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Clinical Development

LBH589 (Panobinostat)

Protocol 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

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List of abbreviations

AE	Adverse Event
CRF	Case Report/Record Form
CRF	Case report/record form
CRO	Contract Research Organization
CRO	Contract Research Organization
CSR	Clinical study report
CTCL	Cutaneous T-cell lymphoma
DACis	Deacetylase inhibitors
DDI	Drug-drug interaction
DS&E	Drug Safety and Epidemiology
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End Of Treatment
HDACs	Histone deacetylases
i.v.	Intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IIT	Investigator-Initiated Trial
IRB	Institutional Review Board
LBH589	Panobinostat
o.d.	Omnia die/once a day
OGD&GMA	Oncology Global Development & Global Medical Affairs
p.o.	Per os/by mouth/orally
QOW	Every other week
QW	Every week
s.a.	Single agent
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TIW	Three-times-a-week

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug or treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Parent Study	The original Novartis-sponsored, Oncology Global Development & Global Medical Affairs (OGD&GMA) study, where the patient was first enrolled and received treatment
Patient Number	A unique identifying number assigned to each patient/subject who enrolls in the study
Roll-over study	A roll-over study allows patients from multiple parent studies spanning multiple indications to continue to be treated within one study after the completion of the parent study/ies
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.

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Amendment 01

Amendment rationale

The main purpose of the amendment is to change the primary endpoint to safety to better characterize the long-term safety of the compound. In addition, the protocol has been amended to include the collection of all AEs (including non-serious AEs) and an investigator attestation of continued clinical benefit.

This roll-over study has been opened since 24-Jun-2013 with 9 total patients enrolled and 3 patients ongoing.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes have been implemented:

Section 1.2.1.2: Updated clinical experience section to include the results from a multicentre phase III study in patients with relapsed or relapsed and refractory multiple myeloma and included title for section 1.2.1.2.1 (Clinical pharmacokinetics and pharmacodynamics).

Section 2.1: The purpose of the study has been updated to better characterize the long-term safety of s.a. oral panobinostat in patients who are on s.a. oral panobinostat treatment in a Novartis-sponsored study and are benefitting from the treatment as judged by the investigator.

Section 2.2: The rationale for the study design has been updated to better characterize the long-term safety of s.a. oral panobinostat in patients being treated in a current Novartis-sponsored study and who are benefitting from treatment with s.a. oral panobinostat.

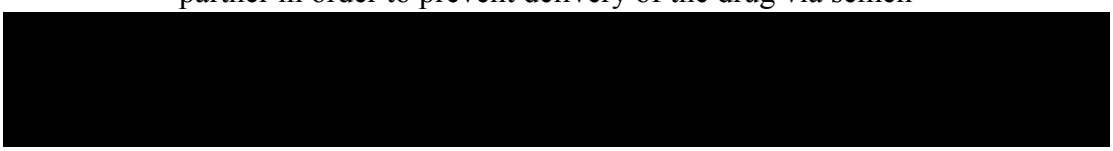
Section 2.4 and 2.5 added per new protocol template.

Section 2.6: Risks and Benefits section added per the new protocol template.

Table 3-1: Updated with revised study objectives. The primary objective is to evaluate long term safety data. The secondary objective is to evaluate clinical benefit as assessed by the investigator.

Section 4.1: Updated to clarify that all adverse events and serious adverse events will be collected continuously throughout the study and to specify that at every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. Updated to include study termination by sponsor as another possible criterion for discontinuation.

Section 5.3 Exclusion criterion #4 updated to clarify highly effective contraception methods and duration of contraception use after stopping study treatment (i.e. 6 months for male participants and 3 months for females). Exclusion criterion #5 added to exclude sexually active males unless they use a condom during intercourse while taking study drug and for 6 months after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen



Previous Section 6.1.5 (Dose escalation guidelines) re-located to section 6.2 per the new template.

Previous Section 6.1.6 (Treatment duration) updated to Section 6.1.5 was modified to specify that at every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

Section 6.2 and 6.2.1 added per the new protocol template.

Section 6.3 added to include information for identifying potential drug-induced liver injury.

Previous Section 6.2 (Concomitant medications) updated to Section 6.4 and Section 6.4.1 added per the new protocol template.

Section 6.4 updated to clarify that no other investigationl therapy should be given to patients and no anticancer agents other than the study medication (panobinostat) should be given to patients during the study. If such agents are required for a patient then the patient must first be withdrawn from the study.

Sections 6.6, 6.6.1 and 6.6.2 added/updated per the new protocol template.

Table 7-1: Updated to include investigator attestation of clinical benefit at every quarterly visit, collection of all adverse events, relevant medical history, monthly at home pregnancy testing for female patients of child bearing potential and the study evaluation completion eCRF page at the end of the 30 day safety follow up.

Section 7.1.3: Updated to specify that the investigator is required to confirm that the patient continues to have clinical benefit at every quarterly visit and may continue receiving study treatment.

Section 7.1.4: Updated to include information on pregnancy and assessment of fertility. Female patients of child bearing potential will now be required to perform monthly home urine pregnancy tests and complete a simple diary with the dates and the outcome of the home urinary test while on study treatment and during safety follow-up (30 days after the final dose of study medication). A pregnancy test (either with serum testing if routinely/locally available or urine pregnancy test) on female patients of child bearing potential is required at the final study visit.

Section 7.1.5, 7.1.6, 7.1.8 and 7.2.3 added per the new protocol template.

Section 7.1.5: Updated to include the completion of the study evaluation completion eCRF page at the end of the 30 day safety follow up.

Section 7.1.5.1: Updated to include study termination by sponsor as another possible criterion for discontinuation.

Section 7.1.7: Updated to include adverse events in safety follow up period.

Section 7.2.1: Updated to include investigator attestation of clinical benefit at every quarterly visit.

Section 8: Updated with new AE/SAE reporting process.

Section 9.1 updated per the new protocol template.

[redacted]

Section 10: Updated statistical analysis section based on revised study objectives.

The protocol summary has also been updated to incorporate all the necessary changes described above.

All instances of Oncology Clinical Development & Medical Affairs (CD&MA) have been updated to Oncology Global Development & Global Medical Affairs (OGD&GMA).

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

Protocol summary:

Protocol number	CLBH589B2402B
Title	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
Brief title	Study to allow access to single agent panobinostat for patients who are on single agent panobinostat treatment in a Novartis-sponsored study and are benefiting from the treatment as judged by the investigator.
Sponsor and Clinical Phase	Novartis, II.
Investigation type	Drug.
Study type	Interventional.
Purpose and rationale	The purpose of this study is to better characterize the long-term safety of single agent panobinostat in patients who are on single agent panobinostat treatment in a Novartis-sponsored, Oncology Global Development & Global Medical Affairs (OGD&GMA) study and are benefiting from the treatment as judged by the investigator.
Primary Objective(s) and Key Secondary Objective	To evaluate long term safety data (SAEs and AEs)
Secondary Objectives	To evaluate clinical benefit as assessed by the investigator
Study design	This is a multi-center, open label study to better characterize the long-term safety of patients being treated in current Novartis-sponsored Oncology OGD&GMA studies and who are benefiting from treatment with single agent panobinostat. There will be no screening period for this study. Eligible patients are to be consented and can start their treatment with panobinostat as soon as they enter the study. All patients must report to the study site for their first visit at which time, a quarterly supply of panobinostat can be dispensed to the patient. Patients must return to the study center on quarterly (every 12 +/- 2 weeks) basis for resupply of study medication at which time drug dispensing and adverse event information will be collected. Patients will continue to be treated until they are no longer benefiting from panobinostat treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol (i.e. pregnancy occurs, etc.), the investigator feels it is no longer in the patient's best interest to continue panobinostat therapy or the patient dies, whichever comes first. A patient will reach the end of study when panobinostat 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 is expected to remain open for 5 years or until such time that enrolled patients no longer need treatment with panobinostat, whichever comes earlier.
Population	Male and female patients, who are currently enrolled in a Novartis-sponsored, Oncology OGD&GMA panobinostat study, are benefiting from treatment with single agent panobinostat and have fulfilled all their requirements in the parent study. All objectives of the parent study must have been reached, and the study must be in the process of being completed & reported.
Inclusion criteria	Patient is currently enrolled in a Novartis-sponsored, Oncology Global Development & Global Medical Affairs study receiving single agent panobinostat and has fulfilled all their requirements in the parent study. Patient is currently benefiting from the treatment with single agent panobinostat, as determined by the investigator. Patient has demonstrated willingness and compliance, as assessed by the investigator, with the parent study protocol requirements.

[redacted]

Exclusion criteria	Patient has been permanently discontinued from panobinostat study treatment in the parent study due to unacceptable toxicity, non-compliance to study procedures, withdrawal of consent or any other reason. Patient has participated in a Novartis sponsored combination trial where panobinostat was dispensed in combination with another study medication and is still receiving combination therapy.
Investigational therapy	Panobinostat 5 mg, 10mg, 15mg and/or 20 mg capsules, dose and dose regimen depending on parent protocol
Efficacy assessments	At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.
Safety assessments	Adverse events and SAEs will be collected continuously moving forward.
Other assessments	Not applicable.
Data analysis	Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits. The assessment of safety will be based mainly on the frequency of AEs and SAEs. As needed, safety information on patients from this protocol will link to the patient identifiers from the parent protocol.
Key words	Panobinostat roll-over study for continued use of panobinostat to patients receiving panobinostat in a Novartis-sponsored Oncology OGD&GMA study which has reached its objectives and who are benefiting from treatment with panobinostat.

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Global changes in the epigenetic landscape are a hallmark of cancer (Jones et al 2007). Recent advancements in the rapidly evolving field of cancer epigenetics have shown extensive reprogramming of every component of the epigenetic machinery in cancer including DNA methylation, histone modifications, nucleosome positioning and non-coding RNAs, specifically microRNA expression (Boumber et al 2011). The reversible nature of epigenetic aberrations has led to the emergence of the promising field of epigenetic therapy, which is already making progress with the recent FDA approval of four epigenetic drugs for cancer treatment: two DNA methyltransferase inhibitors, azacitidine (Vidaza®) and decitabine (Dacogen®), followed by two histone deacetylase inhibitors (DACis), vorinostat (Zolinza®) and romidepsin (Istodax®). So far all four FDA approved epigenetic drugs have shown the greatest efficacy in hematopoietic malignancies, i.e. azacitidine and decitabine in myelodysplastic disorders and leukemia (Issa et al 2006; Kantarjian et al 2006; Issa 2007) and vorinostat and romidepsin in cutaneous T-cell lymphoma (CTCL) (Duvic et al 2007; Grant et al 2010). General features of responses observed with these agents have included the requirement for multiple cycles of therapy, a slow onset of response with some patients experiencing a long-lasting clinical benefit requiring prolonged treatment administration.

Similar observations have been made in clinical trials with other investigational DAC inhibitors, including panobinostat (Prince et al 2009; Duvic et al 2012; Younes et al 2012). In these cases the question has been raised on how to continue treatment of few patients beyond study completion and assure adequate monitoring and proper regulatory reporting of relevant safety information. In order to allow continued access to a given anticancer therapy to patients benefiting from their study treatment, a roll-over study design has been widely used. Currently there are 37 roll-over study protocols posted on clinicaltrials.gov for the treatment of patients with various malignancies (clinicaltrials.gov).

The purpose of this study is to allow continued use of oral panobinostat in patients who are currently receiving single agent (s.a) panobinostat treatment in a Novartis-sponsored, Oncology Global Development & Global Medical Affairs (OGD&GMA) study that has reached its objectives, are not progressing on the current study treatment as defined by the parent protocol and are benefiting from the treatment as judged by the investigator.

This roll-over study is designed to accept patients with various disease origins. Please refer to the parent protocol for the disease background information and rationale for use of panobinostat in their individual indications.

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1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of panobinostat

Panobinostat (LBH589) belongs to a structurally novel cinnamic hydroxamic acid class of compounds and is a pan-inhibitor of Class I, II and IV histone deacetylases (HDACs). HDACs are involved in the deacetylation of histone and non-histone cellular proteins, targeting lysine groups on chromatin and transcription factors and various non-histone proteins such as p53, tubulin, heat shock protein 90 (Hsp90), and retinoblastoma protein (Rb). Panobinostat has shown antitumor activity in preclinical models and in cancer patients and has been formulated as an oral capsule and as a solution for intravenous (i.v.) injection. Both the i.v. and the oral formulations have been investigated in Phase IB/II studies in advanced solid tumors and hematological malignancies.

1.2.1.1 Non-clinical experience

Panobinostat has been developed as an anticancer agent based on its potential to act:

- by exhibiting differential antiproliferative activity against a broad range of solid tumors cell lines and high sensitivity in lymphomas and hematologic malignancies cell lines, including acute myeloid leukemia (AML) and multiple myeloma (MM).
- by inducing consistent tumor growth control in various tumor-bearing xenografted mice and by increasing histone-H3 and -H4 acetylation in excised tumors.
- by showing synergistic or additive anti-tumor effect in combination with other anti-cancer agents such as trastuzumab, docetaxel, bortezomib or standard cytotoxic agents e.g., doxorubicin, fludarabine, Ara-C.

The potent anticancer effects of panobinostat seen in experimental models may result from two distinct mechanisms of action, both related to pan-HDAC inhibition. Panobinostat was shown to affect epigenetic mechanisms of gene expression via inhibition of Class I HDACs, as shown by induction of histone acetylation and consequent induction of cell cycle control genes (i.e. p21) and to inhibit HDAC6 through abrogation of Hsp90 –mediated stabilization of client oncoproteins, resulting in their depletion and in reduced downstream oncogenic signaling (Atadja 2011). Although the pharmacodynamic effects of panobinostat on histone acetylation have been consistently seen in experimental models as well as in cancer patients, histone hyperacetylation does not seem to relate with therapeutic activity. Similar results have been reported for other HDAC inhibitors and thus clinical development of these agents has been broadly approached by targeting various hematologic and non-hematologic malignancies (Atadja 2009, Atadja 2011, Boumber et al 2011).

For the latest information on the pre-clinical pharmacology and toxicology of panobinostat, please refer to the current [Investigator Brochure].

1.2.1.2 Clinical experience

As of 31 December 2011, 35 clinical studies, including clinical pharmacology (CP), Phase I and Phase II trials, as well as two randomized Phase III studies have either been completed or are ongoing. Safety risks associated with panobinostat have been characterized in more than

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2000 patients enrolled in the overall clinical development program. The majority of severe adverse events is hematologic (mainly thrombocytopenia), easily documented with routine hematology tests and manageable with conventional supportive care and dosing modifications. Common non-hematologic toxicities, including gastro-intestinal (GI) toxicity and fatigue, are mild to moderate in severity and generally reversible. They are manageable with dose adjustments. The most common ECG findings include post-baseline increase in frequency of sinus tachycardia, T-waves changes as well as depressed ST segment. They can be readily captured by conventional non-invasive cardiac monitoring (ECGs) and do not appear to be clinically significant. With the intermittent oral dosing schedules (three-times-a-week, weekly or every other week) used in current clinical trials, QTcF above 500 msec is uncommon (6/635 patients, 0.9%) and noted only with the weekly oral dosing regimen. No torsade de pointes has been reported in clinical trials with oral panobinostat.

The efficacy and safety of panobinostat in combination with bortezomib and dexamethasone were evaluated in a randomised, double-blind, placebo-controlled, multicentre phase III study in patients with relapsed or relapsed and refractory multiple myeloma who had received 1-3 prior lines of therapies.

Patients received panobinostat (20 mg taken orally once a day, three times per week, on a 2 weeks on and 1 week off dosing regimen), in combination with bortezomib (1.3 mg/m2 injected intravenously) and dexamethasone (20 mg). Treatment was administered for a maximum of 16 cycles. A total of 768 patients were randomised to either the panobinostat + bortezomib + dexamethasone (n=387) or the placebo + bortezomib + dexamethasone (n=381) arm. Demographics and baseline disease characteristics were balanced and comparable between the study arms.

The median PFS (95% CI) was 12.0 months (10.3, 12.9) and 8.1 months (7.6, 9.2), respectively. Out of the pre-specified subgroup of patients with prior treatment with bortezomib and an immunomodulatory agent (N=193), 76% of patients had received at least two prior regimens. The median PFS (95% CI) was 12.5 months (7.26, 14.03) in the panobinostat + bortezomib + dexamethasone arm and 4.7 months (3.71, 6.05) in the placebo + bortezomib + and dexamethasone arm [HR: 0.47 (0.31, 0.72)].

Regarding safety, the median duration of exposure in the study was 5.0 months. 15.7% of patients were exposed to study treatment for ≥48 weeks. The most common non-haematological adverse reactions were diarrhoea, fatigue, nausea and vomiting. Treatment-emergent haematological toxicities included thrombocytopenia, anaemia, neutropenia and lymphopenia. QTcF >480 and <500 msec was recorded in 1.3% of patients and change from baseline of >60 msec was observed in 0.8% of patients. No patient had an absolute QTcF >500 msec.

1.2.1.2.1 Clinical pharmacokinetics and pharmacodynamics

Single agent oral panobinostat is administered three-times-a-week (TIW) every-week (QW) or every-other-week (QOW). Following oral administration, panobinostat is rapidly absorbed with peak plasma concentrations reached within 1 hour; systemic clearance is 33 L/hour and central volume of distribution 25 liters. Half-life associated with the distribution, initial elimination and terminal elimination phase based on population parameterization are 0.15, 2.3

and 37 hours, respectively. Observed drug accumulation is approximately 1.14 fold with TIW schedule. This is consistent with an effective half-life of 15 hours. Absolute oral bioavailability is 21%.

The extent of binding to human plasma protein is moderate (89.6%) *in vitro* and independent of panobinostat concentration. Panobinostat can be administered without regard to food (Shapiro et al 2012).

Panobinostat is extensively metabolized in patients, with the parent compound accounting for 6-9% of the drug-related exposure in plasma with the remainder accounted for by approximately 40 metabolites. Metabolites formed via the primary metabolic pathways were all inactive for DAC inhibitory activity *in vitro*.

CYP3A4 is the main oxidative metabolizing enzyme of panobinostat with minor involvement of CYP2D6 and CYP2C19. Drug-drug interaction (DDI) studies in cancer patients using standard drug probes have shown a weak interaction between panobinostat and a strong CYP3A inhibitor (ketoconazole) (Hamberg et al 2011) or between panobinostat and a sensitive CYP2D6 substrate (dextromethorphan). In both cases the systemic exposures of panobinostat in the presence of ketoconazole or the systemic exposure of dextromethorphan in the presence of panobinostat increased by 80% and 60%, respectively. Therefore co-administration of a strong CYP3A inhibitor or of a sensitive CYP2D6 substrate with panobinostat is feasible when medically necessary with close monitoring. Based on the results of the ketoconazole DDI study, oxidative metabolism via CYP enzyme is a minor metabolic pathway of panobinostat, suggesting no relevant clinical PK interaction via CYP pathways. Based on *in vitro* and clinical metabolic profile of panobinostat and in-silico prediction, co-administration of panobinostat with a strong CYP3A4 inducer, rifampicin is expected to decrease panobinostat systemic exposure by 70% in patients. Co-administration of panobinostat with strong CYP3A inducers is to be avoided.

For further details, please refer to the current panobinostat [Investigator Brochure].

2 Rationale

2.1 Study rationale and purpose

In various clinical trials with single agent (s.a.) oral panobinostat, it was evident that some patients may benefit from prolonged treatment with this agent well beyond the study objectives have been attained (Prince et al 2009; Duvic et al 2012; Younes et al 2012). Recognizing that it is important to allow these patients to continue their therapy under a controlled, even if less frequent monitoring plan, this multi-center, open-label roll-over protocol has been designed to better characterize the long-term safety of s.a. oral panobinostat in patients being treated in a Novartis-sponsored, Oncology OGD&GMA study who are responding to treatment with this agent.

The purpose of this study is to better characterize the long-term safety of panobinostat in patients who are on s.a. panobinostat treatment in a Novartis-sponsored, Oncology OGD&GMA study that has reached its objectives, who are not progressing on the current study treatment as defined by the parent protocol and are benefiting from this treatment as

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judged by the investigator. Parent studies eligible to participate in the roll-over study will be decided by Novartis. Investigator initiated trials (IITs) will not be included. The objectives of the parent study must have been reached and the parent study must be in the process of being completed and reported.

Patients enrolled in this study will continue to receive s.a. oral panobinostat until one of the following occurs: the patient is no longer benefiting from the treatment (e.g. the underlying disease is progressing), unacceptable toxicity develops, consent is withdrawn, non-compliance with the protocol, the investigator feels it is no longer in the patient's best interest to continue therapy (e.g. pregnancy, etc.), or the patient's death.

2.2 Rationale for the 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, who are benefiting from the treatment with oral panobinostat.

The design of this roll-over study is widely used in cancer clinical programs to allow access to an effective study treatment to those patients who are benefiting from this therapy well beyond trial objectives completion. The study protocol is also designed to gather long-term safety information in cancer patients who are eligible to transfer into this roll-over study. The well-known safety profile of panobinostat supports the rationale for a less frequent visit schedule more adapted to standard of care practice with monitoring focused on adverse events reporting. This will ensure not only adequate supervision of the patients' well-being but also proper regulatory reporting of relevant safety information.

2.3 Rationale for dose and regimen selection

The dose/s and regimen/s provided in this roll-over study protocol are those defined in the parent protocols for each enrolled patient. Therefore, depending on the capsule strength/s used in the parent protocol, s.a. panobinostat will be provided as 5-mg and/or 20-mg hard gelatin capsules. At the time of transition to the roll-over study, the starting dose and regimen of oral panobinostat should be the same as the last assigned dose and regimen that were given in the parent study. Dosing modifications thereafter (following the starting dose) may be done at the discretion of the investigator based upon what is in the patient's best interest.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

2.6 Risks and benefits

Based on the last edition of the IB, the risk/benefit assessment of panobinostat (LBH589) is considered favorable and unchanged. The risks of single agent panobinostat are well characterized by a large safety database and no significant new safety signals have emerged since previous editions of this IB. This assessment serves as a basis for the safety monitoring

of panobinostat tested in combination with other cancer agents in ongoing clinical studies. As appropriate, monitoring of patients is required in the clinical development protocols and no protocol changes have been or are planned to be made. Management of adverse events remains confined to clinical monitoring per protocol and appropriate dose and schedule modifications with supportive care as clinically indicated.

Consistent with the safety profile from the extensive experience with panobinostat single agent studies, the major toxicities associated with the active combination of panobinostat with bortezomib and dexamethasone in MM patients involved the same adverse events noted during single agent treatment. However, the overlapping toxicity, primarily hematologic, GI and constitutional in nature was apparent with respect to frequency and severity due to the combination regimen. Cardiac toxicity was unremarkable. The known toxicities could be predicted and could be effectively managed with established clinical interventions. In the context of the significant clinical benefit panobinostat provides to MM patients with limited treatment options, its tolerability is considered acceptable.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate long term safety data (SAEs and AEs)	Frequency and severity of AEs/SAEs	
Secondary		Refer to Section 10.5.2
To evaluate clinical benefit as assessed by the investigator	Proportion of patients with clinical benefit as assessed by the investigator at scheduled visits	

[redacted]

4 Study design

4.1 Description of study design

This is a multi-center, open-label study to better characterize the long-term safety of s.a. oral panobinostat to in patients being treated in 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, these unscheduled visits will not be captured in the eCRF, but rather only in the source documents at the study center.

All adverse events and serious adverse events will be collected throughout the study.

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].

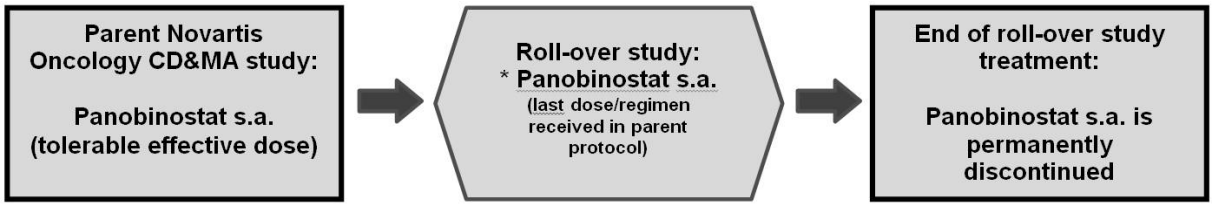
Patients will continue to be treated in the roll-over protocol until they are no longer benefiting from the s.a. oral panobinostat treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue s.a. oral panobinostat therapy, pregnancy occurs or the patient dies, or study is terminated by sponsor, whichever comes first. At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

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.

[redacted]

Figure 4-1 Study design



4.2 Timing of interim analyses and design adaptations

No interim analyses are planned.

4.3 Definition of end of 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.

4.4 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 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.

5 Population

5.1 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.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient is currently enrolled in a Novartis-sponsored, Oncology OGD&GMA study receiving s.a. oral panobinostat and has fulfilled all their requirements in the parent study.
2. Patient is currently benefiting from the treatment with s.a. oral panobinostat as determined by the guidelines of the parent protocol and according to the Investigator's clinical judgment.

[redacted]

3. Patient has demonstrated compliance, as assessed by the investigator, with the parent study protocol requirements.
4. Willingness and ability to comply with scheduled visits, treatment plans and any other study procedures.
5. Written informed consent obtained prior to enrolling into the roll-over study.
    - If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patient has been permanently discontinued from s.a. oral panobinostat study treatment in the parent study due to unacceptable toxicity, withdrawal of consent, non-compliance to study procedures or any other reason (including progression of disease).
2. Patient has participated in a Novartis sponsored combination trial where panobinostat was dispensed in combination with another study medication and is still receiving combination therapy.
3. Patient is pregnant or nursing (lactating) at time of entry into the roll-over protocol. Pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
4. Women of child-bearing potential and male patients with sexual partner(s) of child-bearing potential unwilling to use highly effective methods of contraception during dosing and for a specified duration (6 months for male participants and 3 months for females) after stopping study treatment.

    Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to enrolling). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. Women using hormonal contraceptives should additionally use a barrier method of contraception.

    Note: In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before entering the roll-over protocol.

    - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical

[redacted]

profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

- If a study patient becomes pregnant or suspects being pregnant during the study or within 30 days after the final dose of panobinostat, the Investigator/Study Doctor needs to be informed immediately and ongoing study treatment with panobinostat has to be stopped immediately.

5. Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 6 months after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.

6 Treatment

6.1 Study treatment

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

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Strength	Dosing Regimen
Panobinostat	Capsule for oral use	5 mg, 10mg, 15mg and/or 20 mg depending on parent protocol	Per parent protocol

The dose/s and regimen/s provided in this roll-over study protocol are those defined in the parent protocols for each enrolled patient, hence this may differ for patients enrolling from various studies.

Panobinostat will initially be provided as 5 mg and/or 20 mg hard gelatin capsules, depending on the strength/s used in the parent protocol. If the need arises at a later time, also 10mg and/or 15mg capsules might be used. The investigational treatment is to be stored in a secure locked area while under the responsibility of the investigator. Receipt and dispensing of investigational treatment must be recorded by an authorized person at the investigator's site.

Patients will be instructed to take panobinostat orally with a glass of water, at the last assigned dose and schedule received in the parent protocol, either consistently with food or consistently without food. The capsule should be swallowed as a whole and should not be chewed or crushed. Dietary habits at the time of enrolling in the study from the parent study should be kept as consistent as possible throughout the study.

[redacted]

6.1.2 Ancillary treatments

Not applicable

6.1.3 Rescue medication

Not applicable

6.1.4 Guidelines for continuation of treatment

The starting dose of oral panobinostat should be the same as the last assigned dose and schedule that was given in the parent study. Assigned dose is the dose as designated by investigator and does not include unintended changes or error in dosing in parent protocol.

Dose modification thereafter (following the starting dose) may be done at the discretion of the investigator based upon what is in the patient's best interest.

In case patients do not tolerate the dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. These dose adjustments may be delays in dosing and/or reductions in the dose being administered. Dosing should always be temporarily discontinued if the physician determines it is in the best interest of the patient. All dose modifications should be recorded in the source documents and on the Dosage Administration Record Form.

Patients receiving a reduced dose of panobinostat due to toxicity who are clearly benefiting from panobinostat and whose AE(s) remain grade < or = 1, which the patient believes is/are tolerable may at the discretion of the Investigator after agreement by the Sponsor return to the initial dosage in 5mg/increments. Dose re-escalation should be reviewed on a case basis and requires agreement between Sponsor and Investigator. No more than 2 dose reductions are permitted (i.e. the minimum dose patients may receive is 5 mg/day).

6.1.5 Treatment duration

Patients will continue to be treated until they are no longer benefiting from s.a. oral panobinostat, develop unacceptable toxicities, withdraw consent, are non-compliant with the protocol, the investigator feels it is no longer in the patient's best interest to continue panobinostat therapy (e.g. disease progression, pregnancy, etc.) or the patient dies, whichever comes first. A patient will reach the end of the roll-over study when panobinostat is permanently discontinued. A 30-day safety follow-up should be conducted after the last dose of panobinostat. At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

The study is expected to remain open for 5 years or until such time that enrolled patients no longer need treatment with s.a. oral panobinostat, whichever occurs first. The study can be terminated at any time for any reason by Novartis.

6.1.6 Starting dose rationale

The starting dose of panobinostat should be the same as the last dose that was given in the parent study. After this, the dose of panobinostat is based on the investigator's judgment.

[redacted]

6.2 Dose modifications

For patients who do not tolerate the specified dose, dose adjustments are permitted in order to allow the patient to continue treatment. The following guidelines should be applied.

If a patient requires a dose delay more than 28 days from the intended day of the next scheduled dose, the patient should be considered for discontinuation of treatment. If, however, the patient was clearly benefitting from treatment and the cause of the delay has resolved, the patient may be able to restart treatment after discussion with Novartis. This option should be used with the highest amount of caution keeping the safety of the patient in mind, and evaluating whether or not the benefit outweighs the risk.

6.2.1 Non-Cardiac Toxicity Dose Modifications

Treatment dose and/or schedule modification may be required based on individual tolerability. Clinical judgment on how to continue the treatment should be exercised when a patient experiences adverse drug reactions.

If a dose reduction is required, the dose of panobinostat should be reduced by decrements of 5 mg (i.e. from 20 to 15 mg or from 15 to 10 mg). The dose should not be reduced below 10 mg daily and the same treatment schedule should be maintained.

6.2.2 Thrombocytopenia

If patients experience thrombocytopenia (TCP), panobinostat may need to be temporarily withheld and the subsequent dose may need to be reduced. In patients with Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) grade 3 ($<50x10^9$/L, complicated by bleeding), or grade 4 ($<25x10^9$/L) thrombocytopenia, panobinostat therapy should be withheld and resumed at a reduced dose upon recovery to ≤ grade 2 ($\geq 50x10^9$/L).

Discontinuation of treatment may be considered if thrombocytopenia does not improve despite the treatment modifications described above and/or the patient requires repeated platelet transfusions.

[redacted]

Table 6-2 Thrombocytopenia dose modifications

Thrombocytopenia grade on day of treatment	Modification of panobinostat starting dose	Panobinostat dose on recovery to ≤ grade 2 thrombocytopenia (≥50 x 10^9/L)
Grade 3 with bleeding Platelets <50 x 10^9/L	Omit dose	Resume at reduced dose
Grade 4 Platelets <25 x 10^9/L	Omit dose	Resume at reduced dose

6.2.3 Gastrointestinal toxicity

Gastrointestinal toxicity is very common in patients treated with panobinostat. Patients who experience diarrhea and nausea or vomiting may require temporary dose discontinuation or dose reduction.

Table 6-3 Diarrhea dose modifications

Adverse drug reaction	Grade on day of treatment	Modification of panobinostat starting dose	Panobinostat dose on recovery to ≤ grade 1
Diarrhoea	Grade 2 despite anti-diarrheal medicinal product	Omit dose	Resume at the same dose
	Grade 3 despite anti-diarrheal medicinal product	Omit dose	Resume at reduced dose
	Grade 4 despite anti-diarrheal medicinal product	Discontinue	Discontinue

At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated with anti-diarrheal medication (e.g. loperamide). Prophylactic anti-emetics should be administered at the discretion of the physician and in accordance with local medical practice.

6.2.4 Neutropenia

Neutropenia may require temporary or permanent dose reduction.

Table 6-4 Neutropenia dose modifications

Neutropenia grade on day of treatment	Modification of panobinostat starting dose	Panobinostat dose on recovery to grade 2 neutropenia (<1.5-1.0 x 10^9/L)
Grade 3 neutropenia (<1.0-0.5 x 10^9/L)	Omit dose	Resume at same dose
Grade 4 neutropenia (<0.5 x 10^9/L) or febrile neutropenia (<1.0 x 10^9/L and fever ≥38.5°C)	Omit dose	Resume at reduced dose

[redacted]

In case of grade 3 or 4 neutropenia, physicians should consider the use of growth factors (e.g. G-CSF) according to local guidelines. Discontinuation of treatment may be considered if neutropenia does not improve despite the dose modifications and/or despite the addition of colony stimulating factor therapy according to local medical practice and treatment guidelines, and/or in case of severe secondary infections.

6.2.5 Follow-up for toxicities

Patients who treatment is interrupted or permanently discontinued from study treatment due to an AE or abnormal laboratory value should be followed at least once a week during drug hold and be followed for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. All patients will be followed for AEs and SAEs for 30 days following the last dose of panobinostat.

6.2.6 Dose modification of panobinostat for prolonged QTcF interval

All cardiac events should be treated as per the local standard of care and referred to a cardiologist if clinically indicated. The central and/or local readings of ECGs will use the Fridericia correction for QTc interval assessment: QTcF. Any final decisions concerning panobinostat dose modifications or permanently discontinuing the patient from study treatment due to QTcF prolongation will be based on the assessment performed by the Investigator.

In case of average QTcF > 450 ms pre-dose:

- Assess the quality of the ECG recording and the QT value and repeat if needed
- Do not initiate study treatment
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before initiating study treatment.
- Review concomitant medication use for other causes for QT prolongation, and for drugs with the potential to increase the risk of drug exposure related QT prolongation (e.g concomitant use of strong CYP3A4 inhibitors)
- Within 7 days, repeat triplicate pre-dose ECG if average QTcF > 450 ms, do not initiate study treatment
- If average QTcF ≤ 450 ms, initiate study treatment.

In case of average QTcF > 480 ms, (or average QTcF prolongation >60 ms from baseline) any time after first dose of panobinostat until end of panobinostat treatment:

- Assess the quality of the ECG recording and the QT value and repeat if needed.
- Interrupt panobinostat treatment
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
- Review concomitant medication use for other causes of QT prolongation, and for drugs with the potential to increase the risk of drug exposure related QT prolongation.
- Check study drug dosing schedule and treatment compliance
- Consider more frequent ECG monitoring (e.g. approximately every 2-3 hours between 2 hours post treatment and 6 hours post treatment) until average QTcF is ≤ 480 ms)

[redacted]

After confirming ECG reading at site, if average QTcF > 480 ms:

- Interrupt panobinostat treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist
- If average QTcF confirmed > 480 ms:
- Correct electrolytes, eliminate culprit concomitant treatments, and identify clinical conditions that could potentially prolong the QT
- Consult with a cardiologist (or qualified specialist)
- Increase cardiac monitoring as indicated (e.g., perform approximately hourly ECGs at between 2h post dose of 6h post dose on the same day an average QTcF > 480 ms is reported and pre-dose and at 2h post dose and the next dosing days) until the average QTcF returns to ≤ 480 ms
- After resolution within 7 days to ≤ 480 ms, consider re-introducing panobinostat treatment at the same or reduced dose, and increase ECG monitoring (e.g., pre-dose panobinostat and 2h post panobinostat) for the next treatments:
- If average QTcF remains ≤ 480 ms, continue planned ECG monitoring during subsequent panobinostat treatment.
- If average QTcF recurs > 480 ms after re-introduction of panobinostat treatment or remains > 480 ms for more than 7 days prior to re-introduction, discontinue patient from study treatment.
- Please note that for unscheduled ECGs at any time during panobinostat treatment:
- If a single QTcF is > 480 ms, two additional ECGs should be performed. The three ECGs should be separated by 5-10 minutes. The average QTcF of those three ECGs should be calculated and used for determination of panobinostat dose modifications.

6.2.7 Suggested management of selected adverse events

One of the most common adverse events associated with treatment with oral panobinostat is reversible thrombocytopenia; the degree of thrombocytopenia is dose-dependent. Other side effects include fatigue (dose-dependent), nausea, vomiting and diarrhea.

Diarrhea is especially problematic since, when more severe, can affect drug exposure and result in patient discontinuation. Diarrhea can be controlled with the following regimen which includes of the use of loperamide.

- Patient should be instructed to contact physician at the onset of diarrhea
- Patient should be encouraged to maintain adequate oral hydration (at least 240 ml every 2 hours) with the onset of diarrhea.
- The patient should be instructed to have loperamide readily available and to begin treatment for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient.
- Loperamide 4 mg should be taken at the first loose stool or more frequent than usual bowel movements, followed by 2 mg as needed, no more frequently than every 4 hours, not to exceed a total of 16 mg in 24 hours.

[redacted]

- Patients with diarrhea ≥ grade 2 despite this loperamide regimen should interrupt treatment with panobinostat as described in Table 6-3.
- If the above regimen is inadequate then additional evaluation and treatment should be pursued as medically indicated.
- Replacement i.v. fluids and electrolytes may be used as appropriate.
- Additional treatment should be provided in accordance with institutional standard of care and/or local guidelines.
- Premedication with loperamide is not recommended.
- The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

For orally administered panobinostat, no grade 4 QTc has been reported with "interrupted" dosing schedules. For oral dose of 20 mg or 60 mg given three times weekly, the incidence of grade 3 QTc prolongation ranges from <1% to 6%. The largest QTc change is seen approximately five days after the drug is given and does not correlate with drug serum levels.

For detailed safety information as well as the list of adverse drug reactions (i.e. those AEs considered causally related to panobinostat), please refer to the latest panobinostat IB.

6.2.8 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

[redacted]

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3 Concomitant medications

All medications and significant non-drug therapies (including physical therapy and blood or platelet transfusions) administered at the time of entry into this rollover protocol through 30 days after the last panobinostat dosing and the reasons for therapy use should be reported in the source documents at the study center. Medications include not only physician prescribed medications, but also all over-the-counter medications, vitamins, herbals and alternative therapies.

The following restrictions apply during the study:

- No other investigationl therapy should be given to patients.
- No anticancer agents other than the study medication (panobinostat) should be given to patients during the study. If such agents are required for a patient then the patient must first be withdrawn from the study.

The following recommendations should be followed for the use of medications that may affect or may be affected by panobinostat treatment:

- For patients who require chronic anticoagulant therapy while on panobinostat therapy, low molecular weight heparin (LMWH) should be the preferred anticoagulant medication. In patients for whom low molecular weight heparin use is to be initiated, the degree of thrombocytopenia should be considered, coagulation parameters monitored, and dose of anti-coagulant adjusted accordingly.

- Concomitant use of strong CYP3A4/5 inhibitors (including, but not limited to, ketoconazole, itraconazole, ritonavir, clarithromycin and telithromycin) should be avoided. If medically necessary, close clinical monitoring of signs and symptoms of panobinostat related AEs is recommended when long-term (≥ 1 week) concomitant administration of any strong CYP3A inhibitors occurs, as this may increase the exposure of panobinostat. Co-administration of panobinostat with a moderate or weak CYP3A inhibitor is allowed. Star fruit, pomegranates or pomegranate juice, grapefruit juice that are known to inhibit CYP3A should be avoided during treatment with panobinostat. In patients with hepatic impairment receiving concomitant medicinal products which are strong CYP3A4 inhibitors, treatment with panobinostat should be avoided due to lack of experience and safety data in this patient population.
- In silico data showed that the systemic exposure of panobinostat may be decreased by 70% in the presence of strong CYP3A4 inducers (including, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort). Even though no clinical data are available, panobinostat blood concentrations may be reduced by CYP3A4 inducers. Concomitant use of strong CYP3A4 inducers should be avoided.
- Concomitant use of medications which are known sensitive CYP2D6 substrates (including, but not limited to, tamoxifen, propafenone, risperidone, thoridazine) are to be used with caution. Patients should be carefully monitored for potential signs and symptoms of toxicity and may require dose titration or dose reduction of a sensitive CYP2D6 substrate which also has a narrow therapeutic window (e.g., the ratio of toxicity exposure is ≤ 2-fold higher than the efficacious or therapeutic exposure).
- Granulocyte growth factors (G-CSF) or red blood cell transfusion may be used for severe neutropenia or for severe anemia, respectively, according to institutional guidelines.
- Patients who were receiving recombinant erythropoietin or darbepoetin alfa prior to starting study drug may continue to receive their pre-study doses throughout the trial.
- Palliative radiation therapy may be permitted, but the need for radiation therapy is usually indicative of disease progression.
- Analgesics for tumor-related pain can be maintained during the study. However, an increase in analgesic use for control of tumor-related pain may indicate disease progression. If an increase in analgesic medication from study entry is required during the study, the patient should be evaluated for progression of disease.
- Anti-emetic medications may be used at the discretion of the Investigator, but consider preferentially the use of metoclopramide. Prophylactic anti-emetics except those listed in Appendix 14.1 can be administered at the discretion of the Investigator. Intravenous dolasetron is contraindicated for preventing nausea and vomiting associated with cancer therapy based on FDA drug safety warning (communication dated 17-December-2010).
- Concomitant use of anti-arrhythmic medicines (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine, and sotalol) and other drugs known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, chlarithromycin, methadone, moxifloxacin, bepridil and pimozide) is not recommended.
- DAC inhibitors (including valproic acid) for any clinical indication are to be avoided while on panobinostat treatment.

[redacted]

For additional information regarding these and other medications please refer to Appendix 14.1 and for detailed safety guidance, please refer to the Investigator's Brochure.

6.3.1 Use of Bisphosphonates (or other concomitant agents)

Not applicable

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled in the roll-over study 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 subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the clinical trial database. Additionally, an eCRF will be completed that identifies the patient by gender, date of birth, previous (parent) study, site/center and patient number.

6.4.2 Treatment assignment or randomization

All consented patients who meet all the inclusion criteria and none of the exclusion criteria are eligible to receive panobinostat.

6.4.3 Treatment blinding

Not applicable

6.5 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.5.1 Study treatment packaging and labeling

Panobinostat for the roll-over study is provided as global open label supply, packed and labeled under the responsibility of Novartis Drug Supply Management. Study treatment labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient. Please note that clinical supplies of panobinostat will be labeled as "LBH589". Should panobinostat become commercially available during the course of this study, drug may be sourced and labeled in-country and the locally-approved form and packaging will be used.

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and

designated site personnel have access. Upon receipt, the panobinostat should be stored according to the instructions specified on the drug labels and in the current [Investigator's Brochure].

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

The drug supply can only be destroyed once the study drug accountability check has been performed by the monitor. The supply of panobinostat can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. Patients must return to the study center at least on a quarterly (every 12 +/- 2 weeks) basis for resupply of study medication. 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.

The table indicates in the "Category" column which assessments produce data to be entered in the database (D).

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol reference section	Enrollment	Quarterly (every 12 +/- 2 weeks) visits during treatment phase								End of treatment (EoT)	30 day safety follow-up post last dose of study drug/End of Study
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9+**	**777**	**501/778**
Obtain informed consent	D	7.1.2	x										
Parent Study History (e.g. subject's previous study, site and patient number)	D	7.1.2.3	x										
Demography (e.g. gender and date of birth)	D	7.1.2.3	x										
Relevant medical history/current medical conditions	D	7.1.2.3											
Inclusion/exclusion criteria	D	5.2 / 5.3	x										
Adverse events and serious adverse events*	D	8.1.1 & 8.2.2	continuous										x
s.a. oral panobinostat dosing administration	D	7.1.3	x	continuous									
Pregnancy testing	D, S	7.1.4	continuous										
Confirmation of Clinical Benefit from Study Treatment	D	7.2.1	x	x	x	x	x	x	x	x	x		
End of treatment	D	7.1.5										x	
Study Evaluation Completion	D	7.1.5											x

*SAEs will be reported to the Novartis safety database within 24 hours of investigator or treating physician's knowledge of the event from the time the patient signed informed consent until at least 30 days after the patient stopped study treatment (see Section 8).
Note: All other assessments are performed as per standard of care at the site and will not be captured in the CRF.

[redacted]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

At the enrollment visit, the patient will need to complete a written informed consent. There will be no screening period for this study. Once consented, patients will be evaluated for eligibility via the inclusion and exclusion criteria.

7.1.2.1 Eligibility screening

Not applicable.

7.1.2.2 Information to be collected on screening failures

Not applicable.

7.1.2.3 Patient demographics and other baseline characteristics

For patients that are eligible to participate in this roll-over study, the patients' gender, date of birth, previous study, site/center and subject number, and relevant medical history will be collected.

7.1.3 Treatment period

The starting dose of panobinostat should be the same as the dose that was given in the parent panobinostat study. A quarterly (every 12 +/- 2 weeks) supply of 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. At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. At this time the dose of panobinostat is based on the investigator's judgment. The patients may return to the clinic more frequently at the physician's discretion as clinically indicated or as per standard of care. These unscheduled visits will only be captured in the source documents at the study center and not in the eCRF. All adverse eventsand serious adverse events will be collected and documented in the eCRF.

The study is expected to remain open for 5 years or until such time that enrolled patients no longer need treatment with panobinostat and all follow-up is completed, whichever comes earlier.

7.1.4 Pregnancy and assessment of fertility

Since highly effective contraception is required during the study, female patients of child bearing potential are required to test negative for a pregnancy (either with serum testing if routinely/locally available or urine pregnancy test) before enrolling into the study.

[redacted]

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during the study and for 3 months after the final dose of panobinostat.

Highly effective contraception is defined as either:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to enrolling). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. Women using hormonal contraceptives should additionally use a barrier method of contraception.

If patient has tested negative at the end of study on the parent study, no pregnancy testing is required if enrollment into this study is carried out on the same day or within few days (maximum 5 days) from each other.

Female patients of child bearing potential are required to perform monthly home urine pregnancy tests and complete a simple diary with the dates and the outcome of the home urinary test while on study treatment and during safety follow-up (30 days after the final dose of study medication).

A pregnancy test (either with serum testing if routinely/locally available or urine pregnancy test) on female patients of child bearing potential is required at the final study visit.

Any positive results will be recorded in the database and followed up as per Section 8.4.

7.1.5 Discontinuation of study treatment

Patients will continue to be treated until they are no longer benefiting from panobinostat treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, lost to follow-up or other administrative problem, the investigator feels it is no longer in the patient's best interest to continue panobinostat therapy (e.g., pregnancy, disease progression, adverse events) or the patient dies, whichever comes first.

At the time the patient discontinues study treatment, a visit should be scheduled as soon as possible, at which time the assessments listed for the End of Treatment (EOT) visit will be performed. EOT information will be completed in the eCRF giving the date and reason for stopping the study treatment (see Section 7.1.5.1).

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for a safety evaluation approximately 30 days

following the last dose of study treatment. The completion of the Study Evaluation Completion eCRF page is required any time a patient discontinues from the study and must be completed 30 days after the end of treatment.

Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's withdrawal from the study and record this information on the appropriate eCRF page.

A patient will reach the end of study when panobinostat treatment is permanently discontinued and there will be **no** further follow-up study visits.

7.1.5.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

Patients may be withdrawn from the study if any of the following occur:

1. Adverse event(s).
2. Subject withdrew consent.
3. Lost to follow-up.
4. Administrative problems.
5. Death.
6. Disease progression.
7. Protocol deviation.
8. Pregnancy.
9. Study terminated by sponsor

7.1.5.2 Replacement policy

Not applicable.

7.1.6 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

[redacted]

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.7 Follow up for safety evaluations

All patients must be followed up for safety evaluations for 30 days after the last dose of study treatment. At the end of this period, the investigator should contact the patient to inquire about any adverse events or serious adverse events observed during this period. This could be done via a phone contact. Following this, there are **no** further follow-up study visits.

Patients lost to follow up should be recorded as such on the appropriate eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Data collected should be added to the Adverse Events eCRF.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

7.2.2 Other assessments

No additional tests will be performed on patients entered into this study.

7.2.3 Safety and tolerability assessments

Safety will be monitored by collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.4 Pharmacokinetics

Not applicable.

7.2.4.1 Analytical method

Not applicable.

[redacted]

7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Any ongoing adverse events from the parent study will be captured as medical history in the roll-over database. Any AE that begins (or worsens) after signing of the informed consent for the roll-over and during the 30-day (or 28-day) safety follow-up period defined in the parent protocol should be reported in both clinical databases.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the current version of Common Terminology Criteria for Adverse Events (CTCAE).

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through the EOT eCRF page.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (start and end dates)

[redacted]

3. Its relationship to the study treatment (reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator’s discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the laboratory abnormality would still, by definition, be an adverse event and must be reported as such.

[redacted]

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data and including acute pancreatitis, interstitial lung disease, ischaemic colitis, hepatic dysfunction, pneumonia, sepsis, renal dysfuction, cardiac failure, ischaemic heart disease, pericardial effusion, tachyarrhythmias, and venous thromboembolism. AESIs are discussed in detail in the Investigator Brochure.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAE that begins or worsens after signing of the informed consent for the roll-over and during the 30-day (or 28-day) safety follow up period defined in the parent protocol should be reported as an adverse event in both clinical databases; however, only one SAE will be sent to Novartis.

[redacted]

- Any SAE that begins or worsens during the 30-day (or 28-day) safety follow-up period specified in the parent study should have an SAE report submitted to Novartis with the parent protocol study number.
- Any SAE that begins or worsens after the 30-day (or 28-day) safety follow-up period specified in the parent study should have an SAE report submitted to Novartis with the roll-over protocol study number.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

It is important to use the right SAE form with the correct protocol number for these two scenarios, to avoid confusion in SAE processing. For a patient already on the roll-over protocol but follow up information is reported for the previous SAEs in the parent protocol, it must be clearly labeled that this is for the parent protocol number.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure (new occurrence) or Package Insert and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable. This is an open-label study.

[redacted]

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to panobinostat of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother. The collection of this information could last for up to 12 months following the birth of the child. The Study Doctor and Novartis may decide what pertinent information is collected as necessary or indicated based on the study.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between [Investigator Brochure] updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

[redacted]

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRFs is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

10.1 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting.

10.1.1 Full Analysis Set

Not applicable.

10.1.2 Safety Set

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

10.1.3 Dose-determining analysis set

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data characteristics will be summarized descriptively for the Safety Set.

10.3 Treatments (study treatment, compliance)

Dose administration data will be summarized using the Safety Set.

10.4 Primary objective

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

[redacted]

10.4.1 Variable

See Section 10.5.3.

10.4.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested.

10.4.3 Handling of missing values/censoring/discontinuations

Not applicable.

10.4.4 Supportive analyses

No supportive analysis will be performed.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

The secondary objective of the study was to evaluate clinical benefit as assessed by the investigator. Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits.

10.5.3 Safety objectives

The assessment of safety will be based mainly on the frequency of AEs and SAEs.

10.5.3.1 Analysis set and grouping for the analyses

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

1. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
2. post-treatment period: starting at day 30+1 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

Summary tables of adverse events (AEs) have 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.

[redacted]

10.5.3.3 Other safety data

Not applicable.

10.5.3.4 Tolerability

Not applicable.

10.6 Interim analysis

Not applicable.

10.7 Sample size calculation

Not applicable.

10.8 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

[redacted]

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Additional consent form

Not applicable.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

[redacted]

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site, prior to study start.

[redacted]

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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[redacted]

14 Appendices

14.1 Concomitant medication

In general, medications listed in Table 14-1 should be avoided and medications listed in Table 14-2 and Table 14-3 are to be used with caution when co-administered with panobinostat. The use of any of the drugs in Table 14-1, Table 14-2 and Table 14-3 in combination with panobinostat must be discussed with the Sponsor.

14.1.1 Medications which are known to prolong the QT interval and/or induce Torsades de pointes ventricular arrhythmia should be avoided

It is of great importance to avoid such drugs listed below in Table 14-1 in combination with panobinostat, especially in the presence of electrolyte abnormalities, notably decreased potassium or magnesium levels commonly associated with diuretic usage.

This is not a comprehensive list of medications which may prolong the QT interval and/or induce Torsades de pointes. This list of medications was developed in collaboration with an external cardiology consultant and represents those medications which are deemed to have an unacceptable risk of co-administration with panobinostat.

The following website may be referenced as a supplemental guide for drugs which have been associated with Torsades de pointes or prolonging the QT interval but at this time lack substantial evidence for causing Torsades de pointes: azcert.org/medical-pros/drug-lists/drug-lists.cfm.(version 3/25/2008).

Medications listed on the website which do not appear in Table 14-1 above may be used with caution at the discretion of the investigator.

Ondansetron (a known CYP2D6 substrate, see Table 14-3) has prolongation but has not been shown to cause Torsades de pointes. Therefore, ondansetron is not per se prohibited when combined with panobinostat but caution is to be exercised and close monitoring for signs and symptoms of QT prolongation is recommended.

Table 14-1 Medications which are known to prolong the QT interval and/or induce Torsades de Pointes to be avoided

All Class IA antiarrhythmics	Quinidine Procainamide Disopyramide any other class IA antiarrhythmic drug
All Class III antiarrhythmics	Amiodarone Sotalol Dofetilide Ibutilide any other class III antiarrhythmic drug
Macrolide antibiotics*	Erythromycin clarithromycin
Quinolone antibiotics*	Sparfloxacin
Antifungals	pentamidine

[redacted]

Antimalarials	Halofantrine chloroquine
Antihistamines	Astemizole terfenadine
Anti-emetics	Chlorpromazine Domperidone Droperidol dolasetron (intravenous and oral)^
Antipsychotics	Thioridazine Mesoridazine Chlorpromazine pimozide
Miscellaneous drugs	arsenic trioxide bepridil domperidone cisapride levomethadyl methadone
* Note: azithromycin, ciprofloxacin, levofloxacin, pefloxacin, ofloxacin, tosufloxacin, difloxacin, temafloxacin, fleroxacin, acrosoxacin, nalidixic acid and enoxacin are allowed. ^ Intravenous dolasetron is contraindicated for preventing nausea and vomiting associated with chemotherapy based on FDA drug safety communication dated December 17, 2010. Based on this finding, both intravenous and oral dolasetron are prohibited to be taken with panobinostat.	

14.1.2 Medications which are known strong CYP3A4/5 inhibitors to be avoided

Panobinostat is a substrate of CYP3A4/5 with minor involvement of CYP2D6, and CYP2C19 in *in vitro* evaluation of its metabolism. Thus, a clinical drug-drug interaction study was conducted using ketoconazole, a strong CYP3A inhibitor, in combination with panobinostat in study CLBH589B2110.

Multiple ketoconazole doses at 400 mg increased $C_{max\ and}$ AUC of panobinostat by 1.6-and 1.8-fold, respectively, but with no change in T_{max} or half-lives in 14 cancers patients. The less than 2-fold increase in panobinostat AUC upon co-administration of a strong CYP3A inhibitor is considered a weak drug inhibition and not clinically relevant, as panobinostat doses at least 2-fold greater than the evaluated 20 mg dose (i.e., 40 mg and 60 mg have been safely administered in patients. Thus, co-administration of panobinostat with a moderate or weak CYP3A inhibitor is allowed. However, clinical monitoring of signs and symptoms of panobinostat treatment related to adverse events is recommended when long-term (≥ 1 week) concomitant administration of any strong CYP3A inhibitors and panobinostat is medically indicated or investigated in a clinical study.

Patients with impaired liver function (as defined by NCI CTEP criteria) (Synold et al 2007) are recommended not to receive panobinostat concomitantly with strong CYP3A inhibitors because potential interaction has not been established in this population.

[redacted]

Table 14-2 Medications which are known strong CYP3A4/5 inhibitors to be used with caution

Macrolide antibiotics*	Telithromycin troleandomycin
Antifungals (azoles)	Ketoconazole Itraconazole Posaconazole voriconazole
Antidepressants	nefazodone
HIV protease inhibitors:	Indinavir Nelfinavir Ritonavir Saquinavir lopinavir
Miscellaneous drugs or products	[1] Star fruit and pomegranate product and juice convaptan

* azithromycin and regular orange juice are allowed.

[1] Hidaka et al (2004).

Although clarithromycin is a known strong CYP3A inhibitor, it is also known to prolong QT intervals which is listed in Table 14-1 and is prohibited to be taken with panobinostat. This drug is thus not listed again in Table 14-3.

This is not a comprehensive list of medications which may inhibit CYP3A4/5. The above list was compiled by using information listed under "draft guidance for industry, drug interaction studies, CDER 2006", Indiana University School of Medicine drug interaction tables at medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp and "drug interaction database" from University of Washington.

Additional updated versions with moderate and weak CYP3A inhibitors, which are meant to be used as a guide, may be found at the following website: medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp.

14.1.3 Medications which are known CYP2D6 substrates to be used with caution

Panobinostat was also shown to be a CYP2D6 inhibitor (K_i 0.17 μM) *in vitro*. Thus, clinical drug-drug interaction study with panobinostat as CYP2D6 inhibitor and dextromethorpan as CYP2D6 substrate was recently conducted in study [CLBH589B2109].

Multiple panobinostat doses increased C_{max} and AUC of dextromethorphan by a mean of 1.8- and 1.6-fold respectively, but with no change in T_{max} in 17 cancer patients. An approximately 2-fold increase in dextromethorphan AUC upon co-administration with panobinostat indicated that *in vivo* CYP2D6 inhibition of panobinostat is weak.

As the study was conducted using a sensitive CYP2D6 substrate which resulted in a weak inhibition, drugs with a large therapeutic index such as anti-emetics, anti-hypertensives, and anti-depressants are generally safe to be co-administered with panobinostat.

[redacted]

Patients should be carefully monitored for potential signs and symptoms of toxicity and may require dose titration or dose reduction of a sensitive CYP2D6 substrate which also have a narrow therapeutic window (e.g., the ratio of toxicity exposure is ≤ 2-fold higher than the efficacious or therapeutic exposure).

Table 14-3 Medications which are known CYP2D6 substrates to be used with caution

Beta blockers	S-metoprolol Propafenone timolol
Antipsychotics	Aripiprazole Haloperidol Risperidone thioridazine
Antidepressants	Amitriptyline Clomipramine Desipramine Imipramine Fluoxetine Paroxetine Venlafaxine duloxetine
Antiarrhythmics	Mexilletine flecainide
Others	Codeine Dextromethorphan Tamoxifen tramadol
Anti-emetics	ondansetron^
^ Intravenous dolasetron is a CYP2D6 substrate and contraindicated for preventing nausea and vomiting associated with chemotherapy based on FDA drug safety communication dated December 17, 2010. Please see Table 14-1.	

This is not a comprehensive list of CYP2D6 substrates. Additional updated versions of this list, which are meant to be used as a guide, may be found at the following website: medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp.

[redacted]