The number and percentage of patients in the Full Analysis Set (FAS) with any protocol deviation will be tabulated by the CSR-reportable deviation categories.

All protocol deviations will be listed using FAS.

2.4.4 Antineoplastic therapy

Prior antineoplastic medications for hematologic disease, including PV, will be listed and summarized by preferred terms using the FAS. Duration of prior antineoplastic use will be summarized descriptively. The reason for discontinuation of therapy will also be summarized categorically.

All data related to prior antineoplastic medication will be listed by patients using FAS.

2.4.5 Date of first/last administration of study drug

The start date of study drug is defined as the first date when a non-zero dose of study drug was administered and recorded on the Dosage Administration Record (DAR) eCRF.

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on DAR eCRF.

2.4.6 Extent of exposure

All exposure analyses will be performed on Safety set.

2.4.6.1 Dose intensity and exposure

Definitions of duration of exposure, cumulative dose, average daily dose, actual dose intensity (DI), planned dose intensity (PDI), relative dose intensity (RDI), percentage of days dosed, percentage of days the planned/intended dose was received, as well as intermediate calculations, include:

- Duration of exposure (days): last date of study drug − first date of study drug + 1
- Cumulative dose (mg): total dose of study drug taken by a patient in the study
- Number of dosing days (days): duration of exposure − number of zero dose days
- % Days dosed: 100 x number of dosing days / duration of exposure (days)
- % Days with planned dose: 100 x number of days with planned dose / duration of exposure (days)
- Average daily dose (mg/day): cumulative dose (mg) / number of dosing days (days)
- DI (mg/day): cumulative dose (mg) / duration of exposure (days)
- PDI (mg/day): cumulative planned dose (mg) / duration of exposure (day)
- RDI (%): 100 x DI (mg/day) / PDI (mg/day)

Duration of exposure to study drug, actual cumulative dose, percentage of actual days dosed, percentage of days the planned dose was received, average daily dose, DI and RDI (including categories: <70, 70-90, >90) will be summarized descriptively. In addition, the duration of exposure to study drug will be categorized into time intervals; frequency counts and percentages of patients with exposure in each time interval will be presented.

The derived parameters above will also be listed using Safety set.

2.4.6.2 Dose changes

The number and percentage of patients with dose interruption, reduction and increase will be summarized in the safety set. Dose interruption, reduction and increase are defined as follows:

- **Interruption** is defined as any period of zero total daily dose followed by a non-zero dose.
- **Reduction** is defined as any decrease from the immediate prior non-zero total daily dose. Zero daily doses are not regarded as reductions.
- **Increase** is defined as any increase from the immediate prior non-zero total daily dose.

The number and percentage of patients with dose interruption, reduction and increase, along with reasons for dose change or dose delay will be summarized using Safety set.

The duration of dose changes (days) will be summarized.

Listings of all doses of the study drug along with dose reduction, increase and interruption and reasons for dose change or dose delay will be presented. The derived parameters above will also be listed using Safety set.

2.4.7 Concomitant Medications

Concomitant medications and significant non-drug therapies after the start of the study treatment and up to 30 days after the last dose date will be summarized by ATC code the Safety Set. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment. All concomitant medications and significant non-drug therapies will be listed using Safety set, including any prior medications and significant non-drug therapies starting and ending prior to the start of study treatment.

2.5 Analysis for the primary objective

The primary objective is to evaluate safety data in patients with PV who are hydroxyurea-resistant or -intolerant. The safety set will be used for the analysis of clinical safety data.

2.5.1 Variable

Refer to section 2.8.1.

2.5.2 Statistical hypothesis, model and method of analysis

No statistical hypotheses will be tested in this ETP.

2.5.3 Handling of missing values

Missing/partial dates for prior anti-neoplastic therapy, adverse event, death and dosing record will be imputed. Details imputation rules for missing dates are described in section 4.4.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of the secondary efficacy objectives

2.7.1 Analysis for secondary efficacy objectives

There will be three secondary efficacy endpoints (i-iii). All three endpoints will be summarized descriptively by visit using the FAS. No formal statistical hypotheses will be tested.

i. Change in Hct levels from Baseline to each visit
ii. Change in spleen length from Baseline to each visit
iii. Change in MPN-SAF TSS score from Baseline to each visit

In addition to change from baseline analyses, descriptive statistics by visit in terms of n, mean, median, SD (standard deviation), min and max will also be provided for each of the secondary efficacy variables. Patients with an evaluable baseline score and at least one evaluable post

baseline score during the treatment period will be included in the change from baseline analyses. In addition to the secondary efficacy objectives, number of phlebotomies patients received since their last visit will be summarized by visit.

A listing for each secondary variable will also be provided by patient using FAS.

2.7.1.1 Handling of missing values

No imputation will be applied for missing value.

2.7.2 Patient-reported outcomes

The MPN-SAF TSS will be used to collect data on the patient's disease-related symptoms. No formal statistical test will be performed. The details on the questionnaire as well as the derivation of raw and standardized scores are provided.

Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled based on the instrument manual. No imputation will be applied if the total or subscale scores are missing at a visit.

2.7.3 Biomarkers

Not applicable

2.7.4 Resource utilization

Not applicable

2.8 Safety evaluation

The overall observation period will be divided into mutually exclusive segments:

We have

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. If applicable, post-treatment period: starting at day 31 after last dose of study medication.

2.8.1 Adverse events

Adverse events (AE) will be coded using the MedDRA dictionary that provides the system organ class and preferred term information. CTCAE version 4.03 or higher will be used for reporting AE severity. Treatment-emergent AEs starting on or after the date of first study medication (including AEs that start within 30 days after the discontinuation of the study medication) will be reported.

All AE will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum severity grades, except where otherwise noted. A patient with

multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event.

The following selection of AEs will be listed and summarized separately using Safety set. All these AEs will be summarized for all grades and for grade 3 or 4 side-by-side.

- AEs regardless of study drug related
- AEs suspected to be study drug related
- On-treatment deaths, by primary system organ class and preferred term
- All deaths, by primary system organ class and preferred term
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related
- AEs leading to discontinuation of study drug
- AEs leading to discontinuation of study drug that are suspected to be study drug related
- AEs requiring dose adjustment or study drug interruption
- AEs requiring concomitant medication or non-drug therapy.
- Adverse events which are not serious adverse events, regardless of study drug relationship
- AEs of Specific safety event categories (SEC)
- SAEs adjusted for patient-year exposure, regardless of study drug relationship

Specific safety event categories (SECs) include hematopoietic thrombocytopenia (SMQ), hematopoietic erythropenia (SMQ) and hematopoietic leukopenia (SMQ), hemorrhage (SMQ) and infections (SOC). The naming of SMQs and grouping of preferred terms into corresponding SMQs will be based on the MedDRA version 17.0.or higher. When discussing these SECs in the CSR, the clinical review will be undertaken to ensure the correct interpretation on the analysis results based on SMQs.

The number (%) of patients with specific safety event categories will be summarized using the Safety set. Exposure (patient-years)-adjusted summaries will also be generated for these specific safety event categories.

Deaths which occurred during the study treatment or within 30 days after discontinuation of the study treatment will be listed and Safety set will be used. All deaths will also be listed using Safety set.

Note that patients will be discontinued from the study if dose is interrupted more than 8 weeks due to AE.

2.8.2 Laboratory values

Laboratory values will be converted to SI units and analyzed using NCI CTCAE grades version 4.03 or later.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-visit summaries will be generated separately for hematology:

- shift tables using CTCAE grades to compare baseline to the worst on-treatment value,
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on treatment value
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

Boxplots will be presented for selected hematology over time using Safety set.

Listing for serum and urine pregnancy data will also be provided by patients where available using Safety set.

2.8.3 ECG analysis

Not applicable

2.8.4 Analysis of vital signs

Vital sign assessments will be performed in order to characterize basic body function. The parameters collected are weight (kg), body temperature (°C), sitting systolic and diastolic blood pressure (mmHg).

Clinically notable elevated values are defined as:

- Systolic BP: 160 mmHg and an increase 20 mmHg from baseline
- Diastolic BP: 100 mmHg and an increase 15 mmHg from baseline
- Body temperature: 39.1°C
- Weight: increase from baseline of 10%

Clinically notable below normal values are defined as:

- Systolic BP: 90 mmHg and a decrease 20 mmHg from baseline
- Diastolic BP: 50 mmHg and a decrease 15 mmHg from baseline
- Body temperature: 35°C
- Weight: decrease from baseline of 10%

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for weight, body temperature and sitting diastolic and systolic BP using Safety set.

Vital signs data (weight, body temperature, pulse rate, sitting systolic blood pressure and diastolic blood pressure) will be summarized by visit and Safety set will be used.

Descriptive statistics will be tabulated for baseline and change from baseline at each post-baseline time point for each vital sign measure using Safety set.

Patients with clinically notable vital sign abnormalities will be listed using Safety set. All vital sign assessments will be listed by patient and vital sign parameter. In the listings, clinically notable values will be flagged.

2.9 CSR Section 9.7.2 – Sample size and power considerations

2.9.1 Sample size

The planned sample size of approximately 500 patients was chosen based on the expected accrual rates and the planned duration of the trial. It was not based on any statistical consideration. The actual sample size may differ from this planned number.

2.9.2 Power for analysis of key secondary variables

Not applicable

3 Appendix 16.1.7 Randomization scheme and codes

This section of the RAP document presents a short account of the randomization procedures.

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Appendix 16.1.7: Randomization scheme and codes

Document type: Clinical Study Report - Appendix 16.1.7

3.1 Randomization scheme and codes

Each patient is identified in the study by a Patient Number that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center

No., as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No.

Since this is an open label single arm study, **no** randomization will be needed; however, IRT (Interactive Response Technology) will be used to assign patient numbering. The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Patient Number must not be reused for any other patient and the Patient Number for that individual must not be changed, even if the patient is re-screened. If the patient fails to be dosed, the reason will be entered into the Screening Log page.

3.2 Treatment assignment

Prior to dosing, all patients who fulfill all entry criteria will be assigned to treatment via IRT.

The investigator or his/her delegate will contact the IRT and confirm that the patient fulfills the protocol's entry criteria.

3.3 Treatment blinding

Not applicable

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Appendix 16.1.9: Documentation of statistical methods

Document type: Clinical Study Report - Appendix 16.1.9

4 Appendix 16.1.9 Documentation of statistical methods

The statistical methods used to perform the analyses presented in the clinical study report will be described in Section 9.7. Section 16.1.9 will provide further details of the statistical methods not already provided in Section 9.7.

4.1.1 Study day

Definitions will be applied for all situations:

- Study day for post-randomization event = event date – first dose date + 1
- Study day for pre-randomization event = randomization date - event date

The first day of study drug is study day 1.

If duration is to be reported in weeks, duration in days will be divided by 7, likewise if in months, then duration in days will be divided by 30.4375 and if in years, duration in days will be divided by 365.25.

4.2 Analysis populations

The populations are detailed in Section 9.7.1 of the Clinical Study Report.

4.3 Safety evaluations

The text below gives more detailed instructions and rules needed for programming of the analyses described in Section 2.8.1.

4.3.1 Baseline

The last available assessment before or on the start date of study drug is defined as “baseline” value or “baseline” assessment. If an assessment is planned to be performed prior to the first dose of study drug in the protocol and the assessment is performed on the same day as the first administration of study drug, it will be assumed that it was performed prior to study drug administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline.

Patients who will start treatment and discontinue from the study on the same day may have 2 different sets of data collected on study day 1, one being reported to day 1 visit, the other reported to the end of treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

4.3.2 Multiple assessments within post-baseline visits

For all analyses regarding abnormal assessments or analyses based on worst post-baseline value (vital signs, ECOG performance status), all post-baseline values will be included (scheduled, unscheduled, repeat). All unscheduled and repeat measurements will be included in listings.

4.4 Handling of missing or partial dates

For patients not known to have died prior to the cut-off date:

- All events with start date before or on the cut-off date, and with end date missing or after the cut-off date will be reported as "continuing at the cut-off date".
- This approach applies, in particular, to AEs and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

For patients known to have died prior to or on the cut-off date:

- All events with start date before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed to the death date.
- This approach applies, in particular, to AEs and concomitant medication reports. For these events, the imputed end date will not appear in the listings.

4.4.1 AE date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. Missing date for AE will be handled according to rules specified below. A partial date is simply an incomplete date e.g. DDOCT2001: the days are missing from this DDMMMYYYY date.

Partial AE start dates, if left partial, would ultimately mean the following:

It would not be possible to place the AE in time. Therefore the treatment/dosage at the time of the event would be unknown. So the event could not be reported/summarized appropriately – if at all.

Therefore it is important to perform date imputation to ensure that as many data events are represented as correctly as possible. Of course partial and/or missing dates should also be caught as edit checks and passed back to the investigator for resolution.

There **will be no** attempt to impute the following:

- **Missing** AE start dates
- AE start dates **missing the year**
- Partial/missing AE **end dates**

Table 4-2 AE/treatment date abbreviations

	Day	Month	Year
Partial AE start date	<not used>	AEM	AEY
Treatment start date (TRTSTD)	<not used>	TRTM	TRTY

The following matrix Table 4-3 describes the possible combinations and their associated imputations. In the light grey boxes the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 4-3 AE partial date imputation algorithm

	AEM Missing	AEM < TRTM	AEM = TRTM	AEM > TRTM

AEY Missing	NC Uncertain (D)	NC Uncertain (C)	NC Uncertain (C)	NC Uncertain (C)
AEY < TRTY	Before TRTSTD (B)	Before TRTSTD (C)	Before TRTSTD (B)	Before TRTSTD (A)
AEY = TRTY	Uncertain (E)	Before TRTSTD (A)	Uncertain (A)	After TRTSTD (A)
AEY > TRTY	After TRTSTD (E)	After TRTSTD (A)	After TRTSTD (B)	After TRTSTD (A)

Table 4-4 AE/treatment date relationship and imputation legend

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC/Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

The following Table 4-5 gives a few examples.

Table 4-5 AE imputation example scenarios

Partial AE start date	Treatment start date	Relationship	Imputation calculation	Imputed date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

4.4.2 Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

4.4.3 Incomplete date for anti-neoplastic therapies

Prior therapies

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that for scenario (B) will be replaced to be 'start date of study drug -1'.

End date:

Imputed date = min (start date of study drug, last day of the month), if day is missing; Imputed date = min (start date of study drug, 31DEC), if month and day are missing.
If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Post therapies

Start date

Imputed date = max (last date of study drug + 1, first day of the month), if day is missing;

Imputed date = max (last date of study drug + 1, 01JAN), if day and month are missing.

4.4.4 Incomplete date for death

All dates must be completed with day, month and year.

If the day or month is missing, death will be imputed to the maximum of the last contact date (excluding the date of death) and the following:

- Missing day: 15th of the month and year of death
- Missing day and month: July 1st of the year of death

4.4.5 Incomplete dates for last dose of INC424

Scenario 1

If the last date of study drug is after the cut-off date or is completely missing and there is no end of treatment eCRF page and no death date the patient should be considered to be on-going and use the cutoff date for the analysis as the last dosing date

Scenario 2

If the last date of study drug is completely or partially missing and there is EITHER an end of treatment eCRF page OR a death date available then imputed last dose date:

= 31DECYYYY, if only Year is available and Year < Year of min (EOT visit date, death date)

= Last day of the month, if both Year and Month are available and Year = Year of min (EOT visit date, death date) and Month < the month of min (EOT visit date, death date)

= min (EOT visit date, death date), for all other cases

The imputed date will be compared with start date of study drug.

If the imputed date < start date of study drug, then last date of study drug is set to start date of study drug; otherwise, use the imputed date.