NOVARTIS

Clinical Development

LBH589 (Panobinostat)

CLBH589B2402B / NCT01802879

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

RAP Module 3 – Detailed Statistical Methodology Amendment 1

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Version	Date	Changes
Version 1.0	24-Mar-2014	Original
Version 1.1	14-June-2016	The following changes have been made under RAP amendment 1: **Section 2 (Statistical methods planned in the protocol and determination of sample size)** The objectives of the study were updated accordingly based on protocol amendment 1 **Section 5.5 (Efficacy evaluation)** Investigator benefit assessment was added **Section 5.6 (Safety evaluation)** AEs summary was added

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Abbreviation

Abbreviation	Detail
AE	Adverse event
BSA	Body surface area
CRF	Case Report/ Record Form
CSR	Clinical study report
DAR	Dose administration record
ECG	12 lead electrocardiogram
PT	Preferred term
RAP	Report and analysis plan
SAE	Serious adverse event
s.a.	Single Agent
VAP	Validation and planning

1 Introduction

1.1 Document content

This Report Analysis Plan (RAP) module describes the planned statistical analyses. A clinical study report (CSR) will be produced at the completion of the trial.

This module is structured as

- A draft of Section 9.7 of the CSR [Statistical methods planned in the protocol and determination of sample size]
- A draft of Appendix 16.1.9 (Documentation of statistical methods).

Appendix 16.1.9 text will contain details of statistical methods and issues that are too long to include in the CSR text.

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 statistical analysis has taken place.

1.2 References

Please refer to the following documents:

- CSR template (Full or Abbreviated Clinical Study Report)
- Master Analysis Plan for LBH589
- Guidelines for content of Statistical Appendices of the Clinical Study Report
- Clinical Study Protocol for study CLBH589B2402B
- Case Report Forms for study CLBH589B2402B

2 Objectives and endpoints

Objectives and related endpoints are described in Table 2-1 below altogether with the planned analysis of collected data.

Table 2-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To evaluate long term safety data (SAEs and AEs)	Frequency and severity of AEs/SAEs	AEs/SAEs from safety database will be reviewed and reported as part of the regular pharmacovigilance activities.
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	Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits.

3 Study design

3.1 Description of study design

This is a multi-center, open-label study to better characterize the long term safety of s.a. oral panobinostat in patients being treated in a current Novartis-sponsored, Oncology OGD&GMA study and who are benefiting from the treatment with s.a. oral panobinostat as determined by the guidelines of the parent protocol (for which the study objectives have been met) and based on the investigator's clinical judgment.

This roll-over study will not include screening period as patients will transfer directly from the parent study and commence with panobinostat as soon as they are consented and meet inclusion criteria of the roll-over protocol. All patients must report to the study site for their first visit and commence study participation. At that time, a quarterly (12 +/- 2 weeks) supply of oral panobinostat will be dispensed to the patient or as per local practice.

Patients must return to the study center on a quarterly (every 12 +/- 2 weeks) basis for resupply of study medication at which time limited drug dispensing information will be collected. Changes in dosing which might occur any time during the study treatment will be documented on the dose administration page.

Patients may return to the study center more frequently at the physicians' discretion as clinically indicated or as per standard of care, however, data from these visits will not be captured in the eCRF, but rather only in the source documents at the study center.

Reported AEs/SAEs, defined as per standard Novartis guidelines, will be collected continuously throughout the study in the safety database.

Patients entering the roll-over protocol should be followed at the investigator's discretion for known and/or clinically notable AEs that occur on panobinostat treatment as described in the current version of the [Investigator Brochure].

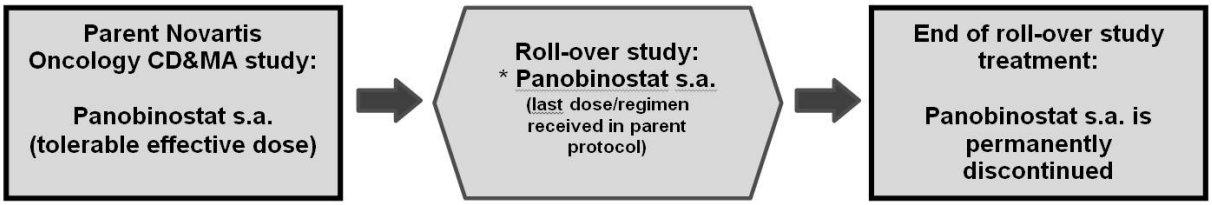
Patients will continue to be treated in the roll-over protocol until they are no longer benefiting from the s.a. oral panobinostat treatment, develop unacceptable toxicities, withdraw consent,

are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue s.a. oral panobinostat therapy, pregnancy occurs or the patient dies, whichever comes first.

A patient will reach the end of the study treatment when s.a. oral panobinostat treatment is permanently discontinued. A 30-day safety follow-up after last dose of study drug should be conducted.

The study is expected to remain open for 5 years or until such time that enrolled patients no longer need treatment with panobinostat, whichever occurs earlier.

Figure 3-1 Basic Study Design



***Note:** The starting dose and schedule of s.a. panobinostat will be the same as the last assigned dose and schedule received in the parent study.

3.2 Timing of interim analyses and design adaptations

No interim analyses are planned.

3.3 Definition of end of the study

End of study is defined as either a 5 year duration or when all patients in this study have permanently discontinued panobinostat treatment and the end of treatment visit plus the 30-day safety follow up have been performed for each patient (and no further follow-up is needed), whichever comes earlier.

3.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in [Section 7.1.3 of the study protocol]. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

4 Population

4.1 Patient population

The study population is constituted of patients with various malignancies who participated in a Novartis-sponsored, Oncology OGD&GMA clinical trial for their specific indication and qualify to transfer to this roll-over protocol.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5 CSR Section 9.7 – Statistical methods planned in the protocol and determination of sample size

5.1 CSR Section 9.7.1 – Statistical and analytical plans

The statistical analysis of this study will be performed by Novartis personnel. SAS® version 9.3 or later version will be used in all analyses.

This study follows an open-label, multi-center design. It is planned that the data from all centers that participate in this protocol will be pooled and utilized.

5.2 Data included in the analysis

Patients will continue to be treated in the roll-over protocol until they are no longer benefiting from the s.a. oral panobinostat 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 s.a. oral panobinostat therapy, pregnancy occurs or the patient dies, whichever comes first.

A patient will reach the end of the study treatment when s.a. oral panobinostat treatment is permanently discontinued. A 30-day safety follow-up after last dose of study drug should be conducted.

The study is expected to remain open for 5 years or until such time that enrolled patients no longer need treatment with panobinostat, whichever occurs earlier.

All data reported in the database will be included in the analyses.

5.3 Analysis populations

The following populations will be considered in the data analysis:

Full Analysis Set (FAS): consists of all patients who received at least one dose of panobinostat after enrolling into the roll-over protocol.

Safety set: consists of all patients who received at least one dose of panobinostat after enrolling into the roll-over protocol.

FAS and safety set are defined the same.

5.4 Patients and treatments

5.4.1 Patient disposition

Patient disposition will be summarized for the FAS by the number of patients who discontinue along with the reason for discontinuation according to the data recorded on the end of treatment CRF panel.

5.4.2 Background and demographic characteristics

Age and gender will be summarized. Patients' parent studies will also be summarized so patients in this study can be linked to their parent studies for more information.

5.4.3 Extent of study drug exposure

5.4.3.1 Drug exposure

All study medication data will be summarized using the safety set.

Duration of exposure will be summarized by dose regimen. For the purposes of analysis, the following rules will be applied:

If the last entry in the dose administration CRF page has a reported end date which is non-missing and before the last known date patient took the study drug from the end of treatment CRF page, the gap between those 2 dates will be filled-in by imputing the dose assigned at the beginning of the study.

This rule will be applied before using any of the following definitions.

Date of first dose is defined as the date of first intake of panobinostat in this study. This will be considered as treatment day 1. There is no study day 0.

Date of last dose is defined as follows:

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

5.4.3.2 Dose changes

Dose administrative records for all patients will be listed. For patients with dose change, reasons will be displayed.

5.4.4 Prior and concomitant therapy

No prior and concomitant therapy information is collected for this study.

5.5 Efficacy evaluation

Proportion of patients with clinical benefit as assessed by the investigator will be listed using FAS.

5.6 Safety evaluation

All safety analyses will be performed based on the safety set.

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

- On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication;
- Post-treatment period: starting at day 30+1 after last dose of study medication.

Adverse events (AEs)

Adverse events (AEs) will be summarized in tables to include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all safety data (including those from the post-treatment periods) will be listed and those collected during the post treatment period are to be flagged. The incidence of treatment emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event, throughout the study and for 30 days after the last dose of the study medication.

Other safety data

No laboratory tests, ECG, and vital signs will be collected.

5.7 Other analysis

5.7.1.1 Interim analysis

There will be no interim analysis for this study.

5.8 CSR Section 9.7.2 – Sample size and power considerations

There will be 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 panobinostat.

Clinical Development

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Appendix 16.1.9: Documentation of statistical methods

Document type: Clinical Study Report - Appendix 16.1.9

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1 Introduction

The statistical methodology used (Section 9.7) will be described and discussed in the main part of the clinical study report. In Appendix 16.1.9, details of the statistical methods and their justification are provided for the statistical reviewers.

The statistical analysis of this study will be performed by Novartis personnel. SAS® version 9.3 (SAS Institute Inc., Cary, NC, USA) will be used for all analyses. All data are part of the Clinical Database and will be exported to SAS® files for analysis.

2 Definitions and general methodology

2.1 Study drug

Study drug and investigational treatment refer to s.a. oral panobinostat (hereof defined as the study treatment).

2.1.1 Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a nonzero dose of study drug was administered and recorded on the dose administration record (DAR) eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred as the *start of study drug*.

2.1.2 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a nonzero dose of study drug was administered and recorded on the end-of-treatment eCRF.

2.2 Study day

Study days will be calculated relative to the first day of panobinostat 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 panobinostat to the start of panobinostat, e.g., time since diagnosis, study days 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, not day 0. If duration is calculated in months, the duration in days will be divided by **1 month = 30.4375 days**.

2.3 Baseline

There will be no baseline defined for this study.

2.4 Partial dates and imputation rules

Partial dates will be listed as partial dates. For computing time/duration, imputation rules will be used to impute the partial dates. All events with a start date on or before the cut-off date and with an end date after the cut-off date will be reported as 'continuing at the cut-off date'. The same rule will be applied to events starting on or before the cut-off date and not having a documented end date.

Sometimes it may be necessary to impute a date to be able to calculate a specific statistic. If the day and month is missing, it will be replaced by July 1; if only the day is missing, it will be replaced by the 15th of that month. For dates prior to treatment start, the treatment start date – 1 will be used if this imputation makes the date later than the treatment start (for panels without standard imputation rules).

2.5 Screening failure

This roll-over study will not include screening period as patients will transfer directly from the parent study and commence with panobinostat as soon as they are consented and meet inclusion criteria of the roll-over protocol. Hence, screen failure is not applicable for this study.

2.6 Protocol deviations

Protocol deviations as specified in the VAP module 3 will also be identified, summarized and listed. The table below shows the project specific assignment of protocol deviation severity codes to each set used in this trial and identifies the deviation codes corresponding to each severity.

Code	Action	Deviation code
5	Exclude from all safety analyses	n/a
8	Exclude from all analysis	E06
49	Report relevant protocol deviation – include in all analyses	E01, E02, E03, E04, E05, E07, E08, E09, E10, C01, C02, O01, O02, O03, S01, S02, S03, S04, W01, W02, W03, W04

	Severity codes		
Analysis set	**5**	**8**	**49**
Safety analysis set	No	No	Yes

Note: '**Yes**' means include in population, '**No**' means exclude from population

2.7 Patient demographics

Demographic data will be summarized by patient. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented.

2.8 Patient disposition

The FAS will be used for the patient disposition summaries. The number and percentage of patients included in the following categories will be provided:

- Enrolled (treated)
- Treatment ongoing
- End of treatment
- Primary reason of end of treatment:
  - Adverse event (s)
  - Subject withdrew consent
  - Lost to follow up
  - Administrative problems
  - Death
  - Disease progression
  - Protocol deviation
  - Pregnancy
  - Study terminated by sponsor

2.9 Study drug exposure

Duration of study treatment exposure [months] will be summarized by dose regimen of panobinostat. In addition, the duration of exposure to study treatment will be categorized into time intervals in months; frequency counts and percentages will be presented for the number of patients in each interval. The safety set will be used for all summaries and listings.

2.9.1 Duration of study drug exposure

Duration of study drug exposure as well as duration of study drug will be summarized by dose regimen.

Duration of study drug exposure

Duration of exposure (days) = [(date of last administration of study drug) – (date of first administration of study drug) + 1 day]

The date of last administration of study drug is taken from the "dosage administration record" CRF page of the study drug. The calculation of 'duration of exposure' does not consider the potential 'lagging effect' from the last dose.

The duration includes the periods of temporary interruption (of the study drug for any reason). 'Date of first administration of study drug' and 'date of last administration of study drug' is defined in Section 2.1.1 and Section 2.1.2 respectively. For patients who did not take any study treatment the duration of exposure is defined as zero days. If patients are still on treatment at the time of data cut-off, the time for duration of exposure will be calculated until the cut-off date.