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Clinical Development

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An open label, multi-center imatinib roll-over protocol for patients who have completed a previous Novartis-sponsored imatinib study and are judged by the investigator to benefit from continued imatinib treatment

Statistical Analysis Plan (SAP)

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26-Feb-2020	Prior to DB lock	Creation of amendment 1	Amendment 1 was performed on the basis RAP Module 3 using the most up to date SAP template. Majority of changes are related to protocol amendment 1 where the data collection was increased and the objectives were changed.	Changes were done in all sections to align with the most up to date SAP template.
10-Dec-2025	Prior to DB lock	Creation of amendment 2	Section 2.1: clarified which data is to be included in the analysis Section 2.7 and 5.4: time-windows for analysis of clinical benefit were added. Section 2.3.3: added COVID-19 related PDs listing. Section 5.1.1: added one scenario to cover the imputation of the case when both last exposure end date and EOT date are partial Section 2.8.2: AESIs will not be reported	2.1, 2.7, 5.4, 2.3.3, 2.8.2 and 5.1.1
06-May-2026	Prior to DB lock	Creation of amendment 3	Section 2.3.2: Clarification for patient disposition.	2.3.2
			Section 2.8.1: Clarification for SAE listing to also add the dates for the visit.	2.8.1
			Section 2.3.3: Clarification for PD listing, and the path in NCV for COVID-19 related PD.	2.3.3

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List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dosage Administration Record
eCRF	Electronic Case Report Form
FPFV	First Patient First Visit
ICF	Informed Consent Form
IC	Informed Consent
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PA1	Protocol Amendment 1
PT	Preferred Term
RAP	Report and Analysis Process
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CSTI571A2406, an open label, multi-center imatinib roll-over protocol for patients who have completed a previous Novartis-sponsored imatinib study and are judged by the investigator to benefit from continued imatinib treatment.

The content of this SAP is based on protocol CSTI571A2406 Amendment 5.0. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This is a multi-center, open label, phase IV study to better characterize the long-term safety of imatinib in patients being treated in a current Novartis-sponsored, Oncology GDD&GMA study and who are benefiting from treatment with imatinib.

Eligible patients with an informed consent can start their treatment with imatinib as soon as they enter the study. All patients must report to the study site for their first visit at which time, a 6 month supply of imatinib can be dispensed to the patient. It is recommended that patients return to the study center on a quarterly basis (12wks+/- 1wk), however the method of evaluation, whether on-site or remote is at the discretion of the investigator. The adverse event information will be collected. At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. Patients must return to the study center on a 6 month basis (24 weeks +/- 1 week) for resupply of study medication at which time drug dispensing information will be collected.

Patients will continue to be treated until they are no longer benefiting from imatinib treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue imatinib therapy or the patient dies, whichever comes first.

A patient will reach the end of study when imatinib treatment is permanently discontinued and the end of treatment visit has been performed. All patients must be followed up for safety evaluations for 30 days after the last dose of study treatment. Following this there are no further follow-up study visits.

The study will not include a screening phase as patients will transfer directly from parent studies and will commence treatment with imatinib as soon as they are consented and meet the inclusion criteria of the roll-over protocol.

The total number of patients enrolled depended on the number of patients who enrolled in Novartis-sponsored STI571 studies and met eligibility for the current study.

At the end of the study, a final analysis will be performed. No interim analysis is planned.

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
To evaluate long term safety data (SAEs and AEs)	Frequency and severity of AEs /SAEs
Key secondary	
To evaluate clinical benefit as assessed by the investigator	Proportion of patients with clinical benefit as assessed by the investigator at scheduled visits.

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

The statistical analysis of this study will be performed by Novartis personnel or designated CRO. SAS® version 9.4 or higher will be used in all analyses.

The data from all centers that participate in this trial will be pooled and analyzed.

Protocol amendment 1 (PA1) was approved 07-Apr-2016. In this amendment the scheduled visits were changed from annually to quarterly and the regular data collection was increased.

Additional eCRFs were added to collect data related to

- Study Evaluation Completion
- AEs (based on original protocol only SAE yes/no was collected and all SAEs were only collected on safety database)
- Relevant medical history/current medical conditions
- Pregnancy testing (serum/urine)
- Hepatitis screen (only once at next possible visit)
- Confirmation of Clinical Benefit from Study Treatment

However, at the time the PA1 was approved, 152 out of 155 patients were enrolled; 92% of patients were already on study for more than 2.5 years; 25% of patients had already discontinued the study. Only 3 patients entered after PA1 approval.

Therefore, the additional data is not available for patients who already discontinued when PA1 was implemented in the countries, and many of the still ongoing patients only agreed to PA1 in 2017 at their next scheduled visit. Due to this the data may be underestimated.

All data collected will be included in the analysis, regardless of whether it was captured before or after the IC date for PA1 or whether the PA1 IC was signed. **Qualitative data** will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population as the denominator.

Quantitative data will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, 25^{th} – 75^{th} percentiles, minimum, and maximum). In addition, categorical summaries of some of these variables may be provided using appropriate intervals.

2.1.1 Study drug and study treatment

Study drug and study treatment refers to imatinib.

2.1.2 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 imatinib 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 imatinib was administered and recorded on DAR eCRF.

2.1.3 Study day

Study days will be calculated relative to the start date of imatinib which is Day 1. If the event date is greater than or equal to the first dose date, then study day will be calculated as:

Study Day = Event date - Date of first dose + 1.

Time from events prior of imatinib to the start of imatinib will be calculated as:

Study Day = Event date - Date of first dose.

Note that, the day of first dose is day 1 and the day before the date of first dose is day – 1. Day 0 is not defined.

2.1.4 Definition of months and years

Variables in days will be converted to different time unit using the following conversion rule:

- 1 month = 30.4375 days
- 1 year = 365.25 days

2.1.5 Baseline

There will be no baseline defined for this study.

2.1.6 On-treatment assessment

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

1. ***pre-treatment period***: from day of subject's first informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last administration of study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

Safety summaries include only data from the on-treatment period. All data collected will be included in the analysis, regardless of whether it was captured before or after the IC date for PA1 or whether the PA1 IC was signed. In particular, summary tables for adverse events (AEs)

will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent* AEs**) with no restriction based on the timing of collection relative to the PA1 IC date. A separate summary for death including on treatment and post treatment deaths will be provided.

All safety data will be listed and those collected during the post-treatment period will be flagged.

2.1.7 Last assessment date

The last assessment date will be derived for all patients using the latest date among the following:

- Dates of assessment of clinical benefit
- Laboratory dates (Hepatitis screen, pregnancy test (serum/urine))
- Start/End dates from drug administration record
- End of treatment date from end of treatment page
- Start/End dates of AE
- Visit date from SAE information page
- Date of informed consent

2.2 Analysis sets

The **Safety Set** includes all patients who received at least one dose of study medication after enrolling into the roll-over protocol.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Baseline demographics and parent study characteristics

Age, gender, women of childbearing potential (WOCBP), as well as data related to patients' parent studies will be summarized descriptively. All data will also be listed.

All available data related to relevant medical history/current medical conditions will be listed. Medical history/current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The latest MedDRA version available at the time of reporting will be used.

2.3.2 Patient disposition

Patient disposition will be summarized by the number of patients ongoing at the time of analysis and the number of patients who discontinue imatinib along with the reason for discontinuation according to the data recorded on the end of treatment CRF panel. A listing of end of treatment and study evaluation completion data will be provided. For records where the reason for study evaluation completion is death, the date of death will be included; otherwise, the study completion date will be left blank, as it is not captured in the source dataset.

2.3.3 Protocol deviation

Protocol deviation data will be summarized and listed. In addition, patients with any COVID-19 related protocol deviation will be summarized and listed. The COVID-19 related protocol deviation data can be obtained in the NCV from the following folder: Site Management/ Site Management/ Protocol Deviations.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

All study treatment data will be listed.

Duration of exposure will be summarized using the following definition:

- **Duration of exposure (in days)** = (date of last dose – date of first dose) + 1 day

Duration of exposure to study drug 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 Dose administration data along with derived parameters will be listed using Safety Set.

2.4.2 Prior, concomitant and post therapies

No prior, concomitant or post therapy information is collected for this study

2.5 Analysis of the primary objective

The primary objective is to evaluate long term safety as assessed by the occurrence of AEs/SAEs.

2.5.1 Primary endpoint

The assessment of safety will be based mainly on the frequency and severity of AEs and SAEs. Further information is provided in section 2.8.1.

2.5.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested.

2.5.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.5.4 Supportive analyses

No supportive analysis will be performed.

2.6 Analysis of the key secondary objective

The key secondary objective of the study was to evaluate clinical benefit as assessed by the investigator.

2.6.1 Key secondary endpoint

The proportion of patients with clinical benefit as assessed by the investigator will be summarized by periods of 1 year. The following general rule will be applied: If more than one assessment is done during that period, the last assessment performed will be used. The definition of time windows for the analysis of clinical benefit is provided in the Section 5.4.

2.6.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested.

2.7 Analysis of secondary efficacy objective(s)

No other secondary efficacy objectives were analyzed.

2.8 Safety analyses

Safety analyses will be performed on Safety Set. The assessment of safety will be based mainly on the frequency of AEs and SAEs.

2.8.1 Adverse events (AEs)

The regular collection of AEs in the database only started with protocol amendment version 1.0. Based on the original protocol only information if SAE (yes/no) occurred since previous visit was collected, further information related to the SAEs were collected only in the safety database.

The number of patients with SAE will be calculated based on the SAE information (yes/no) collected at each visit from start of study. As the CRF captures whether an SAE occurred since the previous visit, rather than the exact event date, the SAE listing will not include specific SAE dates but will instead report the corresponding visit dates (as recorded in the VIS panel).

In addition, the data collected in the AE panel will be analyzed. AEs will be summarized based on treatment-emergency. AEs will be deemed treatment-emergent if they start or worsen from day of first dose of imatinib to 30 days after last dose of imatinib. All AEs will be listed regardless of the onset date and those collected during the post-treatment period will be flagged.

Based on the data collection of AEs, the number of events will be underestimated.

The incidence of adverse events will be summarized by system organ class and/or preferred term, severity based on CTCAE grades, relation to study treatment and SAEs.

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology using the latest available MedDRA version at the time of the analyses and the information of MedDRA version will be specified in the footnote of relevant outputs.

For the legal requirements of ClinicalTrials.gov and EudraCT, two tables on treatment-emergent AEs which are not serious adverse events with an incidence greater than 5% and treatment-emergent SAEs and SAEs suspected to be related to imatinib has to be provided by

system organ class and preferred term using the safety set. In addition to the number of patients affected, those tables will also report the number of occurrences of AEs/SAEs.

The rule for the calculation of the number of occurrences that is provided in the summary of serious and non-serious adverse events required for the legal requirements of ClinicalTrials.gov and EudraCT is the following:

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence of SAE, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to imatinib and SAEs irrespective of study treatment relationship will also be provided by SOC and PT. Due to the fact that the regular AE data collection only started with IC date for PA1, the table related to SAE will be produced directly from the safety database and only the table related to non-serious AEs will be programmed using the data from the clinical database.

2.8.2 Adverse Events of Special Interest

Adverse event of special interest (AESI) will not be reported for this study since Glivec safety profile is well known.

2.8.3 Deaths

Deaths occurring on-treatment (i.e. within 30 days after discontinuation of imatinib) as well as all deaths will be summarized and listed.

2.8.4 Laboratory data

Data collected for hepatitis screen (hepatitis B surface antigen (HBs Ag) and antibodies to hepatitis B core antigen (HBc Ab / anti HBc) as well as data for serum and/or urine pregnancy test will be listed.

2.8.5 Other safety data

No other safety data is collected.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

No interim analysis is planned for this study.

3 Sample size calculation

There was no sample size calculation for this study. All consented patients who meet all the inclusion criteria and none of the exclusion criteria are eligible to receive imatinib.

4 Change to protocol specified analyses

The secondary objective "To evaluate clinical benefit as assessed by the investigator at scheduled visits" would require to evaluate the proportion of patients with clinical benefit by periods of 3 months. Taken into account that the study duration and that the collection of data related to clinical benefit was only implemented 2 years after FPFV this table would become huge without given useful information. Thereafter the proportion of patients with clinical benefit will be summarized by periods of 1 year.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation is applied to missing/partial start date.

For patient who discontinued study treatment, the date of last administration of study treatment dose is defined as the date of the last non-zero dose of the study drug treatment reported in the DAR CRF page.

The following notation will be used for the imputation of the missing/partial dose end date:

	Day	**Month**	**Year**
Missing/partial dose end date	Not used	MON	YYYY
EOT completion date	Not used	EOTM	EOTY

The following rules should be used for the imputation of the dose end date for a given study treatment component:

Table 5-1 Imputation of dose end dates

	Dose end date		
	Missing	**Partial Date**	
		Day and month are missing	**Day is missing**
No EOT page and no death date	The patient should be treated as on-going and the LPLV date should be used as the dose end date		
EOT completion date is partial			
a) EOT day and month are missing	Set to the earliest of (the latest visit/assessment date*, 31DEC EOTY)	Set to the earliest of (the latest visit/assessment date*, 31DEC YYYY)	Set to the earliest of (the latest visit/assessment date*, last day of the month MON)
b) EOT day is missing	Set to the earliest of (the latest visit/assessment date*, last day of the month EOTM)	Set to the earliest of (the latest visit/assessment date*, 31DEC YYYY, last day of the month EOTM)	Set to the earliest of (the latest visit/assessment date*, last day of the month MON, last day of the month EOTM)
EOT completion date is complete	Set to EOT date		
a) YYYY<EOTY		Set to 31DEC YYYY	Set to last day of the month MON
b) YYYY=EOTY		Set to EOT date	If month < the month of EOT date (EOTM) then set to last day of the month MON. If month = the month of EOT date (EOTM) then set to EOT date.

* as defined in section 2.1.7

After imputation, the imputed date will be compared with the start date of study treatment. If the imputed date is < start date of study treatment then the start date of study treatment will be used.

If start date is missing then end date should not be imputed.

5.1.2 AE date imputation

Every effort will be made to get the missing information on partial dates. However, despite best efforts, some partial dates might still exist in the database. They will be listed as is. If AE end date is available or imputed and the imputed AE start date is later than the AE end date, then imputed AE start date should be set to the AE end date. If needed in a calculation (e.g. duration), the standard Novartis Oncology imputation rules will be used:

Table 5-2 Imputation of start dates (Adverse events)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then set to the min(informed consent, earliest visit date) e.g., earliest date from the visit dataset

day	• If available month and year = month and year of study treatment start date then set to the study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

5.1.3 Incomplete date for death

All dates must be completed with day, month and year. The following imputation will only take place when despite best efforts these cases could not be resolved during data cleaning:

Table 5-3 Imputation of death date

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

Missing Element	Rule
day, month	• If available year, then impute to maximum (last assessment date*, 01JULYYYY)
day	• If available month and year, then impute to maximum (last assessment date*, 15MONYYYY)

* last assessment date is defined in section 2.1.7

The imputed dates will only be used to define if death occurred on-treatment. The death date will be listed as is.

5.2 AEs coding/grading

AEs will be coded using the latest MedDRA version available at time of database lock while National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 will be used for reporting AE severity.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

CTCAE grade 5 (death) will not be used in this study; rather, this death information will be collected on the EOT or SEC eCRF page.

5.3 Statistical models

5.3.1 Primary analysis

Not applicable.

5.3.2 Key secondary analysis

Not applicable.

5.4 Definition of time-windows for analysis of clinical benefit

For clinical benefit, time windows will be used to identify data to be considered for the specific analysis at a specific time point. The time windows are defined so that there are no gaps between the planned assessments, i.e. every assessment including additional unscheduled assessments would be assigned to one specific time point. If there is more than one assessment within the time window, the last available assessment in that time window will be used. Time windows are defined based on date of first study drug intake (= Study Day 1). Table 5-4 shows the time windows for the analyses of clinical benefit.

Table 5-4 Time windows for analyses of clinical benefit

Planned assessment	Time window
Week 24 (Day 168)	Day 2 to Day 251

Planned assessment	Time window
Week 48 (Day 336)	Day 252 to Day 419
Week 72 (Day 504)	Day 420 to Day 587
Week 96 (Day 672)	Day 588 to Day 755
Year 3 (Day 1008)	Day 756 to Day 1175
Year xx (Day xx*7*48)	Day ((xx*48 - 24) * 7) to Day ((xx*48 + 24) * 7-1)

xx = Every year until data is available

6 Reference

Not applicable.