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Clinical Development

TMT212A/Trametinib

CTMT212A2X01B (MEK114375) / NCT01376310

A Rollover Study to Provide Continued Treatment with Trametinib to Subjects with Solid Tumors or Leukemia

Statistical Analysis Plan (SAP)

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Table of contents

List of abbreviations

AE	Adverse Event
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SOC	System Organ Class

Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CTMT212A2X01B, a multi-center, non-randomized, open-label, phase II, rollover study conducted in subjects with solid tumors or leukemia who have previously participated in a Trametinib study (parent study) and who are clinically benefitting from continued treatment and have an acceptable safety profile with Trametinib.

The content of this SAP is based on protocol CTMT212A2X01B (MEK114375) amendment 7. All decisions regarding final analyses, as defined in the SAP document, have been made prior to database lock.

1.1 Study design

This Phase II, multicenter, non-randomized, open-label, rollover study is designed to provide continued access to Trametinib to subjects with solid tumors or leukemia who have previously participated in a Trametinib study (parent study) and who are clinically benefitting from continued treatment and have an acceptable safety profile with Trametinib. Subjects will be enrolled into the appropriate cohort based upon the treatment received in their parent study. Enrollment into this study will be dependent upon the site's agreement to participate in this study. It is estimated that approximately 250 subjects will be enrolled in this study. Subjects may continue treatment in the rollover study until no longer clinically benefitting, unacceptable toxicity, withdrawal of consent, have access to local commercial supply of Trametinib or the study is terminated early.

Cohort A will consist of subjects who have completed < 24 weeks of treatment with Trametinib monotherapy during their participation in the parent study.

Cohort B will consist of subjects who have completed $\geq$ 24 weeks of treatment with Trametinib (either as monotherapy or combination therapy with an approved anti-cancer agent) during their participation in the parent study.

The study will consist of a transition visit, a continuous dosing treatment period, and a final study visit. Safety assessments will be performed throughout the study, including physical examinations, vital sign measurements (blood pressure, pulse rate, respiratory rate and temperature), 12-lead electrocardiograms (ECGs), echocardiograms (ECHOs)/MUGA scan, clinical laboratory assessments, and monitoring of AEs. Additional safety assessments may be necessary for subjects on a combination treatment. Assessment of clinical activity will be performed using local standard of care imaging practices and the appropriate assessment criteria (e.g., Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) as determined by the investigator to determine continued study participation and treatment with trametinib. Only subjects who are demonstrating clinical benefit as determined by the investigator as well as an acceptable safety profile will be allowed to continue treatment on study and will

continue treatment until no longer receiving clinical benefit, unacceptable toxicity, withdrawal of consent, or commercial supply of trametinib becomes available to the subject.

This statistical analysis plan (SAP) details the planned analyses required for a clinical study report.

1.2 Study objectives and endpoints

The primary objective of this study is to provide continuing treatment with trametinib either as monotherapy or as part of a combination regimen for subjects with solid tumors or leukemia who have previously participated in a trametinib study and who continue to receive clinical benefit as well as have an acceptable safety profile with trametinib. There are no formal endpoints for this study.

2 Statistical methods

2.1 Data analysis general information

The tables, figures and listings will be generated by a designated CRO. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The final analysis will take place after the last subject, last visit has occurred. It is anticipated that this trial will remain open until local commercial supply of trametinib becomes available or early termination of the study.

General analysis conventions

Pooling of center: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small size of centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) 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 or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, study drug refer to trametinib.

Study treatment refers to trametinib, trametinib + an approved anti-cancer agent.

The study treatment component refers to trametinib or an approved anti-cancer agent.

Treatment

For presentation in the outputs, the following treatment descriptors will be used on all applicable summaries, figures, and listings:

- Cohort A,
- Cohort B.

Date of first/last administration of study drug

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug was administered and recorded on the Study Treatment Exposure (ST EXPOSURE) eCRF. For simplicity, the date of first administration of study drug will also be referred as start date of study drug.

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 ST EXPOSURE eCRF.

Date of first/last administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment was administered and recorded on the ST EXPOSURE eCRF. For example, if the 1st dose of study drug A is administered on 04JAN2010, and the 1st dose of its combination partner, drug B, is administered on 03JAN2010, the date of the first administration of study treatment is on 03JAN2010). For the sake of simplicity, the date of the first administration of study treatment will also be referred as the ***start of study treatment***.

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment was administered and recorded on the Study Treatment Exposure eCRF . For example, if the last dose of Trametinib is administered on 15APR2010, and the last dose of a combination partner is administered on 17MAY2010, the date of last administration of study treatment is then on 17MAY2010.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

Baseline is defined as the most recent non-missing value prior to the first dose of study treatment.

On-treatment assessment/event and observation periods

Adverse events, serious adverse events, death will be assigned to the treatment periods defined below. Flag variables indicating the treatment period will be added to these datasets.
On-treatment is defined as the time from first dose of study treatment on this trial until the earliest of 30 days after the last dose of study treatment. If an event occurs on the same date as the first dose of study treatment on this trial, then the event will be considered as occurring during the on-treatment period.
Post-treatment is defined as any time beyond the on-treatment period.

If dates are incomplete in a way that clear assignment to on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period, the so-called ***treatment-emergent*** AEs.

However, safety data per this analysis plan (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

Windows for multiple assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation).

2.2 Analysis sets

Safety

The Safety Set is the primary population of interest in this trial which includes all subjects who received at least one dose of study treatment after enrolling into the rollover protocol.

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis data sets. The date on which a subject withdraws full consent is recorded in the eCRF.

2.3 Subject disposition, demographics and other baseline characteristics

The Safety Set will be used for all baseline and demographic summaries and listings unless otherwise specified.

Basic demographic and background data

The demographic characteristics (e.g., age, ethnicity, sex, height, and body weight) will be summarized and listed. Age will be summarized both as a continuous variable and categorized as < 65 and ≥ 65 years.

Subject disposition

Subject disposition will be summarized using the Safety set. The following will be tabulated:

- Number (%) of subjects, who remained in the trial at the time of data cut-off or final data base lock;
- Number (%) of subjects who discontinued the treatment;
- Number (%) of subjects with primary reason for end of treatment (based on subject status entered in the 'Study Treatment Discontinuation' page);

Listings will be provided for disposition using the Safety set.

Analysis sets

Safety set is the only analysis set for this study.

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

2.4.1 Study treatment / compliance

Dose administration data will be summarized by cohorts using the Safety Set.

Duration of exposure to study treatment

Exposure summaries will be produced by cohorts. Duration of treatment will be summarized in the number of months. The summary will include daily dose and cumulative dose. In addition, a listing of exposure to trametinib, and other anti-cancer agents taken with trametinib will be produced.

Dose exposure

Not applicable.

Dose reductions, interruptions or permanent discontinuations

Not applicable.

2.4.2 Prior, concomitant and post therapies

Not applicable.

2.5 Analysis of the primary objective

Not a formal endpoint and analysis is planned for the primary objective in this study.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

Not applicable.

2.8 Safety analyses

All safety analyses will be based on the safety set. Summaries will be sorted and displayed by Cohort A, Cohort B.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event.

In AE summaries, the primary system organ class (SOC) will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency.

The following AE summaries will be produced: AEs by SOC, PT and maximum grade, summarized by relationship to study drug, seriousness, leading to treatment discontinuation, in addition, a summary of serious adverse events with number of occurrences will be produced.

2.8.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

Adverse events of special interest (AESIs) are defined as AEs within the following categories/groupings of PTs:

- Rash
- Visual changes
- Diarrhea
- Pneumonitis
- LVEF

AESIs are defined at the project level and may be updated based on emergent data to reflect new AESIs of interest at the time of analysis.

For each specified AESI, number and percentage of subjects with at least one event of the AESI occurring during on treatment period will be summarized.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment death and all deaths on-treatment and post-treatment will be produced by system organ class and preferred term. All deaths will be listed, post treatment deaths will be flagged.

Note: The death summaries cover subjects from the Safety Set.

2.8.3 Laboratory data

As a short close-out CSR will be produced, data will not be summarized and listed.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

As a short close-out CSR will be produced, data will not be summarized and listed.

2.8.4.2 Vital signs

As a short close-out CSR will be produced, data will not be summarized and listed.

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 formal interim analysis will be performed.

3 Sample size calculation

There are no statistical hypotheses in this trial therefore there is no sample size calculation. The sample size will be based on the number of subjects completing their parent study of trametinib who are eligible for inclusion in this rollover study. It is estimated that approximately 250 subjects will be enrolled

4 Change to protocol specified analyses

Clinical laboratory data, vital signs, 12-lead ECG, and ECHO/MUGA scan data will not be summarized and listed.

5 Appendix

This will be used later for drafting CSR Appendix 16.1.9.

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for trametinib:

Scenario 1: If the dose end date is completely missing and there is no 'STUDY TREATMENT DISCONTINUATION' page and no death date, the subject is considered as on-going:

The subject should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Subjects with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE date imputation

The following missing dates will not be imputed

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

For other type of missing dates, rules specified in Tables 5-1 to 5-3 will be used

Table 5-1 AE/Treatment Date Abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 5-2 describes the possible combinations and their associated imputations. The upper text indicates the imputation (NC, A, B, C etc.) and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 Imputation algorithm

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

The legend to the above table is shown in Table 5-3.

Table 5-3 Imputation algorithm legends

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

Few examples are shown in Table 5-4.

Table 5-4 Example scenarios

Partial AE start date	Treatment start date	Relationship with TRTSTD	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

5.1.3 Concomitant medication date imputation

Not applicable.

5.1.3.1 Other imputations

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.

Missing death date

All dates must be completed with day, month and year. For cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then impute max [(1 mmm-yyyy), min(last contact date+1 , cutoff date)].
- If both day and month are missing, then impute max [(1 Jan-yyyy, min (last contact date +1, cutoff date)].

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.00.

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). The CTCAE grade of 5 (death) is not used; rather, 'fatal' is collected as AE outcome and death information is also collected on a separate (e)CRF page.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

Not Applicable.

5.4.2 Key secondary analysis

Not applicable.

5.4.3 Secondary efficacy analysis

Not Applicable.

6 Reference

None.