NOVARTIS

Clinical Development & Medical Affairs

LBH589

Clinical Trial Protocol CLBH589H2101 / NCT00946647

A phase Ib/IIb, open-label, multi-center study of oral Panobinostat (LBH589) administered with 5-Azacitidine (Vidaza®) in adult patients with myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) or acute myeloid leukemia (AML)

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List of abbreviations

5-Aza	5-azacytidine, Vidaza®
ADME	Absorption, distribution, metabolism, and elimination
AE	Adverse event
Akt	V-akt murine thymoma viral oncogene homolog
ALL	Acute lymphocytic leukemia
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
APD	Action potential duration
APL	Acute promyelocytic leukemia
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
ATC	Acute toxic class
ATD	Accelerated titration design
ATRA	All trans-retinoic acid
AUC	Area under the curve
b.i.d.	Bis in diem/twice a day
BAPK	Bioanalytics and Pharmacokinetics
BM	Bone marrow
[redacted]	[redacted]
BrdU	5-bromo-2-deoxyuridine
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CEA	Carcino-embryonic antigen
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CK-MB	MB isoenzyme of creatine phosphokinase
C_{max}	Maximum (peak) concentration of drug
CMML	Chronic myelomonocytic leukemia
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CRu	Unconfirmed complete response
CSF	Cerebrospinal fluid
CT	Computed tomography
CTC	NCI common toxicity criteria (version 2.0)
CTCAE	NCI common terminology criteria for adverse events (version 3.0)
CTCL	Cutaneous T-cell lymphoma
CV	Coefficient of variation
CYP450	Cytochrome P450
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid

[redacted]

DNMT	DNA methyl transferase
DSM	Drug supply management
DTIC	Dacarbazine
ECG	Electrocardiogram
CRF	Electronic case record form
ECHO	Echocardiogram
EDC	Electronic data capture
EDM	Electronic data management
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EOS	End of study
FACS	Fluorescent-activated cell sorter
FDA	Food and Drug Administration
FPFV	First patient first visit
FPG	Fasting plasma glucose
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GLP	Good laboratory practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
H3, H4	Histones H3, H4
HAT	Histone acetyltransferase
HbA	Adult hemoglobin
HbF	Fetal hemoglobin
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
hERG	Human ether-a-go-go related gene
Hgb	Hemoglobin
HI	Hematologic Improvement
HIV	Human immunodeficiency virus
HPF	High-power field
HPLC	High pressure (performance) liquid chromatography
HSP90	Heat shock protein 90
IEC	Independent ethics committee
IEP	Immunoelectrophoresis
IMS	Integrated Medical Safety
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent to treat
IRT	Interactive Response Technology
IV	Intravenous(ly)
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
LDH	Lactic dehydrogenase
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LMWH	Low molecular weight heparin

[redacted]

LOH	Loss of heterozygosity
LPLV	Last patient last visit
LVEF	Left ventricular ejection fraction
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCRM	Modified continual reassessment method
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndromes
MDS-U	Myelodysplastic syndrome, unclassified
MedDRA	Medical Dictionary for Regulatory Activities
mg/m^2	Milligrams per square meter
MI	Myocardial infarction
MTD	Maximum tolerated dose
MUGA	Multiple uptake gated acquisition scan
MWF	Monday, Wednesday, Friday
NCI	National cancer institute
NIH	National Institutes of Health
NPGN	Novartis pharmacogenetic network
N/V	Nausea/vomiting
OBD	Optimum biologic dose
p.o.	Per os/by mouth/orally
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic
PD	Progressive disease
PE	Physical examination
PG	Pharmacogenetic
P-gp	P-glycoprotein
PK	Pharmacokinetic
PLT	Platelet
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time
q.d.	Once a day
Q-RT-PCR	Quantitative reverse transcription polymerase chain reaction
QT	QT interval - portion of an electrocardiogram between the onset of the Q wave and the end of the T wave
QTc	ECG QT interval - corrected
QTcF	QR corrected with Fridericia's formula
RA	Retinoic acid
RA	Refractory anemia
RAEB	Refractory anemia with excess blasts
RAEB-T	Refractory anemia with excess blasts in transformation
RARS	Refractory anemia with ringed sideroblasts

[redacted]

RBC	Red blood cell
RAMD	Refractory anemia with multilineage dysplasia
RAMD-RS	Refractory anemia with multilineage dysplasia and ring sideroblasts
REB	Research ethics board
Right BBB	Right bundle branch block
RNA	Ribonucleic acid
RR	Response rate
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAHA	Suberoylanilide hydroxamic acid
SD	Stable disease
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SPEP	Serum protein electrophoresis
STS	Sample tracking system
SUV	Standardized uptake value
T/C	Tumor/control
T3	Triiodothyronine
FT4	Free Thyroxin
TDL	Toxic dose low
TIW	Three times a week
T_{max}	Time to peak concentration
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UNK	Unknown
UPEP	Urine protein electrophoresis
VEGF	Vascular endothelial growth factor
Vidaza®	5-azacytidine, 5-Aza
VS	Vital signs
WBC	White blood cell
WOCBP	Women of childbearing potential
WHO	World health organization
WNL	Within normal limits

[redacted]

Amendment 5 (18-Nov-2016)

Amendment rationale

The CLBH589H2101 study started in December 2009 as a phase Ib dose escalation study of oral panobinostat in combination with 5-Azacitidine (5-Aza). The study was amended to a phase Ib/IIb with a randomized, two-arm, open-label design, adding an active control arm with single agent 5-Aza, with the first patient randomized on 19-March-2012. An interim Clinical Study Report (CSR) was planned, using a cut-off date corresponding to the time when the last patient enrolled in the phase IIb part had completed 12 months of treatment. The corresponding cut-off date was reached on 30-Apr-2014, an interim database lock took place on 30-Oct-2014, and an interim CSR was released on 7-May-2015. At the time of the cut-off date (30-Apr-2014), 17 patients were still on treatment, 4 in the phase Ib and 13 in the phase IIb. As of 01-May-2014, the schedule assessment was changed (as pre-specified in the protocol), leaving the efficacy-related assessments involving aspirate and biopsy samples at the discretion of the investigators.

The results described in the interim CSR suggested an unfavorable benefit/risk profile of the dose and schedule of panobinostat in combination with 5-Aza in this patient population. However, some patients appear to derive benefit from their treatment, based on investigators assessment, and seven of them are still on treatment. The rationale of this amendment 5 is to ensure treatment access for these patients with a limited data collection. Therefore, for the patients ongoing treatment the study will focus on collecting continuously Adverse Events, Serious Adverse Events, Concomitant Medications, and Dose Administration Records information. In addition, information (date and reason) related to End of Treatment and Study Evaluation Completion, date of disease progression as well as Survival information must be provided. All other assessments will be performed at the discretion of the investigators.

To align with the most up-to-date protocol template, the sections 6, 8, 9, 11, and 12 of the protocol have been updated. The Inform Consent was also updated according to the updated template. Furthermore, and in order to align with program level standard language, the pregnancy prevention information will be implemented at the same time as this protocol amendment 5, by means of update of the Informed Consent.

As of this amendment 5 there are 7 patients on treatment, one in the phase Ib and 6 in the phase IIb part of the study.

The detailed changes to the protocol are listed below.

Changes to the protocol

The changes that are made to the protocol are listed below and integrated directly in the protocol with track changes using strike-through red font for deletions, red underlined for insertions.

- Section 6.6.1: paragraph “Study drug supply and resupply, storage, and tracking/drug accountability” has been moved to this section from Section 11.4
- Section 6.6.1.8: reference to Table 7-5 has been updated

[redacted]

- Section 6.6.3: text has been aligned with the visit evaluation schedule described in Table 7-3
- Section 6.6.5: new section added as per DOCE (Discontinuation of Clinical Trial Protocol Elements) guidelines
- Section 6.6.6: section number has been updated and text has been aligned to DOCE guidelines
- Section 6.6.7: new section added as per DOCE guidelines
- Section 6.6.8: section number has been updated and text has been aligned with the visit evaluation schedule described in Table 7-3
- Section 6.6.9: section number has been updated
- Table 7-1: references to Table 7-5 and to Table 7-6 have been updated
- Table 7-2: reference to Table 7-5 has been updated
- Table 7-3: new table added to describe the visit evaluation schedule for patients ongoing treatment at the time of protocol amendment 5
- Section 7.5.1: text has been aligned with the visit evaluation schedule described in Table 7-3
- Section 7.6: former Section 7.6.1 (Adverse Events) has been moved to Section 8.1
- Section 7.6.1: section number has been updated
- Table 7-4: table number has been updated
- Section 7.6.2: table number has been updated and reference to Table 7-5 has been updated
- Table 7-5: table number has been updated and one footnote has been added to align the table with the visit evaluation schedule described in Table 7-3
- Section 7.6.3: section number has been updated and references to Table 7-2 and to table 7-3 have been added
- Section 7.6.3.1: section number has been updated and text has been aligned with the visit evaluation schedule described in Table 7-3
- Section 7.6.3.2: section number has been updated and text has been aligned with the visit evaluation schedule described in Table 7-3
- Section 7.6.3.3: section number has been updated and text has been aligned with the visit evaluation schedule described in Table 7-3
- Section 7.6.3.4: section number has been updated and text has been aligned with the visit evaluation schedule described in Table 7-3
- Section 7.6.3.5: section number has been updated and text has been aligned with the visit evaluation schedule described in Table 7-3
- Section 7.6.3.6: section number has been updated and text has been aligned with the current pregnancy program standard language and updated based on the status of ongoing patients
- Section 7.10: reference to Table 7-6 has been updated
- Table 7-6: table number has been updated

[redacted]

- Section 7.11: reference to Table 7-7 has been updated and text has been aligned with the visit evaluation schedule described in Table 7-3
- Table 7-7: table number has been updated
- Section 7.11.1: text has been aligned with the visit evaluation schedule described in Table 7-3
- Section 8: header has been aligned with the latest Clinical Trial Protocol Template
- Section 8.1: Adverse Events section has been moved here from Section 7.6 and has been updated to be aligned with the current Clinical Trial Protocol template
- Section 8.2: Serious Adverse Events section has been updated to be aligned with the current Clinical Trial Protocol template
- Section 8.3: section has been added to be aligned with the current Clinical Trial Protocol template
- Section 8.4: section number has been updated and text has been aligned with the current Clinical Trial Protocol template
- Section 8.5: section has been added to be aligned with the current Clinical Trial Protocol template
- Section 8.6: section number has been updated
- Section 8.7: section number has been updated and header has been aligned with the latest Clinical Trial Protocol Template
- Section 9: header has been aligned with the latest Clinical Trial Protocol Template
- Section 9.1: section has been added to be aligned with the current Clinical Trial Protocol template
- Section 9.2: section number has been updated and text has been aligned with the current Clinical Trial Protocol template
- Section 9.3: section number has been updated and text has been aligned with the current Clinical Trial Protocol template
- Section 9.3.1: section number has been updated
- Section 9.3.2: section number has been updated
- Section 9.4: section number has been updated and text has been aligned with the current Clinical Trial Protocol template
- Section 11: header has been aligned with the latest Clinical Trial Protocol Template
- Section 11.1: text has been aligned with the current Clinical Trial Protocol template
- Section 11.2: text has been aligned with the current Clinical Trial Protocol template
- Section 11.3: text has been aligned with the current Clinical Trial Protocol template. The paragraph “Amendments to the protocol” has been moved to section 12.1
- Section 11.4: text has been aligned with the current Clinical Trial Protocol template. The paragraph “Study drug supply and resupply, storage, and tracking/drug accountability” has been moved to section 6.6.1
- Section 11.5: section added to be aligned with the current Clinical Trial Protocol template

- Section 11.6: section added to be aligned with the current Clinical Trial Protocol template
- Section 11.7: section added to be aligned with the current Clinical Trial Protocol template
- Section 11.8: section added to be aligned with the current Clinical Trial Protocol template
- Section 11.9: section added to be aligned with the current Clinical Trial Protocol template
- Section 12.1: paragraph "Amendments to the protocol" has been moved here from Section 11.3
- The synopsis has been updated according to the changes described above

IRBs/IECs

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.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 4

Amendment rationale

This amendment is a country-specific, non-substantial amendment for the Republic of Korea to clarify in the Header of Table 6-4 and Table 6-5 that the therein provided dose adjustment recommendations are for panobinostat **and** Vidaza. The Korean Health Authority has given full approval for amendment 3, however requesting to make the above mentioned changes prior to start enrollment in Korea.

The CLBH589H2101 study started in December 2009 as a phase Ib dose escalation study of oral panobinostat in combination with 5-Aza and was amended to a phase Ib/IIb study with a randomized, two-arm, open-label design, adding an active control arm with single agent 5-Aza in October 2011. LPFV of the phase I portion was in June 2011. The first patient was randomized onto the phase II portion in March 2012. As of this amendment, 20 of the planned 80 patients have been enrolled globally.

Changes to the protocol

The changes that are made to the protocol are listed below and integrated directly in the protocol with track changes using strike-through red font for deletions, red underlined for insertions.

Section 6.6.1.8:

- Table 6-4; Header title changes made to provide clarification around dose adjustment recommendations for Panobinostat and Vidaza.
- Table 6-5; Header title changes made to provide clarification around dose adjustment recommendations for Panobinostat and Vidaza.

[redacted]

Amendment 3

The CLBH589H2101 study started in December 2009 as a phase Ib dose escalation study of oral panobinostat in combination with 5-Aza. In October 2011, after the determination of the recommended phase II dose (RPIID) at 30 mg, the study was recently amended to a phase Ib/IIb study with a randomized, two-arm, open-label design, adding an active control arm with single agent 5-Aza. As of this amendment 5 patients are ongoing from the phase Ib part and the first patient was randomized into the phase IIb part on 19 March 2012. It is planned to enroll a total of 80 patients into the phase IIb part.

Amendment rationale

This amendment 3 is a global amendment to provide guidance on dose adjustments for panobinostat and/or 5-Aza in the event of hematological toxicity, in particular thrombocytopenia and neutropenia as well as in the event of non-hematological toxicity for patients enrolled in the phase IIb part.

In the Phase I portion of this study dose modifications were guided by DLT definitions (Section 6.6.1.6). In the Phase II portion, these toxicities are no longer captured as DLTs. A global amendment was necessary to ensure optimal risk management for patients with toxicities and keeping the dose adjustments consistent across sites, avoiding any ambiguity at the end of the study with overall patient drug exposure.

For hematological toxicities, managing grade 3-4 cytopenias with optimal hematological support is necessary to maximize patient exposure to 5-aza and panobinostat. Following optimal hematological support, dose modifications may become necessary to help patients tolerate study treatment. For the non-hematological toxicities the approach was to manage these patients as per the 5-aza label and in keeping with current clinical practice. This helps to maintain patient exposure to 5-aza which has been shown to improve outcomes.

Rationale for other changes in the protocol and the Informed Consent Form for phase IIb part:

Additional editorial corrections were needed in order to provide clarifications, to increase consistency within the protocol as well as with the Case Report Form (CRF), to harmonize with the Novartis Guidance on the Prevention of Pregnancies in Participants in Clinical Trials and to rectify typographical errors throughout.

[redacted]

- To harmonize eligibility of patients with current LBH protocols, Inclusion criteria #6 which defines eligibility of euthyroid patients' will be clarified by removing any mention of supplementation to avoid previous ambiguity.
- To provide clarification around IRT procedures.
- To provide clarification on dose adjustments in Phase II. In particular, this clarification was necessary where a reference was given to the dose escalation levels as described in

[redacted]

Table 6-3 (e.g. Dose adjustments due to prolonged QT interval) as this table is only applicable in the Phase Ib part.

- To provide clarification around bone marrow aspiration and/or core biopsy at screening. This clarification specifies time windows and gives an option not to repeat bone marrow aspiration and/or core biopsy at screening, however is limited to patients where the original bone marrow aspiration and/or core biopsy was performed within 14 days of starting study drug, and the original marrow (or marrow report) has sufficient information to assess diagnosis or eligibility of the patient and perform assessment of response when comparing to the next bone marrow assessment. In addition, the time window for bone marrow collection and peripheral blood collection throughout the study were clarified.
- To provide consistency with the CRF, in particular the visit numbering
- To provide consistency throughout the document that the reduced visit evaluation schedule described in Table 7-2 will have to be followed only for patients who have completed 12 cycles after the data cut-off date for the CSR has been reached.
- To provide clarification around cardiac monitoring for patients in the control arm by adding an introduction to Table 7-4 and removing a footnote.
- To provide consistency between the cardiac monitoring schedules described in Table 7-4 and footnote 13 of Table 7-1, the number of ECGs at screening will be corrected to be "single" in the latter.
- To provide clarification on "seriousness" of Grade 4 events a note was added to section 7.6.1
- To provide clarification in Section 8.2 that pregnancy outcome must be collected also female patients that took study treatment.
- The protocol and the relevant sections of the Informed Consent Form (Phase IIb part) have been updated
  - To align with the Novartis Guidance on the Prevention of Pregnancies in Participants in Clinical Trials, in particular the definition of WOCBP, urinary pregnancy testing during the duration of the study was added and the length of contraception clarified.
  - [redacted]
  - Study title was corrected on the IC Signature Page
- Informed Consent Form for Female Partners was updated to align the time window for contraception with the 5-Aza label.
- [Post-text supplement 3] has been updated to rectify a corrupted sentence
- For consistency with the International Prognostic Scoring System (Greenberg et al, 1997), the score value for category 'poor' and 'intermediate' will be corrected in [Post-text supplement 1 Table 2-3].

Changes to the protocol

The major changes that are made to the protocol are listed below and incorporated directly in the protocol with track changes using strike-through red font for deletions, red underlined for insertions. Where appropriate, changes to the protocol body will be made to corresponding

[redacted]

sections for consistency. Additional minor changes (e.g., correction of typographical errors) and re-phrasing of existing sentences to be more precise in wording are only incorporated directly in the protocol with track changes.

The major changes to the protocol, and the sections affected, are detailed below. Section	**Changes made**
Protocol synopsis	All relevant sections of the protocol synopsis were updated to be consistent with the changes in the protocol body described hereafter.
[redacted]	[redacted]
Section 5.1 Inclusion Criteria	IC #6 was updated to clarify eligibility of patients and empty IC #4 was clarified
Section 6.4.1	IRT procedures were clarified
Section 6.6.1.8 Dose modification, delay and discontinuation	Specific guidance was proposed for the Phase IIb portion in subsections Dose adjustment due to hematologic toxicity and Dose adjustment due to non-hematologic toxicity, including Table 6-4 and Table 6-7.
Section 6.6.1.8 Sub-section on Dose adjustments due to QT prolongations	Reference to Table 6-3 Dose escalation level for dose reduction was replaced.
Table 7-1	Visit numbers in the protocol were aligned with the Case Report Form (CRF) and urinary pregnancy tests were added on Day 1 of each subsequent cycle during study duration
Section 7.1	A new section was added to clarify the use of historical bone marrow collection for disease characterization
Table 7-1 footnote 15 and Section 10	Updated to clarify start of reduced visit schedule
Table 7-1 footnote 13	Typo corrected for number of ECGs at screening
Table 7-4	Editorial changes made to provide clarification around cardiac monitoring for patients in control arm
Section 7.5.1 Efficacy Assessment and Table 7-1 Footnote #14	Time windows for bone marrow aspiration/biopsy and peripheral blood collection were clarified
Section 7.6.1	Note was added
Section 7.6.4.6	Urinary pregnancy testing at monthly intervals during study duration was added and aligned with the definition of WOCBP
[redacted]	[redacted]
Section 8.2	Female patients added
Informed Consent Form for Phase II and Informed Consent Form for Female Partners	Urinary pregnancy tests were added to the tests to be performed during the study treatment and the length of contraception was clarified. [redacted]
Post-text 3 supplement (1st section, first sentence)	Corrupted sentence was corrected
Post-text 1 supplement – Table 2-3	The score value for category ‘poor’ and ‘intermediate’ has been corrected

[redacted]

IRB/IEC/REB Approval

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. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Summary of previous amendments

Amendment 2 (released on 24 October 2011)

The purpose of Amendment 2 is to:

- Collect preliminary efficacy data of panobinostat at the recommended phase II dose (RPIID) level in conjunction with azacytidine (5-Aza/Vidaza®) by introducing a randomized, two-arm, open-label expansion phase, which determines the phase IIb part of the study.
- Revise the eligibility criteria based on new safety information and current clinical practice.
- Update the ECG safety monitoring schedule according to the current LBH589 cardiac safety profile.
- Align the protocol with the current LBH589 guidance on the use of concomitant medications (as specified in the post-text supplement 3).

As of this amendment, the phase Ib part of this study is completed and the recommended phase II dose (RPIID) was established at 30 mg of oral panobinostat once daily on day 3, 5, 8, 10, 12, and 15 in combination with azacytidine (5-Aza/Vidaza®). In total, 31 patients were enrolled in the phase lb part. Eighteen patients were treated at the dose level of 30 mg of panobinostat, 16 of which were evaluable for the MTD determining set. Dose escalation was not continued up to the MTD because of long term tolerability considerations.

Rationale for the phase IIb part

- This amendment introduces a randomized phase IIb part with an active control arm so that the preliminary efficacy of panobinostat at the RPIID level in combination with 5-Aza versus 5-Aza alone can be rigorously studied. The most important advantage of proper randomization is that it minimizes allocation bias and the use of an active treatment comparator overcomes several limitations of a historical comparator, e.g., treatment arms can be balanced adequately with respect to both known and unknown prognostic factors and the confounding effect of imbalances in prior treatment can be controlled.
- Based on the Phase III AZA-001 study data (Fenaux et al 2009a), low response rates have been shown with 5-Aza alone. Assuming an increase in CR response rates can be achieved with the combination over the low rates seen with single-agent 5-Aza, CR including CRi for AML patients and bone marrow CR for MDS/CMML patients have been selected as primary efficacy endpoints in the phase IIb part.

[redacted]

- This randomized phase II part allows collecting safety data of panobinostat in combination with 5-Aza in comparison to single-agent 5-aza. In addition, it allows to better understand the degree of tolerability wherefore safety and tolerability have been selected as secondary endpoints in the phase IIb part.

[redacted]

- Data from the phase III AZA-001 study shows that 90% of the study population achieved a best response by Cycle 9 (Fenaux 2009b). The core clinical study report (encompassing both, the phase Ib and the phase IIb part of the study) will be based on a data cut-off corresponding to the time point where all patients have either completed 12 cycles of study treatment or discontinued study treatment for any other reason, whichever comes first. An addendum to the core clinical study report will be provided at the completion of the study to summarize and/or list the additional safety and efficacy data as appropriate. Patients who have completed 12 cycles of study treatment and are assessed by the Investigator to have the potential to benefit from ongoing treatment will continue their assigned treatment allowing the collection and assessment of safety, efficacy and survival data. After the data-cut off point for the CSR a reduced assessment schedule will be applied.
- Clinical response, the primary efficacy endpoint in the phase IIb part, is assessed by changes in bone marrow and peripheral blood blast percentages based on standardized response criteria proposed by Cheson et al. 2003 and 2006 (as specified in the post-text supplement 1). The proposed open label study design is not likely to impact the objective determination of response based on the Cheson criteria.

Rationale for protocol adjustments related to eligibility criteria, cardiac assessments, ECG monitoring schedule and the current LBH589 guidance on the use of concomitant medications

- Inclusion criterion #4 which defines patients' eligibility according to INR and PTT laboratory parameter has been replaced with a criterion based on evidence of clinically significant mucosal or internal bleeding. The new criterion reflects more closely clinical practice and is aligned with newer AML protocols.
- Due to limited data about the effect of myelosuppression caused by panobinostat, in particular thrombocytopenia, the eligibility criterion based on INR/PTT laboratory values was defined at the time of the original protocol. New safety information with regards to thrombocytopenia showed that irrespective of new or worsening grade 3/4 thrombocytopenia, the incidence of grade 3/4 bleeding events (regardless of causality) was low and may be associated with baseline thrombocyte levels and other risk factors (tumor types, metastases). We recommend that patients who require chronic anticoagulation therapy at study entry or while on panobinostat therapy use low molecular weight heparin (LMWH). However, if the use of LMWH is not feasible, such patients may continue on sodium warfarin while on panobinostat, but a close monitoring of common coagulation parameters, including a PTT/INR should be conducted. Coagulation parameters at study

[redacted]

entry and during the course of the study should be maintained within a therapeutic range as appropriate for the indication.

- During the course of this trial four grade 3 bleeding events of hemoptysis and recurrent bleeding in the oral cavity, intracerebral bleeding, and acute GI bleeding were reported in three patients (30 mg dose cohorts). Hemoptysis and recurrent bleeding in the oral cavity as well as intracerebral bleeding were not suspected to be related to panobinostat. For the acute GI bleeding event a possible relation with the study treatment was reported. However, confounding factors were confirmed by the investigator as the GI bleed was identified to originate from internal hemorrhoids and deemed to be secondary to Grade 4 thrombocytopenia. All patients entered the trial with grade 3 thrombocyte counts which worsened to grade 4 on day 8 of the first cycle but were manageable with platelet transfusions. All events resolved within 3 days and none of the events were considered life threatening or required study drug adjustments.
- MUGA has been added as another validated method to assess cardiac function. Both, ECHO (echocardiogram) and MUGA (multiple gated acquisitions) scan are widely applied methods, used to monitor cardiac function in clinical practice and therapy-induced cardio-toxicity in clinical trials (e.g., with anthracyclines).
- The ECG safety monitoring schedule has been updated according to the current LBH589 cardiac safety profile. This is based on an integrated analysis of completed and ongoing studies using oral panobinostat showing minimal risk of QT prolongation with no clinically significant QTc interval changes. It also showed that the risk of QTc prolongations does not increase over time when oral panobinostat is dosed up to 40 mg three times a week (TIW) every week or 45 mg TIW every other week. An integrated analysis was performed on the pooled centrally reviewed ECG data collected from three Phase I and six Phase II studies of single-agent oral panobinostat in 559 patients with advanced hematologic malignancies or solid tumors (Weber et al 2009). A total of 554 patients had both a baseline and at least one post-baseline ECG measurement (a total of 23.017 ECG assessments). This analysis has shown that oral panobinostat monotherapy at doses up to 40 mg TIW weekly and 45 mg TIW every other week was safe and well tolerated with no clinically significant QTc interval changes observed. Major outliers (QTcF >500 ms) were observed in two patients (less than 1 % of patients) up to doses of 45 mg, and these sporadic cases were generally associated with significant comorbidities (e.g., underlying heart disease, hypertension, and severe electrolyte disturbances). Baseline QTcF and age, but not dosing schedule, were identified as predictive factors for QT prolongation. Significant mean and maximum QTcF interval changes were observed in Cycle 1 on Days 1 and 5 after the first and the third consecutive dose of panobinostat. Beyond Day 5, mean QTcF values showed a trend towards normalization compared with baseline up to the completion of Cycle 2.
- With a dosing interval of 48 hours and the specific dosing schedule in this protocol (panobinostat intake on days 3, 5, 8, 10, 12, and 15), the ECG monitoring schedule was adjusted as follows: Cycle 1 Day 3 (first panobinostat dose), Days 8 and 12 (third and fifth consecutive dose of panobinostat) as well as on Day 3 of Cycle 2 and all subsequent cycles. ECGs time points at screening and EOS visit did not change
- No study-drug related prolonged QTcF has been observed in this study. Two grade 3 QTcF prolongation events have been reported, each one in the 30 mg or 40 mg

[redacted]

panobinostat dose cohort; none of which was suspected to be related to the study treatment. One occurred at C2D18 and the other at C1D26. The individual events resolved from several hours to approximately 2-3 days after their onset and required no actions with regards to the study treatment.

- With this adjusted ECG monitoring schedule, patient safety will remain uncompromised while eliminating excessive tests that are inconvenient for patients.
- To align with the current LBH589 guidance, the use of concomitant medications (as specified in the post-text supplement 3) has been updated. The current LBH589 guidance provides new information for the management of co-medications that prolong the QT interval, are strong CYP3A4/5 inhibitors or are CYP2D6 substrates. It also includes an updated list of medications which was developed in collaboration with an external cardiology consultant and is based on the ARIZONA CERT website on drugs that prolong the QT interval and/or induce Torsades de Pointes or ventricular arrhythmia (...azert.org/medical-pros/drug-lists/drug-lists.cfm). Additional information from the two drug-drug interaction studies [CLBH589B2110] and [CLBH589B2109] were incorporated.
- To date, none of the patients enrolled in this trial were concomitantly treated with dolasetron mesylate which should no longer be used to prevent nausea and vomiting associated with cancer chemotherapy in conjunction with panobinostat (LBH589). With regards to the medications (which have since been removed from the list of prohibited concomitant medications), three protocol deviations with respect to the concomitant use of aprepitant have been reported.

Rationale for other changes in this amendment:

Editorial corrections were needed in order to provide clarifications, increase the consistency of the document and rectify typographical errors throughout.

- The primary objective of the original protocol (specified as the primary objective of the phase Ib part in the proposed amendment) was clarified to indicate that the dose being selected to go forward with, in the phase IIb part, will be based on considerations of the MTD estimation process using the BLRM, and on an overall assessment of safety taking into consideration long term tolerability data from subsequent cycles. The selected dose which would be referred to as the recommended phase II dose (RPIID) could be the same as the MTD but will not exceed it under any circumstance. This specification of the primary objective is consistent with the description of the dose escalation procedure and the statistical principles guiding it, in sections 6.7.1.4 and 10.1.4.2 of the protocol.

[redacted]

- To provide clarifications on study procedures, time points, study visit terminology
  - Section 7.1.8 including table 6-4 header has been rephrased to clarify that only QT interval prolongation is excluded from the general guidance on dose adjustments for non-hematological toxicities. To date, two treatment-related cardiac toxicities (electrocardiogram T-wave inversion and atrial fibrillation and syncope) have been reported. With regards to the T-wave inversion, the study drug was interrupted for one dose (C1D15) and the patient continued the study without any dose adjustments after exclusion of a myocardial infarction and normalization of the electrocardiogram after

[redacted]

two days. Due to the suspected study drug relationship both cases were considered a DLT.

- The first visit (days -14 to -1) where screening activities are to be performed is indicated as 'baseline' visit. The term 'baseline visit' has been replaced with the term 'screening visit'.
- Clarifications for Study Treatment Discontinuation, End of Treatment and End of Study have been provided in sections 6.7.3, 6.7.4 and 6.7.6
- The narrow time window for laboratory evaluations on Day 1 of each cycle, in particular hematology and biochemistry has been extended from 48 hours to 72 hours.
- [redacted]
- [redacted]
- In section 7.5.1 it has been clarified, that if additional non-study response assessments are being performed the number of units for red blood cells and/or platelets transfusions should be collected in the additional assessments transfusion CRF pages. This optional data recording only applies for the additional response assessment.
- Red blood cell count (RBC) has been added in Section 7.5.4.1 (hematology) to provide details on hematology tests to be performed, in particular complete blood count.

- To align with current standard CRF pages
  - Abnormal laboratory value(s) and Abnormal test procedure result(s) are no longer part of the standard EOT CRF page as they are considered AE(s) wherefore they have been removed from the list of End of Study reasons in section 6.7.4.
- To implement the most recent pregnancy protocol language based on the Novartis Guideline on Prevention of Pregnancy
- To align with the working instructions for Eligibility Check prior to Randomization

Changes to the protocol

The major changes that are made to the protocol are listed below and incorporated directly in the protocol with track changes using strike-through red font for deletions, red underlined for insertions. Where appropriate, changes to the protocol body will be made to corresponding sections for consistency. Additional minor changes (e.g., correction of typographical errors) and re-phrase of existing sentences to be more precise in wording are only incorporated directly in the protocol with track changes.

Changes introduced for the phase IIb part

- Study Title has been modified and the phase IIb information added.

[redacted]

- Section 1.3.2 has been added to describe the current data from the phase Ib part of the study
- Section 3: Objectives have been specified to describe the endpoints of the phase IIb part
- Section 4: The Study Design has been modified to introduce the randomized, two-arm phase IIb part.
- Section 6.1 and subsections have been revised with regards to the terminology used for investigational, combination and control drugs.
- Section 6.1.1.2 has been revised to describe how the combination and/or control drug will be supplied in the phase IIb part
- Section 6.3 describes the treatment schedule in the phase IIb part of the study including the addition of Figure 6-2.
- Section 6.5 describes the treatment assignment in the phase IIb part including the addition of subsection 6.5.1 for IVRS procedures.
- Section 6.4.7 has been amended to describe collection and capturing of survival data after End of Study.
- Section 7 and Table 7-1 describes the modifications to patient visit assessments including pharmacokinetic (PK), [redacted] collection timepoints.
- Table 7-2 has been added to describe the treatment visit schedule after 12 cycles [redacted]
- Section 8.3 has been amended to introduce a steering committee for the phase IIb part of the study.
- Section 10 has been updated to reflect the statistical details for the phase I/IIb study.
- The synopsis was updated according to the changes described above.

Changes introduced to adjust with new safety information, the programs updated ECG schedule and post-text supplement on concomitant medications

- Section 5.1 and 5.2 have been amended removing inclusion criteria #4 and adding exclusion criteria #19 and providing clarification on baseline cardiac assessment tests (exclusion criteria #9).
- Section 7.5.3 including Table 7-3 has been adjusted according to the programs updated ECG monitoring schedule and to provide clarification on methods for cardiac assessments
- Table 7-1 (Visit evaluation schedule) including footnotes was revised according to the protocol amendment and the existing protocol
- Post-text supplement 3 has been adjusted to align with the current LBH589 guidance on the use of concomitant medications

[redacted]

Other Changes in this amendment

- The primary objective of the original protocol (specified as the primary objective of the phase Ib part in the proposed amendment) was clarified in all relevant sections of the protocol.
- Section 1.2 was aligned with data on file with regards to response rates for AML patients treated in the B2102 study (manuscript for publication under preparation).
- Clarifications for Study Treatment Discontinuation, End of Treatment, Follow up and End of Study have been incorporated in 6.7.3, 6.7.4, 6.7.5, and 6.7.6
- The list of EOT reasons provided in Section 6.7.4 has been aligned according to the current standard EOT CRF page.
- Clarification on eligibility checks prior to randomization were provided in section 6.5.1 and section 7 of the proposed amendment.
- Clarifications for Screening visit has been incorporated in all relevant sections in the proposed amendment including Table 7-1
- Section 7.1.8 including the header of Table 6-4 has been changed to provide clarification on dose adjustment for cardiac toxicity.
- [redacted]
- Clarification on time-window and study procedures have been incorporated in Section 7.5.4.1 Hematology and 7.5.4.3 Biochemistry.
- Section 8.2 has been aligned with the current pregnancy language
- 2008 has been removed from the reference on the Investigator Brochure in all relevant sections of the protocol.
- Reference to EMA and FDA with regards to the Vidaza product label has been removed in sections 6.1.2.2, 6.7.1.2 and the reference section
- To amend the List of Abbreviations
- Editorial corrections were made in order to provide clarifications, increase the consistency of the document and rectify typographical errors throughout including tables

IRB/IEC/REB Approval

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 and Health Authority approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1 (released on 21 April 2010)

Please refer to Section 1.4 History of amendments

[redacted]

Oncology clinical study protocol synopsis

Investigational drug	LBH589
Protocol no.	LBH589H2101
Study phase	Ib/IIb
Study title	A phase Ib/IIb, open-label, multi-center, study of oral Panobinostat (LBH589) administered with 5-Azacitidine (Vidaza®) in adult patients with Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML) or Acute Myeloid Leukemia (AML).
Background	Tumor cells inactivate transcription of growth control and pro-apoptotic genes in order to sustain proliferation and survival. Methods of gene inactivation include transcriptional silencing by hypermethylation of CpG islands in gene promoter regions and by hypoacetylation of chromatin preventing access of DNA-binding transcriptional regulators to promoter regions of genes. Reversal of these epigenetic processes results in up-regulation of genes that can reverse the malignant phenotype by a number of means including the induction of apoptosis and differentiation. Since these two processes are independent, but mechanistically related, the reversal of both processes can lead to greater gene transcription than the reversal of either one alone. 5-Azacitidine (5-Aza) is a demethylating agent and has been approved by FDA for the treatment of patients with all FAB subtypes MDS and by EMEA for the treatment of patients with high-risk MDS, CMML and AML, not eligible for hematopoietic stem cell transplantation. Panobinostat is a deacetylase inhibitor (DACi) that has been investigated in patients with lymphoid and myeloid malignancies as well as solid tumors. It has shown single-agent activity in cutaneous T-cell lymphoma (CTCL), and hematological disorders including HL, AML, MDS and chronic idiopathic myelofibrosis (CIM). Pre-clinical studies have demonstrated that the administration of a demethylator followed by a deacetylase inhibitor (DACi) leads to greater gene re-expression and apoptosis induction than either alone. Consequently, a number of clinical trials have been conducted by several groups using 5-Aza in combination with DACi agents such as phenylbutyrate, valproic acid, belinostat and vorinostat. Overall, this type of combined therapy appears to be not only safe, but has also shown a superior response rate compared to single agent epigenetic therapy, although this observation needs be confirmed in prospective randomized clinical trials. Of note is that slow onset of response, seen for single agent 5-Aza therapy in MDS, CMML and AML patients, appears to be accelerated by combining 5-Aza with DACi, with a median time to response of 1 course (range, 1 to 3 courses) in contrast with the 4 to 6 courses for single-agent 5-Aza. (Silverman et al 2008) The strong preclinical rationale, encouraging clinical activity of single agent panobinostat, as well as published data showing enhanced clinical activity by combining two epigenetic-modifying agents suggest that panobinostat and 5-Aza can be combined safely and be a therapeutic option of benefit for the patient.

Purpose/rationale	The primary purpose of the phase Ib part of this study is to determine the maximum-tolerated dose (MTD) and/or recommended phase II dose (RPIID) for the panobinostat / 5-Aza drug combination in patients with MDS, CMML or AML. *In vitro*, the combination of a hypomethylating agent and a DAC inhibitor have been shown to have a synergistic effect both in terms of leukemia cell killing, and also in terms of gene reactivation. Based on this concept, a number of early clinical trials have been conducted by several groups using either 5-Aza in combination with agents such as phenylbutyrate (Gore 2006, Maslak 2006), MS-275, or valproic acid (Soriano et al 2007). All these studies have shown promising results compared to hypomethylating therapy alone and support a combined epigenetic therapeutic approach. It is expected that the combination of these two agents can be safely administered and result in clinical benefit for the patients. As per registered label, 5-Aza is given subcutaneously (sc) for 1 week (Day 1-7). Panobinostat will be administered intermittently (Day 3, 5, 8, 10, 12, and 15) over 2 weeks in a 28-day cycle. In the two-arm, randomized phase IIb part of the study patients will be treated with panobinostat at the RPIID in combination with 5-Aza versus 5-Aza alone. The schedule of the phase Ib part will be followed. The primary purpose is to assess preliminary efficacy of this new regimen and to further characterize safety and tolerability.
Objectives	**Phase Ib part** **Primary objectives** • To determine the MTD and/or RPIID of oral panobinostat in combination with a fixed dose of 5-Aza in adult patients with MDS, CMML, or AML. **Secondary objectives** • To characterize the safety and tolerability of panobinostat in combination with 5-Aza in the target patient populations [redacted] As of amendment 2, the primary objective of the phase Ib part has been met and the recommended phase II dose (RPIID) has been determined to be 30 mg of oral panobinostat once daily on day 3, 5, 8, 10, 12, and 15 in combination with 5-Aza as per the registered label (75mg/m^2 on day 1-7). Dose escalation was not continued up to the MTD because of long term tolerability considerations. **Phase IIb part** **Primary objective** • To assess preliminary efficacy of treatment with the panobinostat and 5-Aza combination at RPIID relative to treatment with single agent 5-Aza through the assessment of composite CR (CR or CRi or bone marrow CR). **Secondary objectives** • To assess preliminary efficacy of treatment with the panobinostat and 5-

[redacted]

	Aza combination at RPIID relative to treatment with single agent 5-Aza through the assessment of clinical response other than the composite CR specified in the primary objective, 1-year survival, and time to progression (TTP). • To characterize the safety and tolerability of panobinostat at RPIID in combination with 5-AZA, as well as, 5-AZA alone in the target patient population. [redacted]
Endpoints (efficacy, safety)	**Phase Ib part** **Primary Endpoint**: • Incidence of dose limiting toxicity (DLT) Secondary Endpoints: • Type, duration, frequency and relatedness of Adverse Events (AE). AE severity will also be assessed according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 3.0) • Laboratory (biochemistry, hematology) • ECG monitoring (central review by eRT) [redacted] **Phase IIb part** **Primary Endpoint**: • Composite CR (CR or CRi or bone marrow CR) **Secondary Endpoints**: • Clinical response for AML: PR; for MDS/CMML: PR and Hematologic Improvement (HI) • Overall response (CR or CRi or bone marrow CR or PR) • 1-year survival • Time to progression (TTP) based on the Guidelines for Implementation of IWG response criteria in AML, MDS and CMML according to Cheson 2003 and 2006 [Post-text supplement 1] • Type, duration, frequency and relatedness of Adverse Events (AE). AE severity will be assessed according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 3.0) • Laboratory (biochemistry, hematology) • ECG monitoring (central review by eRT) [redacted]

[redacted]

Study design	This is an open-label, multi-center phase Ib/IIb trial. The primary objective of the phase Ib part is to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RPIID) of oral panobinostat in conjunction with a fixed dose of 5-Aza in adult patients with MDS, CMML or AML. The phase IIb part, that will commence once MTD and/or RPIID is established, has a randomized, two arm design and is designed to assess preliminary efficacy of panobinostat (in combination with 5-Aza) at RPIID relative to 5-Aza alone, the current standard of care, In the phase Ib part, escalating doses of oral panobinostat will be administered in combination with the registered schedule of subcutaneous (sc) of 5-Aza (75 mg/m^2 daily for 7 days). A minimum of three patients constitutes a cohort for each dose level. During this iterative process the dose limiting toxicity (DLT) will be assessed after each cohort has completed Cycle 1. In each subsequent cohort, patients will receive a dose of panobinostat guided by the Bayesian logistic regression model with overdose control (EWOC) together with a standard dose of 5-Aza until the MTD and/or RPIID is determined. Starting dose of panobinostat will be 20 mg. At least 9 evaluable patients need to be treated at a certain dose level before this dose can be declared to be the MTD and/or RPIID. As of August 2011, the recommended phase II dose (RPIID) was determined to be 30 mg of oral panobinostat once daily on day 3, 5, 8, 10, 12, and 15 in combination with azacytidine (5-Aza/Vidaza®). Additional 80 patients will be randomly assigned in a 1:1 ratio into the phase IIb part of the study receiving 30 mg of panobinostat plus 5-Aza (investigational arm) or single agent 5-Aza (active control arm). Single agent 5-Aza will be administered according to the registered label (75mg/m^2 daily for 7 days), Patients will continue treatment until disease progression, unacceptable toxicity or consent withdrawal, whichever comes first The core clinical study report will be based on a data cut-off corresponding to the time point where all patients have either completed 12 cycles of study treatment or discontinued study treatment for any other reason whichever comes first. An addendum to the core clinical study report (encompassing both phase Ib and phase IIb parts) will be provided at the completion of the study to summarize and/or list the additional safety and efficacy data as appropriate. Patients who have completed 12 cycles of study treatment and are assessed by the Investigator to have the potential to benefit from ongoing treatment will continue their assigned treatment allowing collecting and reviewing safety, efficacy and survival data. After the data-cut off point for the CSR, a reduced visit and assessment schedule will be applied.
Population	Adult patients with IPSS INT-2 or high risk MDS, CMML or AML not eligible for HSCT
Inclusion/exclusion criteria	Inclusion 1. Adult patients (age ≥ 18 years) who are candidates for treatment with 5-Aza and present with one of the following: • intermediate-2 or high-risk myelodysplastic syndromes according to the International Prognostic Scoring System (IPSS). OR • AML with multilineage dysplasia and maximum of 30% blasts (former RAEB-T according to FAB) OR • chronic myelomonocytic leukemia (CMML)

[redacted]

	2. ECOG performance status ≤ 2 3. Patients must have the following laboratory values unless elevations are considered due to MDS or leukemia: AST/SGOT and/or ALT/SGPT ≤ 2.5 x ULN; serum creatinine ≤ 1.5 x ULN; serum bilirubin (total and direct) ≤ 2 x ULN; serum electrolytes (e.g. Calcium, Magnesium and Potassium) are within normal ranges for the institution 4. *- Not applicable-* 5. Negative pregnancy test 6. Patients who are clinically euthyroid 7. Written informed consent obtained prior to any screening procedures Exclusion 1. Planned hematopoietic stem-cell transplantation (HSCT) 2. Patients with therapy-related MDS 3. Patients with therapy-related AML and/or relapsed/refractory AML 4. Clinical symptoms suggesting CNS leukemia 5. Concurrent therapy with any other investigational agent 6. Prior treatment with deacetylase inhibitor(s) 7. Prior treatment with 5-Azacytidine or 5-aza-2'-deoxycytidine 8. Time windows for prior therapies: Last dose of therapy, including cytokines and/or retinoids, immunotherapy, low-dose ara-C, investigational agent less than 28 days with the exception of hydroxyurea (24 hours) prior to receipt of study medication or AEs that have not recovered at least to NCI CTCAE Grade 1. 9. Patients with impaired cardiac function including any of the following: • Complete left bundle branch block or use of a permanent cardiac pacemaker, congenital long QT syndrome, history or presence of ventricular tachyarrhythmia, clinically significant resting bradycardia (<50 beats per minute), QTcF > 460 ms on screening ECG, or right bundle branch block + left anterior hemiblock (bifascicular block) • Presence of unstable atrial fibrillation (ventricular response rate >100 bpm). Patients with stable atrial fibrillation are eligible provided they do not meet the other cardiac exclusion criteria • Previous history of angina pectoris or acute MI within 6 months • Screening LVEF <45% by echocardiography or MUGA • Other clinically significant heart disease (e.g. uncontrolled hypertension or history of poor compliance with an antihypertensive regimen). 10. Drugs which may cause QT prolongation and the treatment cannot be discontinued or switched to a different medication prior to starting study drug. 11. Any of concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study. For example: • Uncontrolled diabetes • Active or uncontrolled infection • Uncontrolled hypothyroidism • Acute or chronic liver or renal disease 12. Impairment of gastrointestinal (GI) function or GI disease that may

[redacted]

	significantly alter the absorption of oral panobinostat (e.g., ulcerative diseases, diarrhea, malabsorption syndrome, or small bowel resection). 13. HIV, Hepatitis B/C infection according to the medical history (testing will not be performed). 14. Female patients who are pregnant or breast feeding or patients of childbearing potential (WOCBP) not willing to use a double barrier method of contraception during the study and for 3 months following the last dose of study drug. 15. Male patients whose sexual partner(s) are WOCBP who are not willing to use a double barrier method of contraception, one of which includes a condom, during the study and for 3 months after the end of treatment. 16. Suspected hypersensitivity to 5-Aza or Mannitol 17. Inability to swallow capsules 18. Unwilling or unable to comply with the protocol 19. Patient has evidence of clinically significant mucosal or internal bleeding
Patient numbering	Upon signing the informed consent, each patient in the study will be uniquely identified by a 9 digit patient number, which is a combination of his/her 4-digit center number and 5-digit subject number. In the phase IIb part, a separate numbering scheme, different from the one used in the phase Ib part, will be applied for the 5-digit subject number. The first patient, at each site, in the phase IIb part will be assigned the subject number 10001, and subsequent patients at the site, will then be assigned consecutive numbers (i.e., the second patient is assigned patient number 10002, the third patient is assigned patient number 10003 etc).
Investigational and control drugs	Terminology used: Study drug = panobinostat Combination drug = 5-Aza Control drug = 5-Aza (only in phase IIb part) Study treatment = panobinostat + 5-Aza
Dose, regimen, treatment cycle	A study treatment cycle lasts 28 days. 5-Aza will be administered by sc injection of 75 mg/m^2 on Days 1 to 7. The study drug panobinostat will be administered orally on Days 3 and 5 in week 1, on Days 8, 10, 12 in week 2, and on Day 15 in week 3 of the treatment cycle (= total of 6 oral panobinostat doses).. In the phase IIb part, the planned dose of panobinostat is 30 mg, which is the RPIID, determined in the phase Ib part of the study
Supply, preparation, and administration	Oral panobinostat is available as 5-mg,10-mg (when available) or 20-mg capsules and will be dosed orally on a flat scale of mg/day. In the phase Ib part, 5-Aza will be supplied by the Sponsor (Novartis); For the phase IIb part, 5-Aza will be purchased commercially as part of standard care. 5-Aza will be supplied by Novartis only for patients from those countries where 5-Aza is not available as standard care, or where no alternative method of obtaining or paying for 5-Azabased on the patient's local regulation can be identified. 5-Aza is administered sc Day 1-7 of the treatment cycle according to manufacturer's instructions.
Visit schedule and assessments	See Table 7-1, Table 7-2 and Table 7-3
Efficacy assessment(s)	The IWG criteria for response in MDS, CMML (Cheson et al 2006) and AML (Cheson et al 2003) will apply to evaluate disease response as implemented in [Post-text supplement 1].

[redacted]

Special safety assessment(s)	Serial ECGs will be taken for cardiac safety.
Patient reported outcomes	There are no Quality of Life assessments in this protocol
Pharmacokinetics	Pharmacokinetic samples of panobinostat will be collected at pre-dose on Cycle 1 Days 4, 5, and 8 in all patients participating in the phase Ib part of the study. Whole blood (3 mL per sample) will be collected and stored frozen at < -60C before shipping to Novartis for analysis. Panobinostat plasma concentrations will be measured using a validated LC/MS/MS method with a LLOQ of 0.5 ng/mL or lower. Plasma panobinostat trough levels (C_{min} in ng/mL) will be summarized by study day. No pharmacokinetic samples of panobinostat will be collected and analyzed in the phase IIb part of the study.
[redacted]	[redacted]

[redacted]

	[redacted]
Exploratory Biomarker pharmacodynamic studies involving tumor samples	Not applicable.
Optional Biomarker studies on additional or remaining samples	Not applicable
Data Monitoring Committee	A Data Monitoring Committee will not be in place for this trial. Instead, in the phase Ib part of the study, Novartis and the study investigators agree to convene once each treatment cohort has completed (or earlier in case of DLT) to make decision on whether to escalate the dose any further, or whether to de-escalate and/or expand recruitment into particular cohort/s. This group will also decide when the MTD and/or RPIID for panobinostat in combination with 5-Aza has been reached. In the phase IIb part a steering committee will be established.
Statistical methods and data analysis	**Phase Ib part** An adaptive Bayesian logistic regression model (BLRM) for combination therapy, including the escalation with overdose control (EWOC) principle will be used to guide the dose escalation to determine the MTD of panobinostat in combination with a fixed dose of 5-Aza. MTD will be assessed during the first treatment cycle. Historical data of 5-Aza regimens as well as data from study [CLBH589B2102, arm X] for panobinostat were used to derive informative priors for the model parameters. Each cohort will consist of a minimum of 3 patients fully evaluable for therapy-related toxicities over the first cycle of treatment. A dose limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value occurring at any time and assessed as clinically relevant and is considered to be related to the study treatment, unrelated to disease, disease progression, inter-current illness, or concomitant medications. Toxicities will be assessed using the NCI CTCAE, version 3.0. After each cohort of patients has completed the first cycle of treatment, the posterior distribution for the model parameters will be obtained by simulation. Based on the posterior distribution of all model parameters, the corresponding posterior distributions for probabilities of a DLT are obtained. Dose recommendation within each part of the dose escalation will be based on posterior summaries for each dose combination including the mean, median, standard deviation, 95%-credibility interval, and the interval probabilities for under-dosing, targeted, excessive, and unacceptable toxicity. Once updated, the distribution summarizes the probability that the true probability of a DLT for each dose combination lies in one of the following categories: [0%, 20%) under-dosing

[redacted]

	[20%, 35%) targeted toxicity [35%, 60%) excessive toxicity [60%, 100%] unacceptable toxicity. Following the principle of escalation with overdose control, after each cohort of patients the recommended dose combination is the one with the highest posterior probability of DLT in the target interval [20%, 35%) among the doses fulfilling the overdose criteria: there is less than 25% chance of either excessive or unacceptable toxicity. The dose of panobinostat recommended by the adaptive BLRM may be regarded as information to be integrated with a clinical assessment of the toxicity profiles observed thus far in determining the next dose to be investigated. At least 9 evaluable patients are to be treated at a dose level to declare the dose as MTD and/or RPIID. The recommended phase II dose (RPIID) of panobinostat in combination with a fixed dose of 5-Aza will be based on considerations of the MTD estimation process using the BLRM, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles. All adverse events recorded during the study will be listed and summarized. All serious adverse events will be listed by patients and tabulated by type of adverse event and initial dose level. Any other safety information will be listed and tabulated as appropriate.
	[redacted]
	Phase IIb part The planned sample size is 40 per arm, or in other words, 80 in total. It is deemed that an observed improvement of 50% in composite CR rate is clinically relevant in the phase IIb part of the study. Under the assumption that the composite CR rate in the active control arm is 17% (estimate based on Fenaux et al 2009a), the chance of observing a clinically relevant improvement when there is actually no difference in the true composite CR rates between the arms is estimated to be 23% while the chance of not observing a clinically relevant improvement when there is indeed a substantial difference in the true composite CR rates (true composite response rate in experimental arm is 35%) is estimated to be 19%. For all safety analyses, the safety set will be used. For efficacy analyses, the full analysis set (FAS) will be used. All listings and tables will be presented by treatment arm ('as treated' for the safety analyses, and 'as randomized' for the efficacy analyses). Efficacy variables and endpoints The primary efficacy endpoint will be the composite CR (CR or CRi or bone marrow CR) among all patients in the FAS. The following other efficacy endpoints will be considered as part of the

[redacted]

	secondary efficacy analysis: • Clinical response for AML: PR; • Clinical response for MDS/CMML:PR and Hematologic Improvement (HI) • Overall response (CR or CRi or bone marrow CR or PR) • 1-year survival rate • Time to progression Clinical responses will be summarized by treatment arm, overall and within disease type (i.e. AML or MDS/CMML). Percentage rates for composite CR (CR or CRi or bone marrow CR) will be reported along with 95% confidence intervals for both arms. Exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson 1934). Point estimates and confidence intervals for the difference in rates between the treatment arms will also be reported. The 1-year survival rate will be obtained from the Kaplan-Meier curve and its variance will be estimated by Greenwood's formula. Time to progression will also be analyzed through Kaplan-Meier curves. **Safety variables and analysis** All adverse events recorded during the study will be summarized by treatment arm. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by body system, severity (based on CTCAE grades), type of adverse event, and relation to the study treatment. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient, type of adverse event, and treatment arm. The assessment of safety will be based mainly on the frequency of adverse events, on the number of laboratory values that fall outside of pre-determined ranges, and other safety data.

[redacted]

1 Background

1.1 Overview of myelodysplastic syndromes (MDS)

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of myeloid disorders characterized by ineffective hematopoiesis, dysmorphic hematopoietic cells and low blood cell count. The worldwide incidence is approximately five per 100.000 individuals in the general population and rises with increasing age: 4.9 for people aged 50 to 70 years vs. 22.8 for people older than 70 years (Aul et al 2002). Clinical characteristics are variable and diagnosis is typically made on the basis of abnormalities in bone marrow and peripheral blood appearance. As a result, patients with MDS are at risk for symptomatic anemia, infection and bleeding. MDS can arise *de novo* (primary MDS) or following treatment with chemotherapy, radiation therapy or chemical injury (secondary MDS). Depending on the subtype of myelodysplasia, there is a risk of approximately 50% for development of acute myeloid leukemia (AML), which is often refractory to standard treatment.

MDS are characterized by chromosomal numerical alterations or, more rarely, by chromosomal translocations, involving genes critical in controlling hematopoiesis. Epigenetic alterations may also be influential in disease progression. Epigenetic alterations significantly contribute to neoplastic transformation and have prognostic significance in MDS. Alterations may affect the pattern of histone acetylation, histone methylation and DNA methylation and are extremely common in high-risk MDS. Reversal of abnormalities in DNA methylation may restore expression of genes with tumor-suppressive function and provide a novel approach to therapy of MDS (see Section 1.1.2).

Patients with MDS are generally elderly and the presence of co-morbidities does not allow the use of aggressive chemotherapy or bone marrow transplantation.

Different MDS subtypes have been identified based on shared cellular morphology, and two main classification systems have been developed based on these subtypes.

1.1.1 Classification of MDS

The diagnosis and classification of MDS can be based on the French-American-British (FAB) classification system and the more recent updated WHO classification system. (Tefferi and Vardiman 2008). The World Health Organization (WHO) classification of myeloid neoplasms provides an extension and improvement of the FAB classification. New categories consisting of refractory cytopenia with multilineage dysplasia (RCMD), with (RCMD-RS) or without ring sideroblasts, the 5q-minus syndrome, refractory anemia with excess blast-I (RAEB-I) and RAEB-II, and “MDS unclassified” were added to the classification (Muller-Berndorff et al 2006). Chronic myelomonocytic leukemia (CMML) became part of the new group of MPD/MDS overlap disorders. RAEB in transformation (RAEB-t) was eliminated by lowering the blast requirement in the bone marrow for a diagnosis of AML from 30% to 20%, taking into consideration the fact that patients with 20% to 30% blasts (previously called refractory anemia with excess blasts in transformation [RAEB-T]) might have AML. In addition to similarities in the natural history of RAEB-T and AML, RAEB-T responds to combination chemotherapy in a fashion similar to that of AML. (Albitar et al 2002)

[redacted]

The International Prognostic Scoring System (IPSS) issued in 1997 provides a method for prediciting clinical outcome for patients with MDS [Post-text supplement 1]. Critical factors include risk-based cytogenetic subgroups (good, intermediate, and poor), bone marrow blast percentage and cytopenias. Patients are grouped into 4 risk categories based on total scores from these prognostic factors (Greenberg et al 1997)

Table 1-1 International Prognostic Scoring System and prognosis

Risk group	Score	Median survival (years)	Time to AML transformation (years)
Low risk	0	5.7	9.4
INT-1	0.5-1.0	3.5	3.3
INT-2	1.5-2.0	1.2	1.1
High risk	>2.5	0.4	0.2

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic malignancy that is characterized by both myeloproliferative neoplasm and myelodysplastic syndrome. It is characterized by 1) persistent monocytosis > 1x 10^9/L in the peripheral blood (PB); 2) absence of Philadelphia chromosome and BCR-ABL 1 fusion gene; 3) no rearrangement of PDGFRA or PDGFRB; 4) fewer than 20% blasts in the PB and bone marrow; and 5) dysplasia involving one or more myeloid lineages. Reported median survival time is 20 to 40 months and progression to AML occurs in approximately 15-30%. (WHO 2008)

1.1.2 Treatment options in intermediate-2 (INT-2) and high risk MDS

New agents effective in the treatment of MDS have been identified. Earliest among these agents was azacytidine (5-Aza / Vidaza®), the first drug approved specifically for the treatment of MDS.

The first milestone study for 5-Aza was the Phase III trial conducted by the Cancer and Leukemia Group B (CALGB9221) in 191 MDS patients of all FAB subtypes randomized to receive sc 5-Aza (75 mg/m^2/day for 7 days q 28 days) or best supportive care (BSC). While therapy-related mortality was negligible, overall response reached 60%, compared with 5% in the control arm. Recent re-evaluation of the results of all 5-Aza trials, applying IWG criteria of response to treatment in MDS, has confirmed the efficacy of the drug (Cheson et al 2006), indicating a 10-17% complete remission (CR) rate and validating an overall response of 44-47%. In all studies, achievement of response was obtained after at least four cycles of therapy in 75% of MDS-responding patients, but in some cases there were late in time responders. Mean response duration was 15 months. (Silverman 2002, Silverman 2006) (Table 1-2)

[redacted]

Table 1-2 Hematological response and hematological improvement based on IWG criteria for MDS

Trial	Response (%)			
	Overall	CR	PR	HI
AZA-001 sc (n=179)	51	17	12	49
CALGB9221 (5-Aza sc arm [n=99])	47	10	1	36
CALGB9221 (5-Aza after cross-over [n=51])	35	6	4	18
CALGB8921 sc (n=72)	40	17	0	23
CALGB8421 (5-Aza iv; n=48)	44	15	2	27

Data from (Cheson et al 2000)

The CALGB trial did not succeed in assessing the clinical benefit of 5-Aza on overall survival (OS) because of the cross-over allowed to non-responding patients. Therefore, a prospective, randomized, Phase III, trial was conducted to assess 5-Aza's effect on overall survival in patients with higher risk MDS compared with routinely used MDS treatment regimens. (Fenaux et al 2009a)

In the second milestone trial, the AZA-001 study, 358 patients were randomly assigned to 5-Aza (sc 75 mg/m^2/day for 7 days q 28 days) or conventional care regimens (CCR), consisting of BSC, low-dose ara-C or intensive chemotherapy. Patients with IPSS INT-2 and high-risk MDS, refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T) and modified CMML were enrolled. A total of 113 patients originally classified as MDS according to the FAB classification met the criteria for AML according to the more recent WHO classification (i.e. with >20% bone marrow blasts). The primary endpoint of the study was overall survival. In the ITT analysis, 5-Aza treatment was associated with statistically significant improvement in overall survival (OS), thereby suggesting that 5-Aza, acting as demethylating agent at doses lower than those of initial US-NCI studies as cytotoxic agent, may alter the natural history of MDS. After a median follow-up of 21.1 months, median overall survival was 24.5 months for the 5-Aza group versus 15.0 months for CCR group (HR 0.58; 95% CI 0.43-0.77; stratified log-rank p=0.0001). A subgroup analysis indicated that prolongation of OS with 5-Aza included also patients with unfavorable cytogenetics, in particular a 53.6% hematological improvement (HI) in 5-Aza treated -7/del(7q) patients vs. 18.5% HI in -7/del(7q) patients treated with a CCR (Mufti et al 2008).

1.1.3 Overview of safety profile obtained with 5-Aza

The safety profile emerging from the initial phase I, II and III studies in various tumor types is summarized in Table 1-3 and represents data on file in the US-NCI Investigational Drug Branch for 636 patients receiving 5-Aza alone at various continuous dose levels.

[redacted]

Table 1-3 Summary of major toxic effects of 5-Aza

Percentage of patients with toxic effects							
Dose schedule	Dose range (mg/m^2)	Evaluable patients (n)	Nausea	Vomiting	Diarrhea	WBC (<1500/ mm^3)	PLTs (<$10^5/mm^3$)
Daily x 5, iv	50-400	376	71	70	40	24	9
Daily x 10, iv	0.5-2.4[a]	206	76	93	60	27	29
Daily x 10, sc	27-85	18	44	22	16	22	16
5-Day [c]civ	50-200	36	58	58	[b]Occ.	76	25

[a]Expressed in mg/kg; [b]Occasional; [c] Continuous intravenous infusion

Several of the initial Phase I studies showed leucopenia as a dose-limiting toxicity and a dose-related phenomenon. The mean nadir occurred at 25-40 days with a range of 18-56 days. Recovery took place in 1 to 3 weeks. Thrombocytopenia (< 100 x 10^9/L) was reported in 17% of patients receiving the drug. The mean nadir occurred at 18 days with a range of 13 to 21 days.

Two Phase 2 studies of single agent 5-Aza in high-risk MDS (RAEB and RAEB-T) conducted by CALGB showed myelosuppression as the most common toxicity. On the basis of standard CALGB criteria, grade 3 or 4 leucopenia occurred in 59%, granulocytopenia in 81%, and thrombocytopenia in 70% of patients. When hematological toxicity was reassessed centrally using relative changes in peripheral blood counts compared with those at study entry, a decrease of 50% to 74% was defined as grade 3 and 75% or greater was defined as grade 4. Based on these criteria, grade 3 or 4 leucopenia occurred in 43%, granulocytopenia in 58%, and thrombocytopenia in 52% of patients. Toxicity was transient, and patients usually recovered in time for the next treatment cycle. Infection may have been related to treatment in 20% of patients. Nausea or vomiting occurred in 4%. There was one (< 1%) treatment-related death.

In the Phase III AZA-001 study peripheral cytopenias were the most common grade 3-4 adverse events for all treatments with 91% of patients in the 5-Aza group experiencing neutropenia, 85% thrombocytopenia and 57% anemia. Baseline grade 0-2 cytopenia progressed to grade 3 or 4 during treatment in 74% of patients treated with 5-Aza as compared to 72% of patients on CCRs. Discontinuation because of hematological adverse events was higher (5%) in the 5-Aza arm vs. 2% in the CCR arm. However, 5-Aza could be delivered full dose in 86% of patients, who remained on 75 mg/m^2/day throughout the study with no dose adjustments. The median 5-Aza cycle-length was 28 days (range 28-35); 862 (54%) of the 1611 cycle-lengths were 28 days, 413 (26%) 29-35 days, and 336 (21%) longer than 35 days.

In 2004, 5-Aza (Vidaza®) was granted Marketing Authorization by the FDA for treatment of patients with all FAB subtypes of MDS (Vidaza® PI 2004 and 2008). In 2008 EMEA/CHMP has granted Marketing Authorization in EU for 5-Aza treatment of patients who are not eligible for hematopoietic stem cell transplantation with (a) intermediate-2 and high-risk MDS according to the IPSS; (b) CMML (10%-29% marrow blasts without proliferative disorder); (c) AML with 20%-30% blasts and multi-lineage dysplasia, according to the WHO classification (Vidaza® SPC 2008). For more details on the safety profile please refer to the corresponding Prescribing Information (PI).

[redacted]

1.2 Overview of panobinostat (LBH589)

Panobinostat (LBH589) is a potent class I/II pan-DAC inhibitor (pan-DACi) that has shown anti-tumor activity in pre-clinical models and cancer patients. Deacetylases (DAC) target 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 is formulated as an oral capsule and a solution for intravenous (i.v.) injection. A summary of key clinical data on panobinostat is herewith reported, for details please refer to the Investigator Brochure.

In patients oral panobinostat is rapidly absorbed and maximal plasma concentrations are reached within one hour. Its bioavailability is approximately 40% and the elimination half-life is ~ 16 hours. Using intermittent, i.e. three-times-a-week weekly, administration schedule, the time to reach steady-state panobinostat plasma level is approximately seven days.

Oral panobinostat as a single agent has been tested in hematological malignancies in a large Phase I study [CLBH589B2102] (Spencer 2007, Ottmann 2008). This study was planned to evaluate 2 schedules:

- Arm 1 - three-times-a-week every week
- Arm 2 - three-times-a-week every other week

Within each schedule (arm) patients were assigned to one of two subgroups, based upon the type of their hematological malignancy. Patients with leukemia, MDS and other hematological malignancies characterized by impaired bone marrow were included in subgroup X, while patients with lymphoma or myeloma were included in subgroup Y. The subgroups differed with respect to the definition of hematological dose limiting toxicity (DLT); neutropenia and thrombocytopenia were considered DLT only in the subgroup Y.

Enrollment into study [CLBH589B2102] has been completed to 152 patients. In the study database, clinical data are available for 146 patients (Arm 1: 90 total [64 subgroup X, 26 subgroup Y]; Arm 2: 56 total [33 subgroup X, 23 subgroup Y]). A summary of the dose escalation in Arm 1 and Arm 2 is presented in Table 1-4 and Table 1-5, respectively. Only data on subgroup X are presented since MDS patients were assigned to this subgroup in study [CLBH589B2102]. Information on subgroup Y can be retrieved from the Investigator Brochure.

Table 1-4 Study CLBH589B2102 dose escalation summary - Arm 1 (three-times-a-week every week)

Subgroup	Dose Level (mg)	N. Patients Evaluable/Treated	Cycle 1 DLTs
X (Leukemias, MDS, Myelofibrosis)	20,30	12/16	None
	40	8/10	G3 fatigue-2 pts
	60 (MTD)	12/16	G3 fatigue-1pt
	80	7/11	G3 QTcF prolongation +G3 fatigue-1pt G3 QTcF prolongation-1pt G3 cardiac insufficiency-1pt G3 fatigue-1pt

Table 1-5 Study CLBH589B2102 dose escalation summary - Arm 2 (three-times-a-week every other week)

Subgroup	Dose Level (mg)	N. Patients Evaluable/Treated	Cycle 1 DLTs
X	30,45,60	20/24	None
(Leukemias, MDS, Myelofibrosis)	80[1]	8/9	G3 QTcF prolongation-1pt G3 atrial fibrillation-1pt G3 fatigue-1pt G3 bilirubin-1pt

[1] MTD was not determined for the every other week schedule as this schedule did not show signals of clinical activity of single agent panobinostat in the study population.

[2] Dose escalation above 60 mg was not permitted due to DLTs observed at 80 mg in Group X.

The MTD with the three-times-a-week weekly schedule of single agent panobinostat in patients with leukemias/MDS was declared to be 60 mg.

Across Arm 1 and 2, a total of 4,834 post-dose ECGs were performed in 146 enrolled patients. No dose dependent increase in mean change from baseline QTcF was noted. Five patients (3%) experienced QTcF >500 ms. However, all five patients were among the 76 patients (7%) treated at dose levels ≥60 mg.

A preliminary evaluation of clinical data from 71 patients with AML indicated that:

- no antileukemic activity was observed in patients treated in Arm 2 (three-times-a-week every other week),
- no antileukemic activity was noted as the dose level of ≤40 mg/day, even with the three-times-a-week weekly regimen.

Thirty-six AML patients were treated in Arm 1 (three-times-a-week every week) at dose levels ≥40 mg. According to data on file, CR was reported in 2 (6%) and PR in 1 (3%) AML patients with prior MDS treated at 60 mg. Prolonged SD was reported in additional 2 (6%) AML patients with prior MDS, lasting for more than 14 months. Another patient treated at the 60 mg dose level had no evidence of anti-leukemic effect during treatment, lasting 3 months. CR was reported 1 month after end of treatment. A patient treated at 40 mg had stable disease during study treatment which lasted for 2 months (Ottmann et al 2008). Stabilization of disease for 20 cycles with decrease in bone marrow blasts was observed in one MDS (RAEB-1) patient out of 7 treated with the three-times-a-week every week schedule. A second patient with therapy related MDS and CD4+/56+ hematodermic neoplasm responded with SD and PR for 6 cycles, respectively. The patient went off study due to NHL progression.

1.3 Combination of DNA methyltransferase inhibitors with deacetylase inhibitors

Widespread epigenetic modifications affecting gene expression are well documented in MDS and AML, and hypermethylation of promoter regions of numerous genes have been shown to play an important role in tumorogenesis. The physiologic relevance is that silencing of some genes enables malignant cells to gain a selective advantage, leading eventually to immortality, invasion, and the development of a neoplastic phenotype. DNA methylation and histone acetylation are independent and modulate gene expression. In fact, chromatin status is

[redacted]

determined by chemical modifications occurring directly on DNA. Methylation recruits methyl-binding proteins locally and the latter bind protein complexes containing corepressors, DNA methyltransferases (DNMTs) and histone deacetylases. In cancer, repression of gene expression is maintained by corepressor complexes of proteins recruited by regionally hypermethylated DNA.

Whereas aberrant DNA methylation patterns, changes in chromatin structure and in gene expression are common in different tumor types, studies in leukemias have provided paradigmatic examples for the functional implications of genetic and epigentic alterations in cancer development (Leone et al 2008). In hematological malignancies, methylation turns off tumor suppressor genes to achieve an effect similar to (or complementary to) gene mutations.

Perturbation of the balance of transcriptional regulators may lead to aberrant recruitment of histone deacetylase (HDAC) and silencing of tumor suppressor genes (Moe-Behrens and Pandolfi 2003). Complexes involving DNA methyltransferase and HDACs work in coordination to remove acetyl groups from histone tails and add methyl groups to CpG dinucleotides within gene promoter regions, thereby suppressing gene transcription. Inhibiting each of these enzyme complexes may synergistically remove this aberrant silencing, thus contributing to re-expression of essential tumor-suppressor genes. Therefore the concept of combining demethylating agents with DAC inhibitors - both epigenetic modifiers - provides a sound rational strategy. On this biological background, combination therapy with hypomethylating agents and DAC inhibitors has been attempted.

Combination strategies involving either drug sequencing or co-administration of these agents *in vitro* have shown improved activity with greater expression of previously silenced genes (Cameron 1999, Zhu 2003). In addition clinical studies in hematologic malignancies published to date demonstrate feasibility of the association of the two types of agents in these disease settings.

1.3.1 Clinical experience combining 5-Aza and DAC inhibitors

Promising results have been obtained combining treatment of 5-Aza with different DACi (Table 1-6). Nevertheless, the most interesting results up to now have been obtained with vorinostat in MDS and AML patients, with more than 80% early responses. In this trial, oral vorinostat was combined with the 5-Aza approved sc regimen (d1-7 q 28 days) starting on day 3 of the 5-Aza regimen. This combination was well tolerated in repetitive cycles and was active in lower and higher risk MDS, as well as in AML patients. Median time to response was 2 cycles. Among 18 evaluable patients with high risk MDS and AML 83% responded. Responses including CR occurred, but in 57% of patients the abnormal MDS/AML clone persisted, suggesting a modulating effect of the combination therapy on the clone. (Silverman et al 2008)

[redacted]

Table 1-6 Clinical trials of combination regimens with DNMTi and DACi

Schedule	Diagnosis (Pts n.)	Responses	Toxicity	Reference
5-Aza 75 mg/m^2 d1-7 + valproic acid orally 50, 62.5, 75 mg/kg (d1-7) + ATRA 45 mg/m^2/d (d1-7)	MDS (n= 4) AML (n= 49)	12 CR (22%), 3 CRp (5%), 7 BM response (13%)	CNS toxicity	(Soriano et al 2007)
5-Aza 75 mg/m^2 d 1-7 + phenylbutyrate 200 mg/kg for 5 d after 5-Aza	MDS (n= 2) AML (n= 8)	3 PR (30%)	CNS toxicity, fever, nausea, fatigue	(Maslak et al 2006)
5-Aza 50 mg/m^2 d 1-14, 1-10 or 1-5, 75 mg/m^2 d1-5; 25 mg/m^2 d 1-14 + phenylbutyrate 375 mg/kg/d for 7d after 5-Aza	MDS (n= 13) AML (n=18) CMML (n=1)	4 CR (14%), 1 PR (3%), 6 HI (21%)	CNS toxicity, mild nausea, injection side reactions, asthenia, myelosuppression	(Gore et al 2006)
5-Aza 75 mg/m^2 d SC d 1-5 + escalating doses 150-1000 mg/m^2 30 min IV belinostat after 5-Aza	MDS(n=10) AML (n=12) Myelofibrosis (n=1)	2 CR (10%), 1 PR (5%), 4 HI (19%)	Fatigue, N/V, diarrhea, phlebitis	(Odenike et al 2008)
5-Aza 50 mg/m^2 d SC d1-7 escalating to 75 mg/m^2 d 1-7 + escalating doses of Vorinostat 400 mg/d PO x 7d or 14 d to 600 mg/d PO x 3 d or 7 d, starting on d3 of 5-Aza	MDS(n=20) AML (n= 8) Ongoing	9 CR, 2CRi (CR+CRi 53%), 7 HI (39%), 2 SD (11%)	Fatigue, anorexia, N/V	(Silverman et al 2008)

Overall, the clinical experience on the use of epigenetic therapy in hematological disorders, although limited to phase I studies, suggests that this therapeutic approach is safe, well tolerated, and induces higher response rates compared to the single agent. Of note, the slow onset of response consistently seen with single agent 5-Aza appears to be accelerated by combining 5-Aza with a DACi. (Soriano 2007, Silverman 2008)

1.3.2 Update of clinical experience with combining panobinostat with Vidaza from the phase Ib part of this study

A total of 31 patients, with a median age of 70 years (range 34-81), in 3 dose cohorts were enrolled onto the phase Ib part of the CLBH589H2101 study. Of these patients, 6 were treated at a dose level of 20 mg, 18 at 30 mg, and 7 at 40 mg of panobinostat; 28 patients were evaluable for MTD and used in the Bayesian modeling of the dose-DLT relationship.

One DLT of febrile neutropenia was observed at 20 mg and 4 DLTs of dehydration/fatigue, colitis, a 1-day echocardiogram T-wave inversion, and an atrial fibrillation/syncope were seen at 30 mg. Of the 7 patients treated at the 40 mg dose level, 2 DLTs of hyperbilirubinaemia and nausea/vomiting and one withdrawal of consent most likely related to fatigue (grade 3, not study drug related) were reported. As a result, dose levels at 40 mg and above were not further explored.

Based on safety data of 29 patients, the most frequent AEs suspected to be related to the study treatment were gastrointestinal issues and fatigue. Grade 3/4 treatment-related AEs included thrombocytopenia (8 [28%]), neutropenia (5 [17%]), and febrile neutropenia (6 [21%]). Other frequent AEs of all grades, regardless of study drug relationship, included nausea (19 [67%]),

[redacted]

fatigue (18 [62%]), diarrhea (16 [55%]), vomiting (15 [52%]), thrombocytopenia (13 [45%]), and decreased appetite (12 [41%]). The most common serious AEs (SAEs), regardless of study drug relationship, were febrile neutropenia (8 [28%]) and asthenia (5 [17%]).

At the time of amendment 2, 7 patients are ongoing, 6 of which are enrolled into the 30 mg cohort and have completed currently a median of 6 treatment cycles (range 2-16, 28days/cycle). One patient from the 40 mg cohort is in Cycle 10 and no patient is ongoing from the initial 20 mg dose cohort. Reasons for treatment discontinuations other than DLT were new antineoplastic therapy (n=1), adverse event (n=4); disease progression (n=1), and death (n=1) due to disease progression. The treatment duration is exceeding 5 cycles (range 6-16) in 7 patients treated at 30 mg of panobinostat including 2 patients who were initially enrolled at 40 mg but dose-reduced in cycles 4 and 5, respectively.

Based on the DLTs observed in cycle 1 and taking long-term tolerability data into consideration, oral panobinostat at 30 mg/day on days 3, 5, 8, 10, 12 and 15 of a 28-day cycle can be safely combined with 5-aza at the registered label (75mg/m^2 on day 1-7) in patients with intermediate-2 or high-risk MDS, CMML, or AML and was determined to be the recommended phase IIb dose (RPIID).

1.4 History of Amendments

Amendment 2

Refer to section Summary of Previous Amendments

Amendment 1

The rationale for this amendment is to correct inconsistencies within the protocol and to provide clarifications on timing of study procedures. Moreover, the amendment is intended to clarify an exclusion criterion and to provide further details on study procedures. Amendment1 include the following changes to the protocol:

- To be more precise in wording, exclusion criterion #8 was rephrased in order to express the exclusion criteria according to the excluding condition.
- Timing of study procedures in case of a prolonged cycle: weekly laboratory assessments are required in case of a prolonged cycle. These time points have been set to Day 29 which corresponds to the first day of the first week of the cycle prolongation.
- Clarification on time points for assessment of bone marrow: It was clarified to perform bone marrow assessments at the end of each even-numbered cycle.
- Clarification on study visit terminology: The time point for the last assessments including response variables (hematology, [redacted] bone marrow) was defined at the end of treatment. The term ‘end of study visit’ was replaced with the term ‘end of treatment visit’.
- Cleaning of study visit numbers: The visit numbers have been corrected.
- The assessment of extramedullary disease is part of the response assessment procedure as described in [Post-text supplement 1]. In order to provide clear instructions, the description of assessments of extramedullary disease was added to the study protocol.

[redacted]

- The assessment of transfusion dependency is part of the response assessment procedure. In order to harmonize the assessment of transfusion dependency with the response assessment schedule, it was clarified by adding an end of treatment visit for assessment of transfusion dependency.

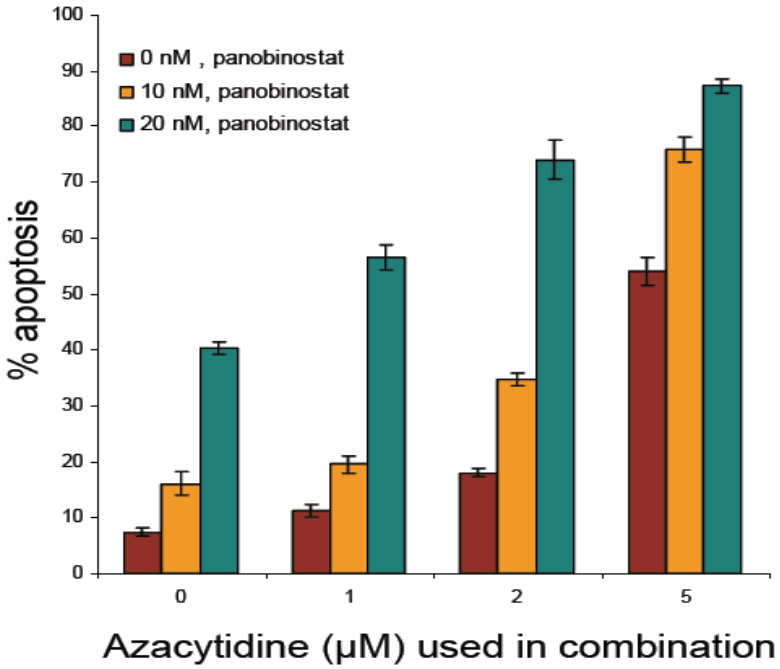
2 Rationale for the investigation of the combination treatment of 5-Aza and panobinostat

2.1 Preclinical and clinical rationale supporting the combination of 5-Aza and panobinostat

Several preclinical studies support the view that pharmacologic targeting of both DNMT and DACi may result in synergistic anticancer activity including data showing synergism for the combination of 5-Aza and panobinostat.

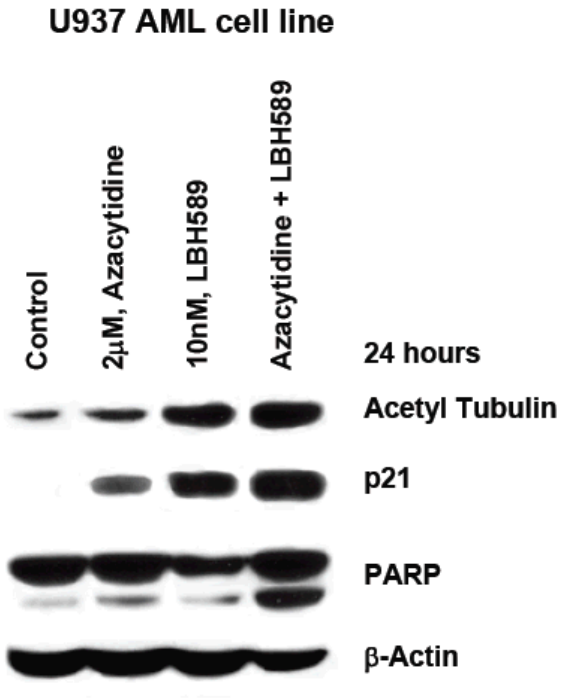
In vitro studies have been conducted to test the effects of combining 5-Aza with panobinostat in leukemic cells. In the first preclinical experiment U937 cells were co-treated with 5-Aza and panobinostat and a dose-dependent apoptosis was measured at 48 hours by Annexin V/PI staining (Figure 2-1). The second experiment indicated synergism of the combination of 5-Aza and panobinostat by inducing the downstream cell cycle regulators p21, acetyl tubulin and Poly(ADP-ribose) polymerase (PARP), a nuclear enzyme activated by DNA breaks, suggesting that the combination potentiates apoptosis, triggers progressive induction of DNA breaks and cell death (Figure 2-2, data unpublished, on file).

Figure 2-1 Dose-dependent induction of apoptosis by *in vitro* combination of 5-Aza and LBH589



[redacted]

Figure 2-2 Expression of cell cycle and apoptotic markers in U937 cell line due to exposure to LBH589 and 5-Aza



These preclinical data support the investigation of this combination in the clinical setting. 5-Aza is already an integral part of treatment especially in higher risk MDS. Although 5-Aza therapy represents a major step forward for patients with higher risk MDS, including significant prolongation of overall survival, all patients will ultimately progress clearly indicating the medical need for new treatment options.

In addition, overall response rate is still quite low and time to response with 5-Aza therapy can last up to 4-5 cycles. Several phase I-II studies combining DNMT and DAC inhibitors have reported encouraging results, the most compelling being the study conducted by Silverman et al. confirming the feasibility of sequential administration of several schedules and doses of 5-Aza and Vorinostat. Median time to response was 2 cycles. Among patients with high risk MDS and AML 10/12 (83%) responded (5CR, 1CRi, 4 HI) but in 57% of patients the abnormal MDS/AML clone persisted, suggesting a modulating effect of the combination on the clone. Being panobinostat is a more potent *in vitro* DACi than Vorinostat (Atadja 2009), it might be reasonable to assume that the combination of 5-Aza and panobinostat, as planned to be investigated in the present protocol, could be able to eradicate abnormal clones.

Oral panobinostat given as single agent has shown clinical activity including CRs in patients with AML (besides patients with relapsed/refractory Hodgkin's disease and CIMF) and stabilization of disease in patients with MDS. (Ottmann et al 2008)

Not all AML or MDS patients respond to DNMT inhibitors such as 5-Aza and most responses are not complete. Responses seen with single agent DAC inhibitors were not impressive. Therefore, there is a need for better therapies to treat this heterogeneous group of

[redacted]

hematological disorders and it is a rational strategy to combine the two epigenetic modifiers 5-Aza and panobinostat in the clinical setting.

2.2 5-Aza dose and schedule

In the present study, the approved dose is 75 mg/m^2 sc on a treatment schedule 7-day q 28 days. In the phase Ib part, 5-Aza will be investigated in combination with escalating doses of panobinostat. In the phase IIb part in combination with panobinostat at RPIID. As per the locally registered product label, a treatment cycle is 28 days, but 14 additional days (up to 42 days) are allowed in order to recover from hematologic toxicity. The approved regimen is the one recommended for the target patient population. Using this regimen will facilitate comparison with results from other trials combining 5-Aza selected regimen with other DACi.

2.3 Panobinostat starting dose and schedule

In the phase Ib part of the study, the oral dose of 20 mg/day represents the proposed starting dose of panobinostat and has been selected based on the following considerations:

- Clinical studies of single agent oral panobinostat in more than 350 patients consistently report a clinical safety characterized by the occurrence of adverse events (AE) of the gastrointestinal tract (nausea, diarrhea) and the hematopoietic system (thrombocytopenia and neutropenia). Additional common toxicities have included fatigue and vomiting. This is expected and in line with preclinical investigations. In 103 patients with primary bone marrow malignancies treated with single agent oral panobinostat 20 mg/day three-times per week every week, the most common AEs were nausea (41%), diarrhea (37%), thrombocytopenia (36%), fatigue (40%), vomiting (26%), pyrexia (27%), and anemia (31%). Grade 3 and 4 thrombocytopenia occurred in 27% of patients, while Grade 3 and 4 fatigue was reported in 7% of patients. Serious Adverse Events (SAEs) with suspected causality to study drug included neutropenia and thrombocytopenia (1.9% each), nausea (1.9%), vomiting and fatigue (1.0% each) and QTcF prolongation (1%). No unexpected toxicities have so far emerged.
- The safety and tolerability of 20 mg oral dosing three-times-a-week in a weekly schedule is being investigated in ongoing phase Ib dose-escalation studies, combining panobinostat with other standard of care compounds in hematologic malignancies. Notably, study [CLBH589B2207] has provided information when combining panobinostat with bortezomib in patients with relapsed or refractory multiple myeloma. Initial analysis of safety data suggests that a dose up to 20 mg/day in combination with standard dose/schedule of bortezomib is safe and well tolerated without occurrence of dose-limiting toxicities (DLTs) in a total of 8 evaluable patients (Sezer et al 2008). In an ongoing investigator-initiated study [CLBH589BUS07T], testing the combination of panobinostat with decitabine in elderly patients with higher risk MDS or AML, the dose of 20 mg three times-a-week has been tolerated without DLTs.
- The probability of excessive or unacceptable toxicity based on the combination Bayesian logistic regression model [Post-text supplement 2] is considered to be less than 1%. Based on prior assumptions derived from historical data of 5-Aza single agent studies and study [CLBH589B2102], the estimate for the probability of excessive or unacceptable toxicity is

[redacted]

12.4% when panobinostat is given together with 75 mg/m^2 of 5-Aza which is far below the overdosing criterion of a probability less than 25%.

- Consequently, the starting dose of 20 mg of oral panobinostat when given for two weeks in a 28 days cycle in combination with 5-Aza is considered to be a clinically acceptable and safe starting dose to be combined with the established doses of 5-Aza.

The recommended phase II dose (RPIID) has been determined to be 30 mg of oral panobinostat once daily on Day 3, 5, 8, 10, 12, and 15 and is proposed as the dose for the phase IIb part of the study.

In the phase Ib as well as in the phase IIb part of the study oral panobinostat will be administered over 2 weeks in a 28-day cycle. 5-Aza and panobinostat will be delivered in a sequential scheme of treatment as follows:

- 5-Aza on Day 1-7 in week 1 of the treatment cycle
- Panobinostat on Day 3 and 5 of week 1 of the treatment cycle
- Panobinostat on Day 8, 10, and 12 of week 2 and on Day 15 of week 3.

Overall 7 doses of 5-Aza (1 week treatment) and 6 doses of panobinostat (2 weeks treatment) will be delivered in a 28 day treatment cycle. The same regimen will be repeated in subsequent cycles. As previously mentioned, the treatment cycle might be extended to 42 days to allow for recovery from toxicity (Section 6.6.1.6)

According to 5-Aza label, treatment should be continued as long as the patient continues to benefit or until disease progression. It is also recommended that patients be treated for a minimum of 6 cycles. Accordingly, the present study stipulates that at least 3 or 4 cycles of the combination 5-Aza and panobinostat should be given unless disease progression or unacceptable toxicity or patient's consent withdrawal are encountered. The rationale for this schedule and its duration is based on the following considerations:

- There are preclinical evidences suggesting that sequential addition of DACi to cells preincubated with DNMTi synergistically reactivates the expression of genes silenced through promoter methylation (Cameron 1999, Zhu 2001).
- Based on this concept, a number of clinical trials have been conducted by several groups using a sequential administration of 5-Aza followed by a DACi such as phenylbutyrate, valproic acid, belinostat and vorinostat (Table 1-6). In all these studies, the DACi inhibitor was delivered following 5-Aza. Two weeks of rest was part of the treatment cycle of 28 days. With this therapeutic approach, evidences of clinical activity and a manageable safety profile were consistently reported, being the most promising results observed with the combination of 5-Aza with vorinostat (Silverman et al 2008). A similar therapeutic approach has been proposed in the present study.
- Although the approved dose and schedule of 5-Aza cause marrow hypoplasia in a limited number of patients (10%), 5-Aza remains a myelosuppressive agent and patients should be monitored for fever, neutropenia, and thrombocytopenia. There is a greater risk of these events occurring during the first two cycles with single agent 5-Aza, after which their frequency is reduced in patients with restoration of hematological function. Mean times to nadir values (across all cycles) for hematological parameters, including absolute neutrophils and platelets, were between 15 and 16 days in the pivotal CALGB 9221 study

of 5-Aza (Silverman et al 2006). On the other hand, preliminary data from the single agent panobinostat Phase I study [CLBH589B2102] suggests that the nadir of treatment-associated thrombocytopenia in patients with reduced blood counts at baseline may occur in the second week of therapy. It is worth noting that clinical experience dictates that continued 5-Aza treatment without dose reduction is critical to improve bone marrow function. In case of the proposed combination of 5-Aza and panobinostat, both agents present overlapping toxicities and thus continued treatment with panobinostat might not allow recovery from toxicity and prompt retreatment in next cycle. Therefore a treatment-free window from day 16 to 28 of the cycle has been preserved in order to allow the patient to recover from toxicities and avoid premature dose reductions or early discontinuations due to overlapping or protracted toxicities. Similar "on/off" dosing schedules have been used with other DAC inhibitors in combination with DNMT inhibitors (see Section 1.3.1).

- Clinical response to 5-Aza in MDS patients follows a typical pattern starting with an increase in platelet counts as first sign of response, followed by an increase in hemoglobin levels. Responses are usually accompanied by a reduction in bone marrow (BM) blasts to less than 5%. Patients can also achieve blast reduction to less than 5% even if this is not accompanied by an improvement in blood counts (Raj and Mufti 2006). Most responding patients demonstrate response at the beginning of the third or fourth month of therapy. Incorporation of 5-Aza into DNA inhibits DNA methyltransferase and induces DNA hypomethylation. This effect is S-phase dependent, and two or more cycles of DNA synthesis are required to alter gene transcription and expression. Thus, three to four cycles of therapy are usually required before an effect becomes clinically apparent.

2.3.1 Drug-drug interaction between panobinostat and 5-Aza

As the oxidative metabolism of panobinostat in human liver is primarily mediated by CYP3A4, with minor contributions by CYP2D6 and CYP2C19, the potential of 5-Aza to inhibit human cytochrome P450 (CYP) enzyme activity was assessed using pooled human liver microsomes. Very little or no inhibition of CYP2D6, or CYP3A4/5 activity was observed at 5-Aza concentrations up to 100 µM, much higher than the concentrations measured in patients with cancer (Rudek et al 2005). In these patients with refractory solid tumors or hematological malignancies, C_{max} values of 5-Aza following 75 mg/m^2/day dosing were 4870.6 ± 1398.1 nM (mean ± standard deviation), which is below the concentration tested for CYP inhibition *in vitro* (Rudek et al 2005). Based on these findings, it is unlikely that 5-Aza would affect the oxidative metabolic clearance of panobinostat *in vivo*.

Conversely, the stability of 5-Aza in human plasma was not affected by the presence of panobinostat (0.5 or 5 µM), indicating that panobinostat is unlikely to inhibit cytidine deaminase, the main catabolic pathway of 5-Aza and other cytidine analogues (e.g. gemcitabine, cytarabine).

In conclusion, a drug-drug PK interaction between panobinostat and 5-Aza is not expected based on this data.

[redacted]

2.4 Target population

The target population for this study is the population of patients with IPSS higher risk MDS, CMML or AML who are candidates for therapy with 5-Aza and who were previously not exposed to therapy with another DNMT inhibitor or DAC inhibitor. All eligible patients will receive 5-Aza approved treatment regimen, which is considered the standard of care for this patient population. The rationale for selecting this patient population is three-fold:

- Patients with IPSS INT-2 or high risk MDS or AML (defined as per WHO as 20-30% blasts in bone marrow) treated with 5-Aza will ultimately progress despite of the overall survival benefit seen with the introduction of 5-Aza. In addition, most seen responses are not complete, the overall response rate is quite low, and responses tend to occur late (after 3 - 4 cycles of therapy). Therefore, there is a need for better therapies to treat this heterogeneous group of hematological disorders providing increased rates of responses earlier.
- In preclinical experiments of 5-Aza plus panobinostat, no evidence for antagonistic activity but the opposite was seen (Section 1.3.1). Adding panobinostat to 5-Aza *in vivo* might translate in a better therapeutic option for patients who are candidates for 5-Aza therapy. The *in vitro* synergistic antileukemic activity of 5-Aza with DACi has been confirmed *in vivo* for other DACi, as well.
- To mitigate the potential risk of increased hematological toxicity, and considering that expected bone marrow toxicity from 5-Aza and panobinostat is clinically manageable, the safety profile of patients will be regularly monitored (peripheral blood cell counts) in order not to expose patients to an unduly high risk of thrombocytopenia, neutropenia and/or infection. In contrast to the continuous 3 times weekly dosing regimen of single agent panobinostat, a treatment break will be introduced from D16 to D28 of each cycle to allow bone marrow recovery, if required.

3 Objectives

3.1 Phase Ib part

3.1.1 Primary objective

- To determine the MTD and/or RPIID of oral panobinostat in combination with a fixed dose of 5-Aza in adult patients with IPSS INT-2 or high risk MDS, CMML, or AML.

3.1.1.1 End-point for primary objective

- Incidence of DLT

3.1.2 Secondary objectives

- To characterize the safety and tolerability of panobinostat in combination with 5-Aza in the target patient population.

[redacted]

3.1.2.1 End-points for secondary objectives

- Type, duration, frequency and relatedness of Adverse Events (AE). AE severity will also be assessed according to NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
- Laboratory (biochemistry, hematology)
- ECG monitoring (central review by eRT)

As of amendment 2, the primary objective of the phase Ib part has been met and the recommended phase II dose (RPIID) has been determined to be 30 mg of oral panobinostat once daily on day 3, 5, 8, 10, 12, and 15 in combination with 5-Aza as per the registered label (75mg/m^2 on day 1-7). Dose escalation was not continued up to the MTD because of long term tolerability considerations.

3.2 Phase IIb part

3.2.1 Primary objective

- To assess preliminary efficacy of treatment with the panobinostat and 5-Aza combination at the RPIID relative to treatment with single agent 5-Aza through the assessment of composite CR (CR or CRi or bone marrow CR).

3.2.1.1 End-point for primary objective

- Composite CR (CR or CRi or bone marrow CR)

3.2.2 Secondary objectives

- To assess preliminary efficacy of treatment with the panobinostat and 5-Aza combination at the RPIID relative to treatment with single agent 5-Aza through the assessment of clinical responses other than the composite CR specified in the primary objective, 1 year survival, and time to progression (TTP).
- To characterize the safety and tolerability of panobinostat at the RPIID in combination with 5-Aza, as well as, 5-Aza alone in the target patient population.

3.2.2.1 End-points for secondary objectives

- Clinical response for AML: PR; for MDS/CMML: PR, Hematologic Improvement (HI)
- Overall response (CR or CRi or bone marrow CR or PR)
- 1-year survival rate
- Time to progression (TTP) based on the Guidelines for Implementation of IWG response criteria in AML, MDS and CMML according to Cheson 2003 and 2006 and specified in [Post-text supplement 1].
- Type, duration, frequency and relatedness of Adverse Events (AE). AE severity will be assessed according to NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
- Laboratory (biochemistry, hematology)
- ECG monitoring (central review by eRT)

[redacted]

4 Study design

This is an open-label, multi-center, phase Ib/IIb study. The phase Ib part of the study is designed to determine the maximum tolerated dose (MTD) and/or the recommended phase II dose (RPIID) of panobinostat administered in a fixed combination of 5-Aza in adult patients with IPSS INT-2 or high-risk MDS, CMML or AML not eligible for HSCT. The phase IIb part, that will commence once MTD and/or RPIID is established, has a randomized, two arm design and is designed to assess preliminary efficacy of panobinostat (in combination with 5-Aza) at RPIID relative to 5-Aza alone, the current standard of care,

In the phase Ib part, patients will receive escalating oral doses of the study drug panobinostat commencing in cycle 1 for a period of two weeks. The dose of 5-Aza will be 75 mg/m^2/day for 7 days.

A treatment cycle is defined as 28 Days in duration. Patients should be treated for a minimum of 6 cycles. Study treatment should be continued as long as the patient continues to benefit or until disease progression or unacceptable toxicity is encountered or consent withdrawal whatever comes first.

At least 3 patients per cohort must be enrolled. During the phase Ib part, patients will be evaluated for DLT (Section 6.6.1.6) using an adaptive Bayesian logistic regression model with overdose control (EWOC) to guide the dose escalation process. Starting dose of panobinostat will be 20 mg. Prior to declaring a dose to be MTD, at least 9 evaluable patients need to be treated at that dose level.

[redacted]

After completion of a given dose cohort, the decision on the dose chosen for the next cohort will depend on the risk assessment using the Bayesian logistic regression method and a medical review of available clinical and laboratory data. Dose-limiting toxicity will be assessed from the safety data of Cycle 1 for each dose level.

The MTD is defined to be the highest daily dose of panobinostat given together with 5-Aza in the first treatment cycle in which the probability to produce medically unacceptable, dose-limiting toxicity (DLT) in more than 35% of the patients is less or equal to 25%. The recommended phase II dose (RPIID) will be based on considerations of the MTD estimation process by the adaptive Bayesian logistic regression model, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at all the different dose levels tested.

As of August 2011, the recommended phase II dose (RPIID) has been determined to be 30 mg of oral panobinostat once daily on day 3, 5, 8, 10, 12, and 15 in combination with azacytidine (5-Aza/Vidaza®).

Additional 80 patients will be randomly assigned in a 1:1 ratio into the phase IIb part of the study receiving 30 mg of panobinostat plus 5-Aza (investigational arm) or single agent 5-Aza (active control arm). Single agent 5-Aza will be administered according to the locally approved label (75mg/m^2 daily for 7 days),

Patients will continue treatment until disease progression, unacceptable toxicity or consent withdrawal, whichever comes first. The core clinical study report (encompassing both, the phase Ib and the phase IIb part of the study) will be based on a data cut-off corresponding to the time point where all patients have either completed 12 cycles of study treatment or discontinued study treatment for any other reason whichever comes first. An addendum to the core clinical study report will be provided at the completion of the study to summarize and/or list the additional safety and efficacy data as appropriate.

Patients who have completed 12 cycles of study treatment and are assessed by the Investigator to have the potential to benefit from ongoing treatment will continue their assigned treatment allowing collecting and reviewing safety, efficacy and survival data. After the data-cut off point for the CSR, a reduced visit evaluation schedule will be applied

5 Population

Adult patients with intermediate-2 or high-risk MDS, AML with multilineage dysplasia and maximum of 30% bone marrow blasts (former RAEB-T according to FAB, currently AML according to WHO definition), or Chronic Myelomonocytic Leukemia (CMML) who are candidates for the treatment with 5-Aza will be enrolled onto the study.

Inclusion/exclusion criteria

The investigator or his/her designee must ensure that all patients who meet the following inclusion criteria are offered enrollment in the study.

[redacted]

5.1 Inclusion criteria

1. Adult patients (age ≥ 18 years) who are candidates for treatment with 5-Aza and present with one of the following:
   - intermediate-2 or high-risk MDS according to the International Prognostic Scoring System (IPSS) OR
   - AML with multilineage dysplasia and maximum of 30% bone marrow blasts (former RAEB-T according to FAB, currently AML according to WHO definition) OR
   - Chronic Myelomonocytic Leukemia (CMML)
2. ECOG performance status ≤ 2
3. Patients must have the following laboratory values unless elevations are considered due to underlying disease:
   - AST/SGOT and/or ALT/SGPT ≤ 2.5 x ULN
   - Serum creatinine ≤ 1.5 x ULN
   - Serum bilirubin (total and direct) ≤ 2 x ULN
   - Serum electrolytes (i.e., Calcium, Magnesium and Potassium) within normal ranges for the institution
4. - Not applicable -
5. Negative pregnancy test
6. Patients who are not clinically euthyroid.
7. Written informed consent obtained prior to any screening procedures

5.2 Exclusion criteria

1. Planned hematopoietic stem-cell transplantation (HSCT)
2. Patients with therapy- related MDS
3. Patients with therapy-related AML and/or relapsed/refractory AML
4. Clinical symptoms suggesting CNS leukemia
5. Concurrent therapy with any other investigational agent
6. Prior treatment with deacetylase inhibitor(s)
7. Prior treatment with 5-Aza or 5-aza-2'-deoxycytidine (decitabine)
8. Time windows for prior therapies: Last dose of therapy, including cytokines and/or retinoids, immunotherapy, low-dose ara-C, investigational agent less than 28 days with the exception of hydroxyurea (24 hours) prior to receipt of study medication or AEs that have not recovered at least to NCI CTCAE Grade 1.
9. Patients with impaired cardiac function including any of the following:
   - Complete left bundle branch block or use of a permanent cardiac pacemaker, congenital long QT syndrome, history or presence of ventricular tachyarrhythmia, clinically significant resting bradycardia (<50 beats per minute), QTcF > 460 ms on screening ECG, or right bundle branch block + left anterior hemiblock (bifascicular block)

- Presence of unstable atrial fibrillation (ventricular response rate >100 bpm). Patients with stable atrial fibrillation are eligible provided they do not meet the other cardiac exclusion criteria
- Previous history of angina pectoris or acute MI within 6 months
- ScreeningLVEF <45% by echocardiography or MUGA
- Other clinically significant heart disease (e.g. uncontrolled hypertension or history of poor compliance with an antihypertensive regimen).

10. Drugs which may cause QT prolongation and the treatment cannot be discontinued or switched to a different medication prior to starting study drug
11. Any of concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study. For example:
    - Uncontrolled diabetes
    - Active or uncontrolled infection
    - Uncontrolled hypothyroidism
    - Acute or chronic liver or renal disease
12. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral panobinostat (e.g., ulcerative diseases, diarrhea, malabsorption syndrome, or small bowel resection).
13. HIV, Hepatitis B/C infection according to the medical history (testing will not be performed).
14. Female patients who are pregnant or breast feeding or patients of childbearing potential (WOCBP) not willing to use a double barrier method of contraception during the study and for 3 months following the last dose of study drug.
15. Male patients whose sexual partner(s) are WOCBP who are not willing to use a double barrier method of contraception, one of which includes a condom, during the study and for 3 months after the end of treatment.
16. Suspected hypersensitivity to 5-Aza or Mannitol
17. Inability to swallow capsules
18. Unwilling or unable to comply with the protocol
19. Patient has evidence of clinically significant mucosal or internal bleeding

6 Treatment

6.1 Investigational and combination drugs

Study drug refers to any Novartis investigational drug(s). For this study, study drug refers to oral panobinostat. Combination drug refers to 5-Aza. For the phase Ib part and in the investigational arm of the phase IIb part of this study, study treatment refers to combination treatment with oral panobinostat and 5-Aza. In the active control arm of the phase IIb part, single agent 5-Aza will be used as control drug

[redacted]

6.1.1 How supplied

Each study site will be supplied by Novartis with open-label oral panobinostat. Immediately before dispensing study drug to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) containing that patient's unique patient number. One component of the packaging has a 2-part label.

Study drug supply and resupply, storage, and tracking/drug accountability

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, the panobinostat should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication 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.

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

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

6.1.1.1 Study drug

Novartis will provide each site with open-label oral panobinostat until it is commercially available. It will be supplied as immediate-release hard gelatin capsules in strengths of 5 mg, 10 mg (when available) and 20 mg which will be given on a flat scale of mg per given day. The capsules are packaged in HDPE bottles with plastic child resistant closures. Following bottle sizes are available for panobinostat (i) 5 mg - 45 capsules per bottle, (ii) 10 mg - 30 capsules per bottle, (iii) 20 mg - 15 capsules per bottle.

6.1.1.2 Combination drug and control drug control

For the phase Ib part, 5-Azacitidine (Vidaza®) will be supplied by Novartis. For the phase IIb part, 5-Azacitidine will be purchased commercially as part of standard care. 5-Azacitidine will be supplied by Novartis only for patients from those countries where 5-Azacytidine is not available as standard care, or where no alternative method of obtaining or paying for 5-Azacytidine based on the patient's local regulation can be identified.

[redacted]

6.1.2 Preparation and storage

6.1.2.1 Study drug

Medication labels will comply with the legal requirements of each country and be printed in the local language. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

6.1.2.2 Combination drug and control drug

5-Aza (Vidaza®); should be prepared and stored in accordance with the manufacturer's instructions.

6.2 Treatment Arms

6.2.1 Phase Ib part

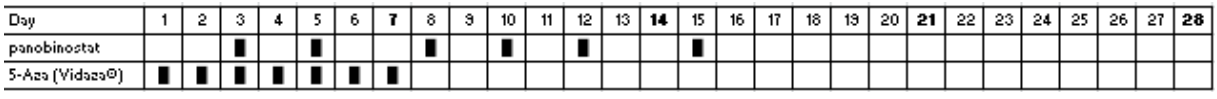
Panobinostat will be dosed on a flat scale of mg/day. In the first week of treatment cycle oral panobinostat dosing starts on Day 3 and is given twice (Day 3 and Day 5), in the second week of treatment panobinostat is given thrice on Day 8, Day 10 and Day 12. In week 3 of the treatment panobinostat is given once (Day 15) (Figure 6-1). Up to a total of six doses of panobinostat will be given per cycle.

Once the MTD and/or RPIID is established, enrollment in the phase Ib part is closed and the phase IIb part of the study will commence. Ongoing patients from the phase Ib part will continue their treatment at the assigned dose level according to the regimen and schedule for the phase Ib part.

Table 6-1 Treatment doses and regimens (Phase Ib part)

Drug	Panobinostat	5-Aza (Vidaza®)
Dose	Escalating doses starting with 20 mg delivered orally	75 mg/m^2 subcutaneously
Regimen	Once daily Day 3, 5 (week 1) Day 8, 10, 12 (week 2) Day 15 (week 3)	Daily for seven days Day 1 to 7 (week 1)
Treatment Cycle	28 Days	

Figure 6-1 Treatment schedule (Phase Ib part)



6.2.2 Phase IIb part

As of this amendment 2, the recommended phase II dose (RPIID) has been determined to be 30 mg of oral panobinostat once daily on day 3, 5, 8, 10, 12, and 15 in combination with azacytidine (5-Aza/Vidaza®); Patients will be randomly assigned in a 1:1 ratio to the phase IIb part of the study receiving 30 mg of panobinostat plus 5-Aza (investigational arm) or single

[redacted]

agent 5-Aza (active control arm). Single agent 5-Aza is the current standard of care and will be administered according to the registered label (75mg/m^2 daily for 7 days).

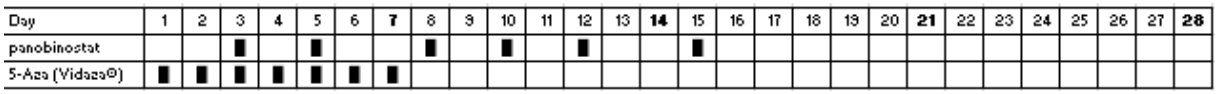
Panobinostat will be dosed on a flat scale of mg/day. In the first week of treatment cycle oral panobinostat dosing starts on Day 3 and is given twice (Day 3 and Day 5), in the second week of treatment panobinostat is given thrice on Day 8, Day 10 and Day 12. In week 3 of the treatment panobinostat is given once (Day 15) (Figure 6-2). Up to a total of six doses of panobinostat will be given per cycle.

Table 6-2 Treatment doses and regimens (Phase IIb part)

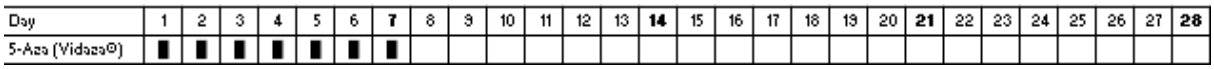
Drug	Panobinostat	5-Aza (Vidaza®)
Dose	30mg (RPIID)	75 mg/m^2 subcutaneously
Regimen	Once daily Day 3, 5 (week 1) Day 8, 10, 12 (week 2) Day 15 (week 3)	Daily for seven days Day 1 to 7 (week 1)
Treatment Cycle	28 Days	

Figure 6-2 Treatment schedule (Phase IIb part)

Investigational arm:



Active control arm:



6.3 Patient numbering

Upon signing the informed consent, each patient in the study will be uniquely identified by a 9 digit patient number, which is a combination of a 4-digit center number and 5-digit subject number. The center number is assigned by Novartis to the investigative site.

For the phase Ib part, at each site, the first patient is assigned subject number 00001, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 00002, the third patient is assigned patient number 00003).

In the phase IIb part, a separate numbering scheme, different from the one used in the phase Ib part, will be applied for the 5-digit subject number. The first patient, at each site, in the phase IIb part will be assigned the subject number 10001, and subsequent patients at the site, will then be assigned consecutive numbers (i.e., the second patient is assigned patient number 10002, the third patient is assigned patient number 10003 etc.).

Only the assigned subject number should be entered in the field labeled "Subject ID" on the CRF. Once assigned to a patient, the patient number will not be reused.

[redacted]

6.4 Treatment assignment

As this trial includes a dose-escalation component, the assignment of a patient to a particular dose level cohort will be coordinated by the Sponsor. For treatment assignment in the phase IIb part of the study IRT procedures will be followed.

6.4.1 IRT procedures

Interactive Response Technology (IRT) will provide contact information and detailed instructions on registration and randomization procedures to each study site.

- At visit 1 the investigator or his/her designee will call to register the patient with IRT.
- Screening procedures may not begin until AFTER the patient has been registered with IRT.
- On Cycle 1, Day 1 (Visit 2) the investigator or his/her designee will again call IRT to randomize an eligible patient to one of the two treatment arms. During this process, eligibility questions must be answered as part of the eligibility check implemented into the system. This process should only occur once the investigator has completed all screening procedures, and considers the patient eligible for participation in this study.
- Study drug kit numbers will be provided to the investigator following successful randomization. This number will be used to provide the randomized patient with the correct study treatment. The investigator or his/her designee must make sure that no study treatment is initiated without calling IRT and that a patient does not start study treatment prior to randomization.
- If the screened and eligible patient fails to be randomized, the IRT must be notified as soon as possible.
- The investigator or his/her designee will notify IRT immediately of patient discontinuation from study.
- Re-supply of panobinostat will occur at 2-month (28 days/month) intervals.
- Medication will be assigned for scheduled visits via the IRT
- Reporting of any emergency code breaks occurrences is not applicable in this trial, since this is an open-label study.

6.5 Treatment blinding

The study is open label.

6.6 Treating the patient

6.6.1 Study treatment administration

The investigator should instruct the patient to take the study treatment exactly as prescribed. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.6.1.1 Study drug administration

- Each dose of panobinostat should be taken with 240 mL of water. Patients should be instructed to swallow the capsules whole and not chew them.

[redacted]

- Panobinostat can be taken with or without food.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.
- Patients must avoid grapefruits, grapefruit juice, Seville (sour) oranges and Seville orange juice during the entire study.
- If the patient forgets to take his/her dose during the morning on a scheduled treatment day then the missed dose should be taken on that same day within 12 hours. After more than 12 hours, that day's dose should be withheld, and the patient should wait to take panobinostat until the next scheduled treatment day. The patient should then continue treatment with the original dosing schedule.

The days when panobinostat and 5-Aza are scheduled together (Day 3 and Day 5 of a treatment cycle), panobinostat should be administered approximately 30 min prior to 5-Aza.

6.6.1.2 Combination Drug and /or Control Drug administration

The dose of 5-Aza will be 75 mg/m^2. 5-Aza should be administered subcutaneously according to the manufacturer's instructions provided in the Vidaza® product information.

6.6.1.3 Dose escalation levels (Phase Ib part)

Starting dose of panobinostat is 20 mg. At all dose levels, the adaptive Bayesian logistic model permits alterations in the dose increments based on the observed toxicities.

Table 6-3 Dose escalation levels

Dose level	Panobinostat oral dose	5-Aza SC
-1	10 mg	75 mg/m^2
1	20 mg	75 mg/m^2
2	30 mg	75 mg/m^2
3	40 mg	75 mg/m^2
4	50 mg	75 mg/m^2
5	60 mg	75 mg/m^2

Panobinostat will be dispensed as follows for the different dose levels:

- Dose Level 1 (20 mg) - one 20 mg capsule to be dispensed
- Dose Level 2 (30 mg) - two 5 mg capsules and one 20 mg capsule to be dispensed
- Dose Level 3 (40 mg) - two 20 mg capsules to be dispensed
- Dose Level 4 (50 mg) - two 20 mg capsules and two 5 mg capsule to be dispensed
- Dose Level 5 (60 mg) - three 20 mg capsules to be dispensed
- If dose level -1 (10 mg) is used - two 5 mg capsules to be dispensed.

The maximum inter-cohort dose escalation permitted is 100%.

6.6.1.4 Criteria for dose escalation and determination of MTD

The primary objective of the trial is to determine the highest safe dose of oral panobinostat that can be given to a patient for a duration of 1 treatment cycle together with a fixed dose of

5-Aza without causing serious, hence dose-limiting side effects/toxicities (DLT) given in a 7-days schedule of 5-Aza.

The MTD is defined to be the highest dose of panobinostat given with 5-Aza in the first treatment cycle. The applied adaptive Bayesian logistic regression model (BLRM) provides a recommendation for the highest dose level of panobinostat in combination with 5-Aza by the dose with maximum probability of targeted toxicity (probability of DLT between 20%-35%). The use of escalation with overdose control (EWOC) principle limits the risk of excessive or unacceptable toxicity (probability of DLT ≥ 35%) to less than 25% (for further details see Section 10.1.4.2 and [Post-text supplement 2]).

In order to be evaluable for the MTD determining set, patients of the safety set need to have received sufficient study treatment as defined in the minimum exposure criteria in cycle 1 (Table 10-1) and had sufficient safety evaluations or discontinued due to DLT in Cycle 1. Patients not experiencing DLT during Cycle 1 must have completed all safety assessments as requested in the protocol during this treatment cycle and meet the minimum exposure criteria to be included in the MTD determining set. Patients who meet the minimum exposure criteria but discontinue early (e.g., for disease progression) will be asked to have all scheduled safety evaluations performed as delineated in the protocol in order to remain evaluable for the MTD determining population. Patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for the MTD-determining set and will be replaced.

At the end of each treatment cohort in the dose escalation part of the study, Novartis will convene a teleconference with the investigators. At the dose escalation teleconference the clinical course (safety information including all DLTs and all ≥ Grade 2 toxicity data during Cycle 1 and ECG) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well. The final decision to dose escalate is not based solely on DLT information, but also on a clinical interpretation of all the relevant toxicity (both DLT and non-DLT) using the BLRM's recommendation as a guideline to the decision making process. The maximum inter-cohort dose escalation permitted is 100%. In any case, the next dose will not exceed the recommended dose by the BLRM. The parties must reach a consensus on whether to escalate the dose any further, or whether to de-escalate or expand recruitment into particular cohorts. Novartis will prepare minutes from these meetings and circulate them within 24 hours to each investigator for comment prior to finalization.

The recommended phase II dose (RPIID) for panobinostat will be based on the overall assessment of the incidence of DLT of the first treatment cycle as provided by the adaptive BLRM in conjunction with safety data generated across treatment cycles at all tested dose levels.

6.6.1.5 Dose escalation

During the phase Ib part of the study, a minimum of 3 patients will be assigned sequentially to a cohort. A cohort consists of at least three patients eligible for the MTD determining set (see Section 10.1.1). Patients who are not eligible for the MTD determining set will be replaced. The first patient of the first cohort will start study treatment at least one week before the next patients start study treatment.

[redacted]

The Bayesian model will be updated prior to additional enrollment under the following scenarios:

1. If the first 2 patients in a cohort experience DLT prior to the enrollment of the 3rd patient. Enrollment will be halted, the model will be updated, and any new patients will be enrolled at a dose satisfying the overdose criteria, no higher than the current dose level.
2. No additional patients will be enrolled until the current cohort is completed and the model is updated.
3. For cohorts of > 3 patients if the observed number of DLTs exceeds 25% of the currently enrolled patients to that dose level, enrollment will be halted until all patients complete one cycle of dosing or experience DLT. The model will be updated to determine the uncertainty about the probability of DLT at each dose level. New patients will be enrolled at a dose level up to the highest satisfying the overdose criteria.

A decision will be jointly made by the investigators and the sponsor as to the dose level at which to continue dosing.

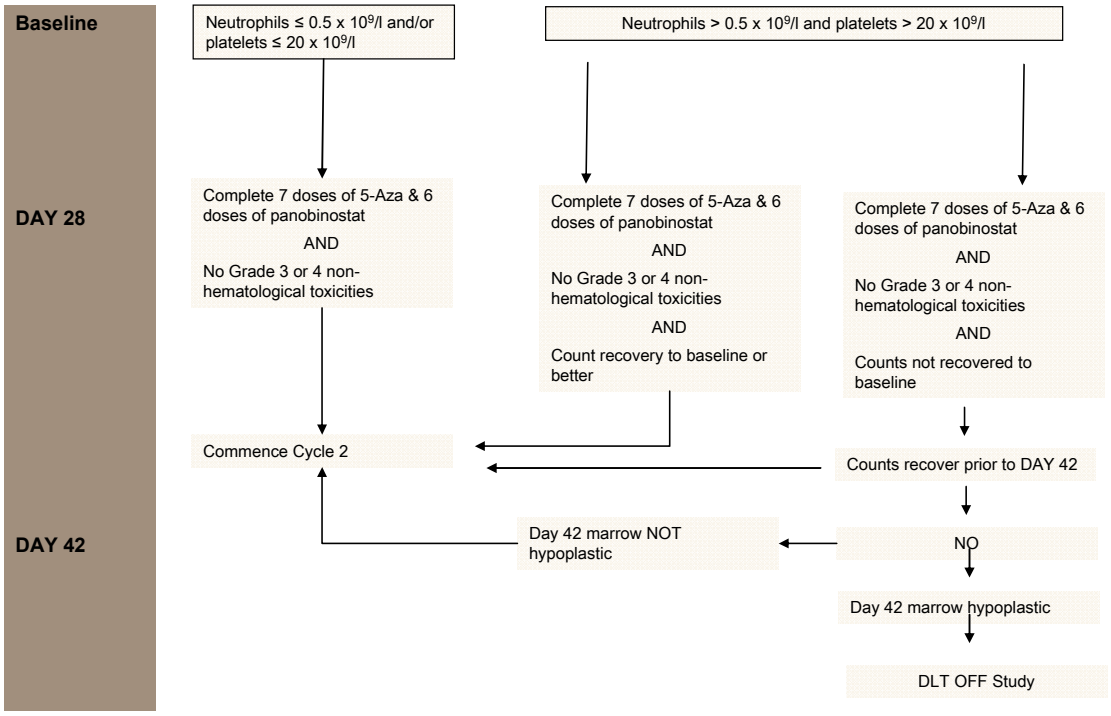
6.6.1.6 Dose-limiting toxicities (For phase Ib portion only)

The DLT is defined as a toxicity requiring treatment withdrawal and includes the following:

- **Non-hematologic toxicity qualifying for DLT**: In all patients, any treatment emergent or new NCI-CTCAE Grade 3 or 4 non-hematological toxicity, attributable to study treatment (either drug in combination). Additionally, treatment-emergent or new Grade 2 peripheral neuropathy attributable to study treatment, customarily considered DLT in cancer clinical studies.
- **Hematologic toxicity qualifying for DLT**: In all patients NCI CTCAE Grade 4 life-threatening febrile neutropenia. A special distinction between patients evaluable or not for hematologic toxicity has been made in this study, considering that the majority of patients representing the target population will have pre-existing severe cytopenias. Management of hematologic toxicity according to baseline blood count values is an integral part of the Vidaza label and common clinical practice in these patient populations. To overcome complexity in implementing the Vidaza label algorithm, a more user-friendly approach based on clinical experience has been used in this study protocol. Hematologic toxicity will not be evaluable unless patients demonstrate baseline neutrophil counts > 0.5 x 10^9/L and platelet counts > 20 x 10^9/L. In these patients, failure to recover neutrophil and platelet counts to equal or higher baseline levels **AND** the demonstration of persistent bone marrow hypoplasia (MH) (<10% overall cellularity and <5% blasts) on Day 42 of Cycle 1 will be considered a hematologic DLT at that dose level (see Figure 6-3). On the other hand, if a patient with the previous baseline values of neutrophils and platelets, experiences persisting cytopenias on Day 42 AND does not exhibit MH on bone marrow biopsy, this condition will not be considered a hematologic DLT and the patient will commence Cycle 2 with the same doses of 5-Aza and panobinostat, provided no non-hematological DLT has been encountered. Patients with pre-existing cytopenias not evaluable for hematological toxicities (baseline neutrophil count ≤0.5 x 10^9/L or platelet count ≤ 20 x 10^9/L) will commence cycle 2 with the same doses of 5-Aza and panobinostat on day 29 (i.e., day 1 of next cycle), if they have not experienced any non-hematological DLT (see Figure 6-3).

[redacted]

Figure 6-3 Cycle 1 DLT decision algorithm for patients not experiencing grade 3 or 4 non-hematological toxicities



The dose escalation procedure including the DLT definitions are aligned with the registered label for 5-Aza. This ensures that patients receiving the full dose of 5-Aza according to the registered label. Also the potential delay of the next treatment cycle to Day 42 is part of the registered 5-Aza label.

6.6.1.7 Follow-up for dose-limiting toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event including clinically significant laboratory values, must be followed at least once a week for 4 weeks, or until resolution or stabilization of the event, whichever comes first. Patient who experience ECG abnormalities should be followed as per Section 6.6.1.8.

6.6.1.8 Dose modification, delay and discontinuation

For patients who are unable to tolerate the protocol-specified dosing schedule regardless of whether a patient is enrolled in the phase Ib or the phase IIb part of the study, dose adjustments are permitted in order to keep the patient on study treatment. Dose modifications for panobinostat must be recorded on the Dosage Administration Record CRF.

Dose adjustments due to hematological toxicity

All patients should receive supportive, hematological measures in accordance with institutional protocols. There will be no dose reductions for panobinostat below 10 mg (dose level -1). Following dose modifications, the cycle duration should return to 28 days.

In AZA-001 pivotal phase III trial (Fenaux et al 2009a), about 90% of patients experienced grade 3-4 neutropenia and/or thrombocytopenia. Seventy-four percent of patients (n=72) with baseline grade 0-2 thrombocytopenia developed grade 3-4 thrombocytopenia during treatment with 5-Aza. However, 151 (86%) of patients remained on 75 mg/m^2 per day throughout the study with no dose adjustments for a median of 9 treatment cycles The median 5-Aza cycle length was 28 days and 21% of the cycles were longer than 35 days. These findings indicate that provided adequate hematological supportive care, patients could continue on 5-Aza therapy and benefit from it. Of note if that median time to response was reported to be 4 months. There is mounting clinical evidence that combining a hypomethylating agent, such as 5-Aza, with DACi may shorten time to response to two cycles (Silverman et al 2008). Therefore, it is paramount to manage grade 3-4 cytopenia and possible residual disease with optimal hematological support in order to keep the patient, if not progressing, on treatment for several cycles to allow study treatment activity to occur.

Hematological toxicity deriving from the combination of panobinostat and 5-Aza and the potential risk for bleeding and infection/sepsis should be weighted against conventional management of the disease and expected treatment benefit for the patients.

For phase IIb portion only:

During the scheduled 2 weeks off of study treatment, neutropenia and thrombocytopenia are anticipated to be resolved to at least patient baseline CTCAE grade. If by Day 28, there is failure to recover from Grade 4 neutropenia or Grade 4 thrombocytopenia to ≥ patient baseline CTCAE grade, then study treatment may be delayed up to Day 42. If these cytopenias persist, Table 6-4 below is offered as guidance for dose reductions in the phase IIb part of the study.

Management of febrile neutropenia

At least one-half of neutropenic patients who become febrile have an established or occult infection and at least one-fifth of patients with neutrophil of <1.0 x 10^9/L has bacteremia. Because the progression of infection in neutropenic patients can be rapid, and because such patients with early bacterial infections cannot be reliably distinguished from non-infected patients at presentation, empirical antibiotic therapy should be administered promptly to all neutropenic patients at the onset of fever. Afebrile patients who are neutropenic but who have signs or symptoms compatible with an infection should also have empirical antibiotic therapy begun in the same manner as do febrile patients. Selection of the initial antibiotic regimens should follow institutional guidance, as well as considering low vs. high risk patients and potential drug-drug interactions with study treatment, i.e. panobinostat (Section 6.6.2).

[redacted]

Dose adjustments due to non hematological toxicity

For all treatment cycles, dosing should not be delayed beyond 42 days.

No dose modifications are required for grade 1 non-hematologic toxicity. Patients experiencing NCI-CTCAE grade 2 non-hematologic toxicity (excluding prolonged QT interval and peripheral neuropathy) may continue treatment with panobinostat at the current dose and schedule if in the best interest for the patient. More frequent monitoring of the patient may be required, and patients should be informed to call the Investigator immediately if there is any worsening of symptoms. (Table 6-6 for phase Ib part and Table 6-7 for phase IIb part)

Dose adjustments due to prolonged QT interval

The cardiac assessment schedule for the phase Ib and the phase IIb parts is shown in Table 7-5. Pre-dose ECG criteria is defined as a QTcF < 480 ms. In case any single **pre-dose** ECG during the treatment cycle shows a QTcF ≥ 480 ms the administration of study drug is not permitted. Instead, dosing should be delayed until the next scheduled day of panobinostat intake and three pre-dose ECGs should be repeated. If, again, pre-dose ECG criteria are not met the patient should be discontinued from the study. In case pre-dose ECG criteria are met panobinostat treatment can be resumed.

If any single **post-dose** ECG shows a QTcF ≥ 480 ms or an increase of more than 60 ms from baseline panobinostat dosing should be delayed until the next scheduled day of panobinostat intake and three pre-dose ECGs done. If pre-dose ECG criteria are not met the patient should be discontinued from the study. In case pre-dose ECG criteria are met (QTcF < 480 ms) panobinostat treatment can be resumed with a 10mg dose reduction.

If **any** single ECG shows QTcF > 500 ms the patient is discontinued from the study.

In case of QT prolongation it is recommended to check and correct patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate concomitant medication. In case the prolongation is due to electrolyte imbalance or concomitant medication the patient can continue the trial once these causes can be eliminated.

The Sponsor should be notified immediately of any QT prolongation that would cause delay of study drug administration, change in panobinostat dose or discontinuation of the patient from the study.

Dose adjustments due to 5-Aza-related renal toxicity

There are no reportings of renal toxicity with panobinostat in the ongoing clinical program. On the other hand, renal tubular dysfunction manifesting as hypophosphatemia, hypokalemia or hyponatremia with or without increases in serum creatinine or blood urea nitrogen (BUN) may infrequently occur with 5-Aza therapy. If serum bicarbonate falls below 20mEq/L and the decrease is considered secondary to 5-Aza the patient should receive oral bicarbonate replacement. If the event cannot be controlled replacement therapy should be continued and the next 5-Aza cycle dosage be reduced by 50%. Other electrolyte disturbances should be treated with appropriate replacement therapy. If serum creatinine or BUN increase by 2-fold

[redacted]

or greater from baseline without any other reasonable explanation and is thought to be secondary to 5-Aza the start of the next cycle of study treatment (5-Aza and panobinostat) should be delayed until values return to baseline and the dosage of 5-Aza should be reduced by 50%. In case doses of 5-Aza are to be reduced for two consecutive times, patient should be removed from the study according to the locally approved label.

Dose adjustments for patients receiving single agent Vidaza

For those patients being treated on the control arm (single agent 5-Aza) the product label should be followed to make dose adjustments as necessary to maintain the patient on treatment.

Table 6-4 Phase IIb only: Panobinostat and Vidaza dose discontinuations/ interruptions/reductions for Grade 4 neutropenia and Grade 4 thrombocytopenia (NCI CTCAEv3.0)

Grade 4 Neutropenia and/or Grade 4 Thrombocytopenia	With Marrow Hypoplasia (<10% overall cellularity and <5% blasts)	Without Marrow Hypoplasia
Day 28	If by Day 28, there is failure to recover neutrophil and/or platelet counts ≥ baseline CTCAE grades or a cytopenia worsens to G4 AND a delay in study treatment is NOT considered to be in the patient's best interest, the investigator may consider reducing panobinostat by 10 mg if the cytopenias are judged to be related to panobinostat*. If the cytopenia occurs in a consecutive cycle, than the product label must be followed for a 5-Aza dose reduction, and panobinostat must be reduced by 10mg.	
Day 42	If by Day 42 there is failure to recover neutrophil and platelet counts ≥ baseline CTCAE grades or a cytopenia worsens to G4 AND persistent bone marrow hypoplasia exists then the dose of 5-Aza should be reduced according to the product label and the investigator may consider reducing the dose of panobinostat by 10 mg*. If this cytopenia occurs in a consecutive cycle, then the product label must be followed for a 5-Aza dose reduction, and panobinostat must be reduced by 10mg. A Cycle should not be delayed beyond day 42.	If by Day 42 there is failure to recover neutrophil and platelet counts ≥ baseline CTCAE grades or a cytopenia worsens to G4 AND there is NO demonstration of bone marrow hypoplasia, then the dose of 5-Aza and panobinostat will remain unchanged, BUT, if the cytopenia occurs in a consecutive cycle, then the dose of panobinostat must be reduced by 10mg*. Cycle should not be delayed beyond day 42.

* Dose reductions below 10mg of Panobinostat are not allowed

[redacted]

Table 6-5 Phase Ib and Phase IIb: Panobinostat and Vidaza dose discontinuations/interruptions/reductions for febrile neutropenia (NCI CTCAEv3.0)

Febrile Neutropenia	Grade 3	Grade 4
ANC <1.0 x 10^9/L; fever ≥ 38.5*C (fever of unknown origin without clinically or microbiologically documented infection	Present	Life threatening
	Promptly install institutional protocol for febrile neutropenia management. Temporarily discontinue panobinostat until recovery to ANC ≥ 1.0 x 10^9/L confirmed for at least 2 consecutive days, and patient becomes afebrile. Then resume with 10 mg panobinostat dose reduction	Discontinue study treatment (panobinostat and 5-Aza) and promptly manage febrile neutropenia according to institutional protocol

Table 6-6 Phase Ib only: Panobinostat dose interruptions/reductions for treatment-emergent/new non-hematological toxicities attributable to study treatment (except for prolonged QT interval)

Toxicity	Grade 1	Grade 2	Grade 3 / Grade 4 (Grade 2 peripheral neuropathy)
First presentation	No modification for Grade 1 For Grade 2: temporary discontinuation until grade 1 then resume at the same dose of panobinostat. If grade 1 not occurred by day 42, discuss with the Sponsor to resume panobinostat at one dose level below		Toxicity qualifies for a DLT#. Patient to be withdrawn*.
Second and subsequent presentations	No modification for grade 1 For Grade 2: temporary discontinuation until grade 1 then resume at a one lower dose level of panobinostat according to the Investigator's judgement. Cycle should not be delayed beyond day 42.		Patient to be withdrawn.
*No further panobinostat. Consider to continue off study with 5-Aza alone according to Product Label # DLT only applicable for the first Cycle of the phase Ib part.			

Table 6-7 Phase IIb only: Panobinostat dose interruptions/reductions for treatment emergent/new non-hematological toxicities attributable to study treatment (except for prolonged QT interval)

Toxicity		
Grade 3	Any Grade 3 for ≥7 days: If this grade 3 Nausea is uncontrolled despite use of standard anti-emetics. If this grade 3 Total bilirubin has a coincident Direct Bilirubin ≥0.5 mg/dl With the exception of ≥Grade 3 QTcF prolongation (QTcF > 500ms) which has separate guidelines	Temporary dose interruption until Grade 1 or patient baseline and then resume panobinostat with a 10mg dose reduction
Grade 4	Any Grade 4 non-hematologic toxicity	Temporary dose interruption until Grade 1 or patient baseline and then resume panobinostat with a 10mg dose reduction

[redacted]

Management of diarrhea

Patients should be instructed to contact their physician at the onset of diarrhea. Each 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. Patients with diarrhea ≥ grade 2 despite this loperamide regimen should interrupt treatment with panobinostat as described in Table 6-6. If the above regimen is inadequate then additional evaluation and treatment should be pursued as medically indicated. Institution of oral fluoroquinolone therapy for patients with persistent diarrhea lasting more than 24 hours and for patients with diarrhea who develop either fever or neutropenia while on chemotherapy has been recommended by experts panel, prompted by the experience from two large phase III studies reporting toxic deaths related to gastrointestinal symptoms frequently attributed to sepsis, sometimes with concurrent neutropenia (Rothenberg et al 2001). 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 published guidelines.

6.6.2 Other concomitant medications

The investigator should instruct the patient to notify the study site about any new medications taken after the start of the study drug. All medications (other than study drug) and significant non-drug therapies administered after the patient starts treatment must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug CRF.

Since panobinostat is metabolized *in vitro* by CYP3A4/5, a clinical drug-drug interaction study between panobinostat and one of the most potent CYP3A4 inhibitors, ketoconazole was conducted in cancer patients [LBH589B2110]. Recent results indicated that following 4 consecutive ketoconazole doses at 400 mg and co-administration of a single oral panobinostat dose of 20 mg, mean C_{max} and AUC of panobinostat increased by 60%. Patients using concomitant medications known to be metabolized by these isoenzymes will not be excluded from the study; however, should be carefully monitored for potentiation of toxicity due to these medications. A list of drugs known to inhibit CYP3A4/5 is provided in [Post-text supplement 3].

5-Aza as well as panobinostat therapy is commonly associated with thrombocytopenia. This may lead to an increased risk of bleeding if concomitantly used with sodium warfarin therapy. It is recommended that patients who require chronic anticoagulation therapy, while on panobinostat therapy, use low molecular weight heparin (LMWH). However, if the use of LMWH is not feasible, such patients may continue on sodium warfarin while on panobinostat, but a close monitoring of common coagulation parameters, including PTT should be conducted.

In vitro assays, panobinostat was shown to inhibit the cytochrome P450 isoenzyme CYP2D6 at low micromolar ranges, thereby suggesting a potential risk of drug-drug interactions with concomitant medications that are also metabolized by CYP2D6. A clinical drug-drug

[redacted]

interaction study with dextromethorphan (a CYP2D6 probe drug) and panobinostat is currently ongoing in cancer patients. In the meantime, patients using concomitant medications known to be CYP2D6 substrates will not be excluded from the study; however, should be monitored for potentiation of toxicity. A list of drugs known to inhibit CYP2D6 is provided in [Post-text supplement 3].

Patients who are currently receiving treatment with any of the medications which are known to have a relative risk of prolonging the QT interval or inducing Torsade de Pointes, who can not either discontinue or switch to a different medication prior to study enrollment, will be excluded from the study. Concomitant administration of agents known to prolong the QT interval or induce Torsade de Pointes while patients are receiving panobinostat is contraindicated. Patients may not begin treatment with these medications unless proactively discussed with the Sponsor. A list of medications known to prolong QT interval is provided in [Post-text supplement 3].

6.6.3 Study treatment discontinuation

At the time the decision is made to discontinue study treatment, an End of Treatment Visit should be scheduled as soon as possible after the last dose of study treatment. All assessments listed for the 'End of Treatment Visit' should be performed (Table 7-1) and the End of Treatment CRFs should be completed with the date and reason for stopping study drug.

As of protocol amendment 5, all assessments listed for the 'End of Treatment Visit' are not mandatory and will be performed at the discretion of the investigator (Table 7-3). However, the End of Treatment CRF pages must be completed with the date and reason for stopping study drug.

All patients must have evaluations for 4 weeks after the last dose of study treatment, including the monitoring of adverse events and concomitant medications (including antineoplastic therapy). If applicable, any adverse events marked as 'continuing' as of the last dose of study medication must be followed at least once per week for at least 4 weeks or until resolution of the event, return to baseline status, or clinical stability is reached. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted by telephone and/or mail for safety evaluations during the 4 weeks following the last dose of study drug. Patients lost to follow-up should be recorded as such on the CRF. If patients refuse to return for these visits or are unable to do so, the patient should be considered off-study, and the 'Study Evaluation Completion' CRF should be completed. Female patients who become pregnant while on panobinostat must be immediately and permanently discontinued from panobinostat treatment and reported to the local Novartis Integrated Medical Safety Department as per Section 8.4.

6.6.4 End of treatment

Once study treatment is permanently discontinued, the patient will be considered to have completed treatment and no more additional study assessments will be performed other than the collection of the 28 day safety follow up data and survival information. The reason for end of treatment will be recorded on the **End of Treatment** CRF.

The reasons for which a patient may end participation on this study are one of the following:

[redacted]

- Subject's condition no longer requires study drug
- Adverse event(s)
- Protocol deviation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Disease progression/relapse

6.6.5 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 must make every 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.

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

6.6.6 Follow-up for safety evaluation

All patients must be carefully monitored for AEs and concomitant medications (including antineoplastic therapy) for 30 days after the last dose of study treatment.

Data collected should be added to the Adverse Events CRF and the Concomitant Medication CRF.

6.6.7 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.

[redacted]

6.6.8 End of study (study evaluation completion)

In this protocol, End of Study (or Study Evaluation Completion) is defined as the time when the 28 day safety follow up is completed and no more additional study assessments (other than the collection of survival information) are planned to be performed. In the Study Completion CRF one of the following (primary) reasons for End of Study should be recorded:

- Significant protocol deviation
- Patient withdrew consent
- Lost to follow-Up
- Administrative problems
- Death
- New anti-cancer treatment
- Disease progression/relapse
- Follow up phase completed as per protocol

Survival information will be collected by telephone contact every three months for the first year after study evaluation completion, thereafter every six months till death or lost of follow-up. The information is to be recorded in the Survival Information CRF page. The investigator should show 'due diligence' by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls.

The core clinical study report will be based on a data cut-off corresponding to the time point where all patients have either completed 12 cycles of study treatment or discontinued study treatment for any other reason whichever comes first. An addendum to the core clinical study report will be provided at the completion of the study to summarize and/or list the additional safety and efficacy data as appropriate.

Patients who have completed 12 cycles of study treatment and are assessed by the Investigator to have the potential to benefit from ongoing treatment will continue their assigned treatment allowing collecting and reviewing safety, efficacy and survival data. After the data-cut off point for the CSR, a reduced visit evaluation schedule will be applied. All sites will be informed per Novartis Investigator Notification when the data cut-off date has been reached and the patient's can move to the reduced schedule of assessments.

As of protocol amendment 5, data collection for the ongoing patients is further limited as described in Table 7-3.

6.6.9 Emergency unblinding of treatment assignment

Not applicable.

[redacted]

7 Visit schedule and assessments

For the phase IIb part, following registering in IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in IRT system. Please refer and comply with detailed guidelines in the IRT manual.

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.

[redacted]

Table 7-1 Visit evaluation schedule for Phase Ib and Phase IIb part

Examination	**Screening**	**Cycle 1 (28 days - additional visit in () if cycle is extended beyond day 28)**													**Cycle 2 through CSR cut off date (28 days - additional visits in () if cycle is extended beyond day 28)**													**EOT[15]**	**28d Fu[16]**	**EOS[17]**	**Survival Fu[18]**
Visit	**1**	**2**		**3**					**6**		**601**	**7**	**8**	**9**	**10**		**11**					**12**			**13**	**14**	**15**	**777**	**501**	**778**	
Day of cycle	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**22**	**(29)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**22**	**(29)**				
Demography/Informed Consent	X																														
Inclusion/Exclusion Criteria	X																														
Relevant medical history/ Current medical conditions	X																														
Diagnosis and extent of disease	X																														
Prior antineoplastic therapy	X																														
Height[2]	X																														
IPSS score	X																														
Transfusion dependency[14]	X	X													X												X				
Weight, vital signs[2]	X	X													X												X				
ECOG Performance Status[3]	X	X													X												X				
Hematology[4,14]	X	X							X			X	X	(X)	X											(X)	X				
Coagulation[5]	X	X													X												X				
Biochemistry[6]	X	X							X			X	X	(X)	X							X¥			X	X¥	(X)	X			
Urinalysis[7]	X																										X				

[redacted]

Examination	**Screening**	**Cycle 1 (28 days - additional visit in () if cycle is extended beyond day 28)**													**Cycle 2 through CSR cut off date (28 days - additional visits in () if cycle is extended beyond day 28)**													**EOT[15]**	**28d Fu[16]**	**EOS[17]**	**Survival Fu[18]**
Visit	**1**	**2**		**3**					**6**		**601**	**7**	**8**	**9**	**10**		**11**					**12**			**13**	**14**	**15**	**777**	**501**	**778**	
Day of cycle	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**22**	**(29)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**22**	**(29)**				
Pregnancy test for WOCBP[8]	X														X												X			
Thyroid function test[9]	X																										X			
Echocardiogramm or MUGA	X																													
5-Aza		X	X	X	X	X	X	X							X	X	X	X	X	X	X									
Panobinostat dosing				X		X			X	X	X	X					X		X			X	X	X	X					
[redacted]																														
Prior/concomitant medications[11]		CONTINUOUS																									X	X		
Adverse events[12]		CONTINUOUS																									X	X		
ECG[13]	X			X					X		X						X										X			
Antineoplastic therapy since discontinuation of study treatment[16]																											X	X		
PK assessment		Table 7-6																												
Bone marrow exam / Response assessment[14]	X	End of cycle[14]																									X			
Extramedullary disease evaluation[14]	**X**	**End of cycle[14]**																									**X**			

[redacted]

Examination	Screening	Cycle 1 (28 days - additional visit in () if cycle is extended beyond day 28)													Cycle 2 through CSR cut off date (28 days - additional visits in () if cycle is extended beyond day 28)													EOT[15]	28d Fu[16]	EOS[17]	Survival Fu[18]	
Visit	**1**	**2**		**3**					**6**		**601**	**7**	**8**	**9**	**10**		**11**					**12**			**13**	**14**	**15**					
Day of cycle	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**22**	**(29)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**22**	**(29)**					
Survival																																X

¥ done in cycle 2 only

1. Screening evaluations must be performed ≤ 14 days prior to cycle 1 administration of panobinostat and 5-Aza, unless otherwise stated. Baseline demographics will be captured for screening failures as well as the reason for failure.
2. Physical examinations, vital signs, and weight will be performed on the scheduled day, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated.
3. ECOG performance status - Section 8.1. Assessment of ECOG Performance Status will be performed on the scheduled day, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated. If the baseline assessment was performed ≤ 72 hours prior to the first dose of panobinostat, then it does not need to be repeated on day 1 of cycle 1.
4. Hematology - Section 7.6.3.1
5. Coagulation - Section 7.6.3.2
6. Biochemistry - Section 7.6.3.3
7. Urinalysis - Section 7.6.3.4
8. Pregnancy test - Section 7.6.3.6. All females of childbearing potential should complete a serum pregnancy test ≤ 72 hours prior to the administration of study treatment on day 1 of cycle 1 and at the end of treatment. In addition, a urine pregnancy test will be performed in monthly intervals pre-dose on day 1 of each subsequent cycle during study duration.
9. Thyroid function test - Section 7.6.3.5

[redacted]

11. Prior/concomitant medications - Record all medications administered ≤ 4 weeks prior to the administration of study treatment. Record all medications taken during the study on the Concomitant Medications CRF.
12. Adverse events - Section 8.1
13. ECG - 12-lead ECG will be performed at scheduled time points as indicated in Table 7-5. Single ECGs will be done at screening; triplicate ECGs will be done in cycle 1 on days 3, 8, 12 and all subsequent treatment cycles on Day 3 and at EOT.

[redacted]

Examination	Screening	Cycle 1 (28 days - additional visit in () if cycle is extended beyond day 28)													Cycle 2 through CSR cut off date (28 days - additional visits in () if cycle is extended beyond day 28)													EOT[15]	28d Fu[16]	EOS[17]	Survival Fu[18]
Visit	1	2		3					6		601	7	8	9	10		11					12			13	14	15	777	501	778	
Day of cycle	-14 to -1	1	2	3	4	5	6	7	8	10	12	15	22	(29)	1	2	3	4	5	6	7	8	10	12	15	22	(29)				

[redacted]

15. End of treatment visit (EOT) - Patients who permanently discontinue study drug for any reason, will be considered to have completed study treatment, and should not be considered withdrawn from the study. Such patients should be scheduled for a visit as soon as possible, at which time all of the assessments listed should be performed..
16. Follow-up - Section 6.6.6. All patients must be carefully monitored for adverse events and concomitant medications (including antineoplastic therapy) for 28 days following the end of study treatment.
17. Study evaluation completion (EOS) - Section 6.6.8. Once the patient discontinues study drug treatment and no additional study assessments will be performed, the Study Evaluation Completion CRF should be completed.
18. Survival Follow up - Section 6.6.8 - Survival information will be collected by telephone contact every three months for the first year after EOS visit, hereafter every six months.

[redacted]

Table 7-2 Visit evaluation schedule after CSR data cut off date (for the phase Ib and IIb part)

All sites will be informed per Novartis Investigator Notification when the data cut-off date has been reached and the patients can move to the reduced schedule of assessments.

Examination	**(28 days - additional visits in () if cycle is extended beyond day 28)**													**EOT[11]**	**28d Fu[12]**	**EOS[13]**	**Survival Fu[14]**
Visit	**10**		**11**					**12**			**13**	**14**	**15**	**777**	**501**	**778**	
Day of cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**22**	**(29)**				
Transfusion dependency	X													X			
Weight, vital signs	X													X			
ECOG Performance Status	X													X			
Hematology[1]	X												(X)	X			
Coagulation[2]	X													X			
Biochemistry[3]	X										X		(X)	X			
Urinalysis[4]														X			
Pregnancy test for WOCBP[15]	X													X			
Thyroid function test[5]														X			
5-Aza	X	X	X	X	X	X	X										
Panobinostat dosing			X		X			X	X	X	X						
[redacted]																	
Prior/concomitant medications[7]	CONTINUOUS																

[redacted]

Examination	**(28 days - additional visits in () if cycle is extended beyond day 28)**													**EOT[11]**	**28d Fu[12]**	**EOS[13]**	**Survival Fu[14]**
Visit	**10**		**11**					**12**			**13**	**14**	**15**	**777**	**501**	**778**	
Day of cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**22**	**(29)**				
Adverse events[8]	CONTINUOUS																
ECG[9]			X														
Antineoplastic therapy since d/c of study treatment														X	X		
Bone marrow exam/ Response assessment [10]	End of Cycle													X			
Extramedullary disease evaluation[10]	End of Cycle													X			
Survival																	X

1. Hematology - Section 7.6.3.1
2. Coagulation - Section 7.6.3.2
3. Biochemistry - Section 7.6.3.3
4. Urinalysis - Section 7.6.3.4
5. Thyroid function test- Section 7.6.3.5

[redacted]

7. Prior concomitant medications -Record all medications taken during the study on the Concomitant Medications CRF.
8. Adverse Events - Section 8.1
9. ECG - Table 7-5
10. Response assessment - Section 7.5.1 - Bone marrow aspiration and /or biopsy after the data cut off date will be obtained at the discretion of the investigator.
11. End of Treatment visit (EOT) - Section 6.6.4
12. Follow-up - Section 6.6.6 Survival information will be collected by telephone contact every three months for the first year after EOS visit, hereafter every six months.
13. Study Evaluation Completion (EOS) Section 6.6.8
14. Survival follow up - Section 6.6.8
15. Pregnancy test – Section 7.6.3.6

[redacted]

Table 7-3 Visit evaluation schedule as of protocol amendment 5 (for the phase Ib and IIb part)

Examination	**(28 days - additional visits in () if cycle is extended beyond day 28)**													**EOT[1]**	**28d Fu[2]**	**EOS[3]**	**Survival Fu[4]**
Visit														**777**	**501**	**778**	
Day of cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**22**	**(29)**				
MANDATORY ASSESSMENTS																	
5-Aza	X	X	X	X	X	X	X										
Panobinostat dosing			X		X			X	X	X	X						
Prior/concomitant medications[5]	CONTINUOUS																
Adverse events[6]	CONTINUOUS																
Survival																	X
OPTIONAL ASSESSMENTS (to be performed at the discretion of the Investigator)																	
Weight, vital signs	X													X			
ECOG Performance Status	X													X			
Hematology[7]	X												(X)	X			
Coagulation[8]	X													X			
Biochemistry[9]	X										X		(X)	X			
Urinalysis[10]														X			
Thyroid function test[11]														X			
ECG[12]			X											X			
Transfusion	X													X			

[redacted]

Examination	**(28 days - additional visits in () if cycle is extended beyond day 28)**													**EOT[1]**	**28d Fu[2]**	**EOS[3]**	**Survival Fu[4]**
Visit														**777**	**501**	**778**	
Day of cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**22**	**(29)**				
dependency[13]																	
Bone marrow exam/ Response assessment [13]	End of Cycle													X			
Extramedullary disease evaluation[13]	End of Cycle													X			
Antineoplastic therapy since d/c of study treatment														X	X		

1. End of Treatment visit (EOT) - Section 6.6.4
2. Follow-up - Section 6.6.6
3. Study Evaluation Completion (EOS) Section 6.6.8
4. Survival follow up - Section 6.6.8 Survival information will be collected by telephone contact every three months for the first year after EOS visit, hereafter every six months.
5. Concomitant medications -Record all medications taken during the study on the Concomitant Medications CRF.
6. Adverse Events - Section 8.1
7. Hematology - Section 7.6.3.1
8. Coagulation - Section 7.6.3.2
9. Biochemistry - Section 7.6.3.3
10. Urinalysis - Section 7.6.3.4
11. Thyroid - Section 7.6.3.5
12. ECG - Table 7-5
13. Response assessment - Section 7.5.1

[redacted]

7.1 Disease classification/qualification at baseline

A diagnostic bone marrow collection is required to be obtained within 2 weeks of starting study treatment. If cytogenetic results are obtained within 6 weeks prior to start of study treatment, no confirmatory cytogenetic exam is required at baseline.

7.2 Information to be collected on screening failures

Data on patients who fail screening will not be entered into the clinical database. Only information from the Screening Log CRF will be entered.

7.3 Patient demographics/other baseline characteristics

The data that will be collected on patient characteristics at screening include general demographics, relevant medical history, the diagnosis and extent of their disease and details regarding anti-neoplastic treatments they have received in the past.

7.4 Treatments

Compliance to study treatment will be assessed by the investigator and/or study personnel at each visit using capsule counts, medication records, and information provided by the patient and/or caregiver. This information should be captured in the source document and Dosage Administration Record CRF at each visit.

7.5 Efficacy

Efficacy evaluations will be performed and recorded in order to detect anti-leukemic activity of the study treatment (panobinostat and/or 5-Aza). Each patient's disease status will be assessed at screening and periodically throughout the study. Please refer to [Post-text supplement 1] for disease specific criteria for evaluating response and disease progression.

7.5.1 Efficacy assessments

Response will be assessed when a BM aspirates and/or core biopsy is collected as outlined below. The response to treatment will be determined as outlined in [Post-text supplement 1].

- **Bone marrow aspiration and/or core biopsy** must be obtained at screening (within 2 weeks prior to start study treatment), within -5 days of the end of even-numbered cycles, and at the End of Treatment Visit, as well as, at other times at the discretion of the investigator.
  - The bone marrow differential must include any disease-specific criteria for diagnosis and response assessment
- **Peripheral Blood:** Complete blood cell count including WBC; differential including promyelocyte, myelocyte, and metamyelocyte; blast cell count; and platelet count must be performed within 5 days of bone marrow aspirate/biopsies, unless clinically not feasible.
- Transfusion dependency will be assessed at screening and at Day 1 of each cycle, and at the end of treatment visit. If additional non-study response assessments are being performed, the number of units for red blood cells, platelets and granulocytes transfusions must be recorded on the additional assessment transfusion CRF pages.

- Extramedullary disease will be assessed at screening, at each response assessment, at the end of treatment visit and at other times at discretion of the investigator.

For potential auditing purposes, the investigator must maintain the BM smears for each study patient at the site for a minimum of 7 years.

As of protocol amendment 5, response assessment will be obtained at the discretion of the investigator (Table 7-3).

7.6 Safety

7.6.1 Performance status

Table 7-4 ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.6.2 Cardiac assessments

Electrocardiogram (ECG)

A screening 12-lead ECG will be performed to assess study eligibility. Additional 12-lead ECGs will be performed at a minimum at scheduled time points as indicated in Table 7-5 .

All ECGs will be submitted to eRT for central review and results will be faxed back to the investigational site within 1 working day (refer to the eRT Panobinostat Lab Manual for instructions on the collection and transmission of ECGs to the independent reviewer). The centralized readings of ECGs by eRT will use the Fridericia correction: QTcF. The ECG interpretations from eRT will be the formal data entered into the clinical trial database. Local ECGs and eRT central review results will not be reconciled.

All patients treated with panobinostat on this study will have frequent QT monitoring on specified days during Cycle 1. A single screening ECG will be obtained for all patients to determine eligibility to participate. The mean of the 3 ECGs obtained pre-dose on Cycle 1 Day 3 will be calculated by eRT, and will be used as the baseline value to compare to throughout the study.

Treatment decisions will be based on the real-time assessment of QTc values at the clinical center, as determined by the automated machine reading or as measured and calculated by trained personnel at the site. All cardiac events should be treated as per the local standard of care and referred to a specialist, if clinically indicated. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTcF

prolongation will be based on the assessment performed by eRT and after discussion between the Investigator and Sponsor. If the patient does not meet the QT criteria for dosing the patient's serum potassium, magnesium, calcium and phosphorus must be measured immediately, and the patient must receive supplements to correct any low values, as well as con-meds evaluated for possible interaction.

Note: this schedule is only permitted for patients who have had no clinically meaningful cardiac abnormalities identified, and whose QTcF has not increased by ≥ 60 ms from baseline or absolute QTcF is not ≥ 480 ms. Patients who experience a QTcF abnormality should follow instructions given in Section 6.6.1.8.

Table 7-5 Cardiac assessment monitoring schedule

Patients enrolled onto the control arm will have a screening 12-lead ECG only to assess study eligibility. Additional ECGs will be performed if clinically indicated at the discretion of the investigator.

Cycle	Day	Scheduled time point (hours)
Screening[1]	-14 to -1	
Baseline/Cycle 1	3	0h (pre-dose) and 3 hours post dose[2]
Cycle 1	8	0h (pre-dose) and 3 hours post dose[2]
	12	0h (pre-dose and 3 hours post dose[2]
Subsequent Treatment cycles[3]	3	0h (pre-dose)[2]
End of study treatment	Day of End of Treatment Visit	Any time on Day of End of Treatment visit[2]
1) Screening ECG x 1 to be reviewed centrally by eRT to determine eligibility prior to first dosing 2) Three sequential ECGs separated by 5-10 minutes 3) As of protocol amendment 5, ECGs will be performed at the discretion of the investigator Note: (a) If the dose is withheld for any reason other than QTc prolongation, the extensive ECG monitoring will not be required. (b) QTc/QTcF > 500 ms requires the patient is permanently withdrawn from study.		

Echocardiogram or MUGA (multiple uptake gated acquisition) scan

A MUGA scan or echocardiogram to assess LVEF will be performed within the screening period prior to the first administration of study treatment. If the LVEF is < 45% by echocardiogram or MUGA, the patient is not eligible for the study. MUGA scan or echocardiogram may be repeated at the Investigator's discretion if there are signs or symptoms of cardiac dysfunction. Patients should be monitored and assessed with the same technique throughout the study if clinically indicated.

7.6.3 Laboratory evaluations

The following laboratory evaluations will be performed by the institutions' clinical laboratories, or by a laboratory local to the patient, according to the visit schedule in Table 7-1, Table 7-2 and Table 7-3. Novartis must be provided a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or

[redacted]

symptoms, and are considered clinically significant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms, cause study discontinuation or constitute in and of itself an SAE) or require therapy. These events should be recorded on the Adverse Events CRF, as well as the appropriate laboratory CRF and/or comment CRF page.

Screening labs may be repeated, if needed, to obtain acceptable values before the patient would fail screening. Laboratory tests should be collected and analyzed immediately prior to dosing on the scheduled day.

7.6.3.1 Hematology

Hematology tests include the following parameters: Complete blood count (CBC) including a total white blood cell count (WBC), neutrophil count, red blood cell count (RBC), lymphocyte, monocyte, eosinophil, basophil, promyelocyte, metamyelocyte, myelocyte, and blast counts, hemoglobin (Hgb), hematocrit, and platelet count. Automated differential blood counts should be accompanied by peripheral blood smear assessed by a pathologist and results reported in the CRF.

Hematology is done at screening and within 72 hours, on Day 1 of each cycle; then on Day 8, 15, 22 in Cycle 1, and continues weekly in case the treatment cycle is extended beyond Day 28; and at End of Treatment Visit. As of protocol amendment 5, hematology tests will be performed at the discretion of the investigator (Table 7-3).

More frequent examinations may be performed at the investigator's discretion if medically indicated; results should be recorded on the Unscheduled Visit CRFs.

7.6.3.2 Coagulation

The coagulation profile includes prothrombin time (PT) or International Normalized Ratio (INR), partial thromboplastin time (PTT), and fibrinogen. The coagulation profile should be performed at the following time points: Screening (does not need to be repeated at Cycle 1 Day 1 if obtained within -7 days before Cycle 1 Day 1); Pre-dose on Day 1 of every cycle through Cycle 6; Pre-dose on Day 1 of every other cycle there after; End of Treatment visit. As of protocol amendment 5, coagulation tests will be performed at the discretion of the investigator (Table 7-3).

7.6.3.3 Biochemistry

Biochemistry includes the following parameters: urea or BUN, creatinine, sodium, potassium, glucose, calcium, albumin, total protein, total bilirubin (direct and indirect), alkaline phosphatase, AST, ALT, inorganic phosphorous, magnesium, bicarbonate, LDH (screening only), and uric acid.

Biochemistry is done at screening and within 72 hours, on Day 1 of each cycle; then on Day 8, 15, 22 in Cycle 1 and Cycle 2; On Day 15 of each subsequent Cycle, and continues weekly in case the treatment cycle is extended beyond Day 28; and at End of Treatment Visit. If the baseline examination was performed ≤72 hours prior to the first dose of study treatment, it need not be repeated on Day 1. As of protocol amendment 5, biochemistry will be performed at the discretion of the investigator (Table 7-3).

The biochemistry results must be reviewed prior to each administration of study treatment. More frequent examinations may be performed at the investigator's discretion if medically indicated; results should be recorded on the Unscheduled Visit CRFs.

7.6.3.4 Urinalysis

Urinalysis tests include assessment of protein, glucose, blood, and specific gravity. Should an abnormality be noted in the macroscopic exam, a microscopic examination should also be performed, including assessment of WBC/HPF, RBC/HPF, and documentation of any additional findings. Urinalysis should be performed during the screening period and at End of Treatment Visit. As of protocol amendment 5, urinalysis will be performed at the discretion of the investigator (Table 7-3).

No other urinalyses are required, however, more frequent examinations may be performed at the Investigator's discretion if medically indicated; such results should be recorded on the Unscheduled Visit CRF.

7.6.3.5 Thyroid function tests

Thyroid Stimulating Hormone (TSH) and free T4 (free thyroxin) will be measured at screening and at End of Treatment Visit. As of protocol amendment 5, thyroid function tests will be performed at the discretion of the investigator (Table 7-3).

7.6.3.6 Pregnancy test

All women of childbearing potential (WOCBP) should complete a serum pregnancy test within three days prior to the first dose of study treatment on Cycle 1 Day 1 and at the 'End of Treatment Visit'. In addition, a urinary pregnancy test at monthly intervals on Day 1 of each subsequent cycle during study duration must be performed. 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 profile (e.g. age appropriate, history of vasomotor symptoms), total hysterectomy, or have had surgical bilateral oophorectomy (with or without 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.

As of protocol amendment 5, pregnancy tests are not required as all the ongoing patients are considered not of child bearing potential.

7.7 Tolerability

Not applicable.

7.8 Resource utilization

Not applicable.

7.9 Patient-reported outcomes

Not applicable.

[redacted]

7.10 Pharmacokinetic assessment

Part of the phase Ib part of this study is to collect panobinostat plasma trough levels during cycle 1 on days 4, 5, and 8 in combination with 5-Aza. Trough levels (C_{min} values) will be summarized at the study conclusion. No PK assessment will be performed in the phase IIb part of the study.

Three (3 mL) of whole blood per sample will be collected (Table 7-6) in tubes containing sodium heparin. Immediately after collection, the tube should be inverted several times to prevent clotting. Blood samples should then be kept on an ice-water bath at approximately 4ºC until centrifugation. The tubes should be centrifuged as soon as possible but no more than 30 minutes after collection at approximately =800 g at least for 15 minutes to separate plasma. The plasma is to be transferred to a polypropylene screw-cap tube (1.5 mL plasma per tube), the tube capped, and the sample mixed briefly and then immediately placed in a freezer set at < -60ºC until shipment, on dry ice, to Novartis or designated CRO for analysis.

Table 7-6 PK blood sampling

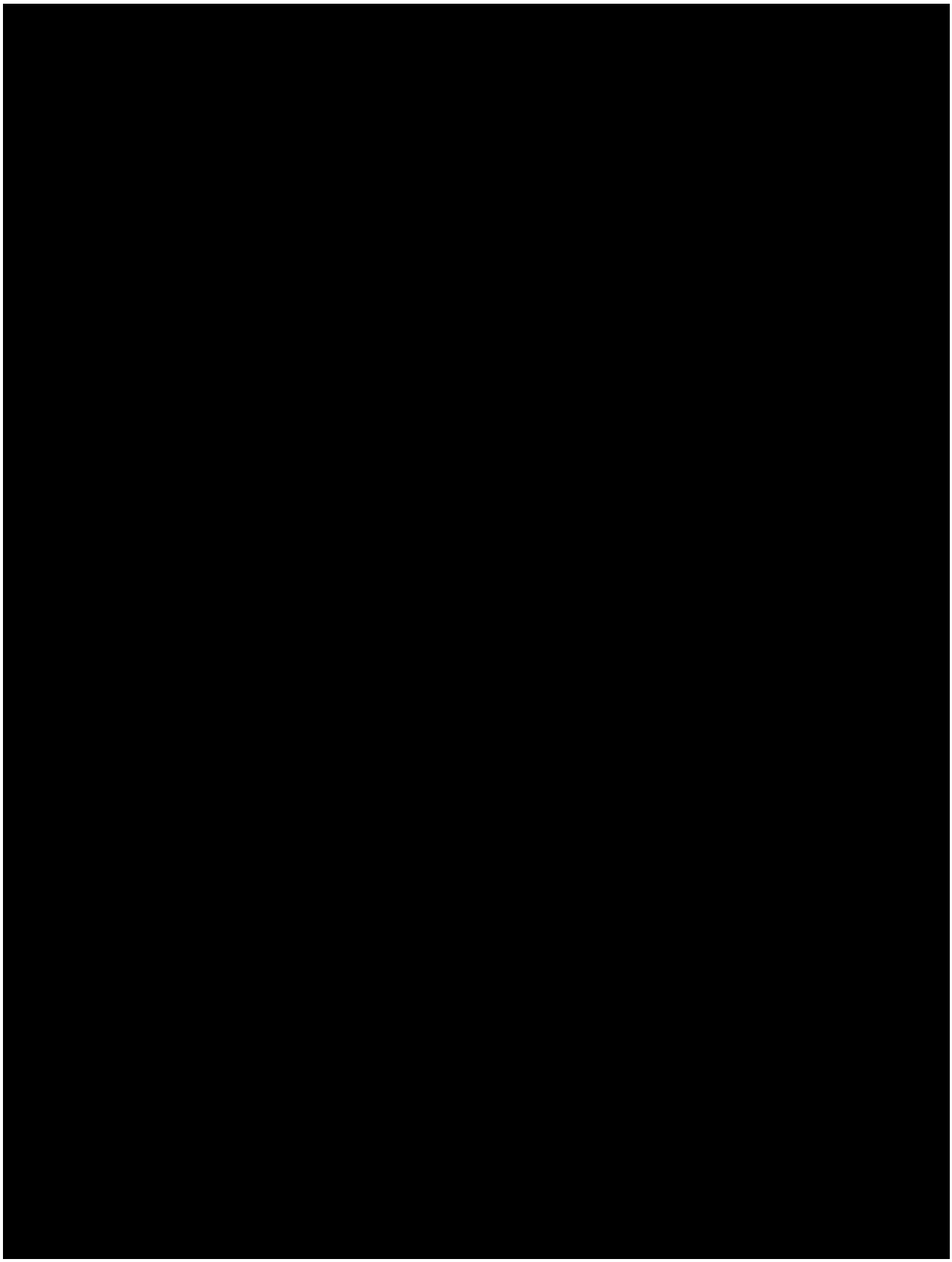
Sample	Volume [mL]	Cycle	Day	PK collection No.	Sample No.	Scheduled time
Blood	3	1	4[b]	1	1	Pre-dose[a]
Blood	3	1	5[b]	2	2	Pre-dose[a]
Blood	3	1	8[b]	3	3	Pre-dose[a]

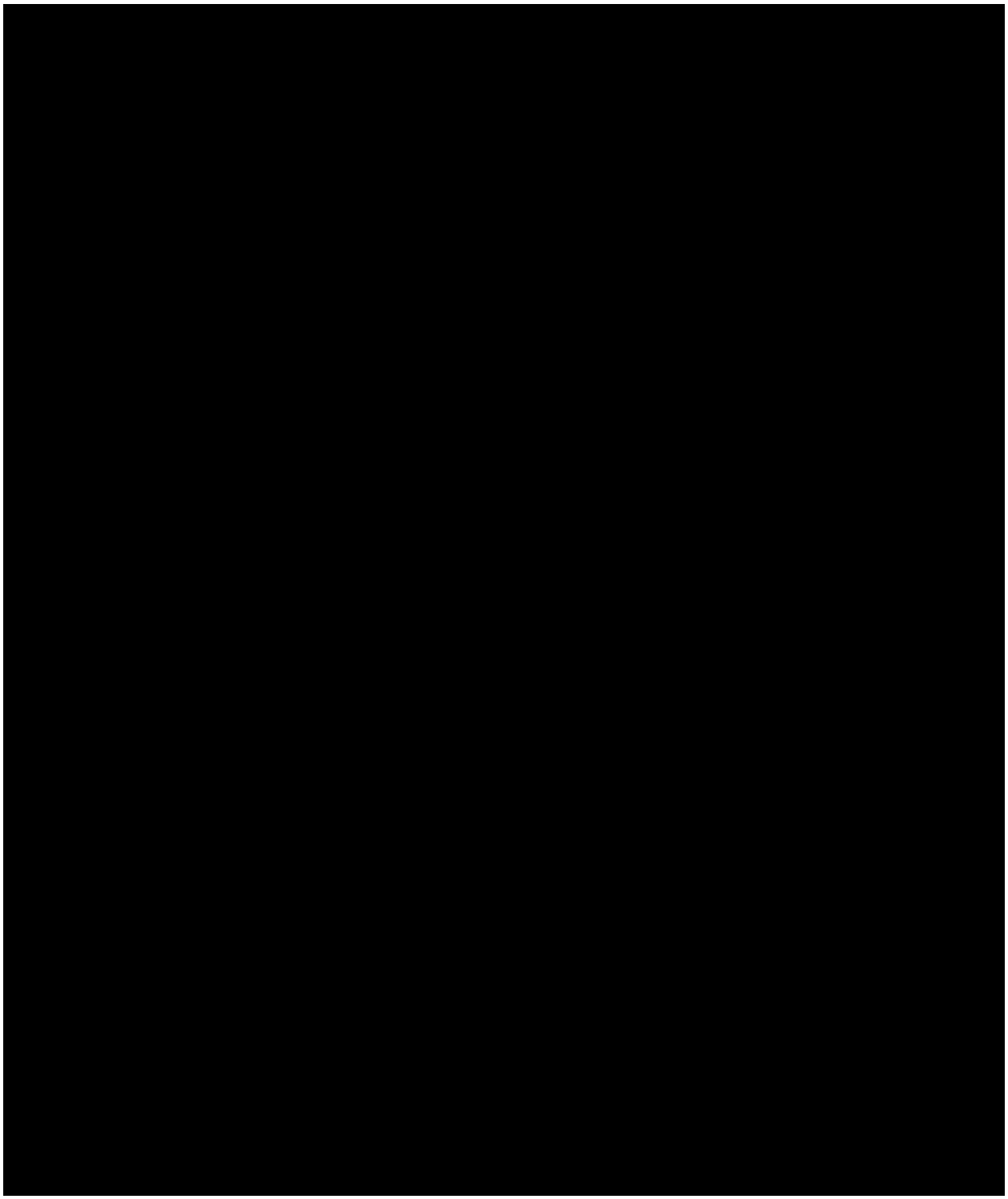
[a.] Take sample within 5 minutes prior to panobinostat dosing; [b.] If panobinostat treatment is delayed from Cycle 1 Day 4 to Day 4, PK sampling days should be shifted accordingly.

Plasma panobinostat concentrations will be measured by a validated LC/MS/MS method with a LLOQ of 0.5 ng/mL or lower. Values below LLOQ will be reported as zero ng/mL.

[redacted]

[redacted]





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).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. 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 and graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0.

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, this information will be collected in the End of Treatment or Survival Information CRF 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 relationship to study treatment (Reasonable possibility that AE is related: No, Yes)
3. Its duration (start and end dates or if continuing at final exam)
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 and which seriousness criteria have been met.

[redacted]

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 (as per International Working Group (IWG) response criteria (Cheson 2003, Cheson 2006), as implemented in the [Post-text supplement 1]), 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 study treatment.

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 lab abnormality would still, by definition, be an adverse event and must be reported as such.

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

[redacted]

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. 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 (e.g. hospitalization to receive blood transfusions)
  - 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
- Protocol exempt SAEs:
  a. Progression of disease (including fatal outcomes), if documented by use of appropriate method, should not be reported as serious adverse event.
  b. Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements. Despite the clinical description of "life-threatening or disabling" provided as general guidance for severity of Grade 4 events in the introduction to CTCAE v. 3.0, this does not automatically indicate that all Grade 4 adverse events or lab abnormalities are SAEs unless they meet the definition of serious as indicated above and as per investigator discretion.

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 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

[redacted]

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.

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 or Package Insert of Vidaza® (new occurrence) 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.

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 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 the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

[redacted]

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.

8.5 Warning 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 IB 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

A data monitoring committee will not be used for this study.

8.7 Steering committee

For the phase IIb part of the study a steering committee will be established. The organization and working principles including a list of members and contact information will be provided in a separate steering committee charter prior to enrollment of the first patient into the phase IIb part of the study.

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.

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 and 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 on CRFs must be traceable to these 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, 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 paper CRFs, designated investigator staff must record the information required by the protocol onto the Novartis CRFs that are printed on multi-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The harvested CRFs will be forwarded to the Medical Documents Reception Center of Novartis (or applicable CRO) by field monitors or by the investigational site, with one copy being retained at the investigational site.

The Principal Investigator is responsible for assuring that the data recorded on CRFs is complete, accurate, and that entry and updates are performed in a timely manner.

9.3.1 Electrocardiogram

ECG data will be collected with a portable, diagnostic electrocardiograph and transmitted electronically to a designated CRO.

[redacted]

[redacted]

9.4 Database management and quality control

For studies using paper CRFs, data will be entered into a fully validated study database by Novartis Data Management personnel (or designated CRO). Following entry from the CRFs, the data are systematically checked by Novartis Data Management personnel (or designated CRO) using programmed checks and data review tools/reports. Data Query Forms (DQF) are created for discrepancies or missing values and sent to the investigational site for resolution. Original signed responses to the DQFs must be returned to Novartis Data Management (or designated CRO) so that resolutions can be entered into the database. Copies of the resolved DQFs are kept with the CRFs at the investigator site.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO). At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). 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 the treatment codes will be unblinded 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.

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for **analysis**.

The clinical study report (encompassing both phase Ib and phase IIb parts) will be based on a data cut-off corresponding to the time point where all patients from the phase IIb part have either completed 12 cycles of study treatment or discontinued study treatment for any other reason whichever comes first. An addendum to the core clinical study report will be provided at the completion of the study to summarize and/or list the additional safety and efficacy data as appropriate. Patients who have completed 12 cycles of study treatment at the data cut-off and are assessed by the Investigator to have the potential to benefit from ongoing will continue their assigned treatment on a reduced assessment schedule allowing collecting and reviewing safety, efficacy and survival data.

10.1 Phase Ib part

10.1.1 Populations for analysis

Safety Set: The safety set includes all patients who received at least one dose of any one compound of the study treatment

MTD determining set: consists of all patients of the safety set who either received sufficient study treatment as defined in the minimum exposure criteria in cycle 1 (patients need to have 100% of the planned dose of each compound, see Table 10-1) and had sufficient safety evaluations (Section 7.6) or discontinued due to DLT in Cycle 1. Patients who do not meet these minimum safety evaluation requirements in cycle 1 will be regarded as ineligible for the MTD determining set.

Table 10-1 Minimum exposure criteria (Cycle 1)

Compound	Scheduled doses	Minimum exposure criterion
Panobinostat	6	6
5-Aza	7	7

Full analysis set: consists of all patients who received at least one dose of study treatment.

10.1.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be listed by patient and/or summarized descriptively by initial doses of panobinostat for the full analysis set (FAS). Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented.

10.1.3 Treatments (study drug, concomitant therapies, compliance)

The actual dose and duration in days of panobinostat and 5-Aza as well as the actual dose intensity (computed as cumulative dose received/actual duration) and relative dose intensity (computed as actual dose intensity/planned dose intensity [= planned cumulative dose/scheduled duration]), will be listed and summarized by means of descriptive statistics by dose cohort, compound and cycle. The daily dose for each patient will be summarized using descriptive statistics (e.g. mean, median, and modal daily doses).

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized by ATC term descriptively.

10.1.4 Primary objective

Refer to Section 3.1.1.1

10.1.4.1 Variable

Estimation of the MTD will be based upon the estimation of the probability of DLT in cycle 1 in the MTD determining set. This probability is estimated by the Bayesian logistic model described in the [Post-text supplement 2]. Estimation of the RPIID will be based on considerations of the MTD estimation process by the use of the BLRM, together with an

[redacted]

overall clinical assessment of safety taking into consideration safety and tolerability data from all cycles.

10.1.4.2 Statistical hypothesis, model, and method of analysis

An adaptive Bayesian logistic regression model (BLRM) and dose escalation criteria similar to that proposed by (Babb Rogatko and Zacks 1998) will be used to guide the dose escalation to determine the MTD of panobinostat in combination with a fixed dose of 5-Aza. Informative priors for panobinostat will be derived based on the DLT rate obtained from a similar trial [CLBH589B2102, arm X] with the similar populations, formulations, dose regimens and for 5-Aza from publications. MTD will be assessed during the first treatment cycle. Each cohort will consist of a minimum of 3 patients fully evaluable for therapy-related toxicities over the first cycle of treatment. Posterior probabilities of the DLT from the model will be summarized. Selection of the next dose will be based on these probabilities as well as on other safety and laboratory data. For details please refer to the [Post-text supplement 2].

Dose recommendation will be based on posterior summaries for each dose combination and the interval probabilities for underdosing, targeted, excessive, and unacceptable toxicity for intervals. Once updated, the distribution summarizes the probability that the true probability of a DLT for each dose combination lies in one of the following categories:

- [0, 20%) under-dosing
- [20%, 35%) targeted toxicity
- [35%,60%) excessive toxicity
- [60, 100%] unacceptable toxicity.

Following the principle of EWOC, after each cohort of patients the recommended dose combination is the one with the highest posterior probability of DLT in the target interval [20%, 35%) among the doses fulfilling the overdose criteria: there is less than 25% chance of either excessive or unacceptable toxicity. The maximum inter-cohort dose escalation permitted is 100%. The dose recommended by the adaptive BLRM may be regarded as information to be integrated with a clinical assessment of the safety data observed thus far in determining the next dose to be investigated. In any case, the next dose will not exceed the recommended dose by the BLRM. Cohorts of at least 3 and up to a maximum of 12 MTD-evaluable patients will be enrolled in the dose-escalation part including at least 9 patients at the MTD. The Bayesian model will be updated prior to additional enrollment under the following scenarios:

1. If the first 2 patients in a cohort experience DLT prior to the enrollment of the 3rd patient. Enrollment will be halted, the model will be updated, and any new patients will be enrolled at a dose satisfying the overdose criteria, no higher than the current dose level.
2. No additional patients will be enrolled until the current cohort is completed and the model is updated.
3. For cohorts of > 3 patients if the observed number of DLTs exceeds 25% of the currently enrolled patients to that dose level, enrollment will be halted until all patients complete one cycle of dosing or experience DLT. The model will be updated to determine the uncertainty about the probability of DLT at each dose level. New patients will be enrolled at a dose level up to the highest satisfying the overdose criteria.

[redacted]

The recommended phase II dose (RPIID) will be based on considerations of the MTD estimation process by the BLRM, together with an overall clinical assessment of safety taking into consideration safety and tolerability data from all cycles at all dose levels tested. The RPIID could be the same as the MTD, but will not exceed it under any circumstance. Cohorts may be expanded at any dose level (or dose combination) below the MTD for further elaboration of safety parameters as required.

For further details of the statistical model and results under a variety of scenarios, please refer to [Post-text supplement 2].

10.1.4.3 Handling of missing values/censoring/discontinuations

Patients who are inevaluable for MTD determination (i.e. patients who are not in MTD determining set) will be replaced. Patients in whom clinical response is unknown will be treated as non-responders. Patients, for whom the post-baseline response assessments cannot be computed because of missing baseline response assessment, will be excluded from the relevant efficacy analyses. Other missing data will be noted as missing on appropriate tables/listings.

10.1.4.4 Supportive analyses

Response will be calculated per patient based on [Post-text supplement 1] for plausibility control of investigator's assessment and will be listed.

10.1.5 Secondary objectives

The secondary objectives are given in Section 3.1.2.1

10.1.6 Population and grouping for the analyses

For all safety analyses, the safety set will be used. For efficacy analyses, the full analysis set will be used. All listings and tables will be presented by initial dose group of panobinostat. Determination of MTD will be based on the MTD determining set.

10.1.6.1 Efficacy variables and analyses

Evidence of anti-tumor activity of panobinostat in combination with 5-Aza will be evaluated based on frequency of best post-baseline response of hematological malignancy assessment. The efficacy population will be used in this analysis.

10.1.6.2 Safety variables and analyses

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs, etc.) will be considered as appropriate. All safety data will be listed. Patients will be summarized by initial dose level of panobinostat.

Those MTD-determining patients who experience dose-limiting toxicity (DLT) will be listed individually by initial dose level and reason for the DLT.

[redacted]

10.1.6.2.1 Adverse events (AE)

All adverse events recorded during the study will be summarized. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by body system, severity (based on CTCAE grades), type of adverse event, and relation to the study drug. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by initial dose group and type of adverse event.

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs, and special tests) will be considered as appropriate.

The probability to detect at least one AE with a certain incidence by as a function of the cohort size is depicted in Table 10-2. Thus, the probability to detect an AE with an incidence of 10% in a cohort of at least 20 patients is higher than 87%.

Table 10-2 Probability of detecting at least one adverse event in cohort as a function of the cohort size

	Sample size										
AE rate	3	4	5	6	7	8	9	12	15	18	20
0.01	0.0297	0.0394	0.0490	0.0585	0.0679	0.0773	0.0865	0.1136	0.1399	0.1655	0.1821
0.05	0.1426	0.1855	0.2262	0.2649	0.3017	0.3366	0.3698	0.4596	0.5367	0.6028	0.6415
0.10	0.2710	0.3439	0.4095	0.4686	0.5217	0.5695	0.6126	0.7176	0.7941	0.8499	0.8784
0.15	0.3859	0.4780	0.5563	0.6229	0.6794	0.7275	0.7684	0.8578	0.9126	0.9464	0.9612
0.20	0.4880	0.5904	0.6723	0.7379	0.7903	0.8322	0.8658	0.9313	0.9648	0.9820	0.9885
0.25	0.5781	0.6836	0.7627	0.8220	0.8665	0.8999	0.9249	0.9683	0.9866	0.9944	0.9968
0.30	0.6570	0.7599	0.8319	0.8824	0.9176	0.9424	0.9596	0.9862	0.9953	0.9984	0.9992
0.35	0.7254	0.8215	0.8840	0.9246	0.9510	0.9681	0.9793	0.9943	0.9984	0.9996	0.9998

10.1.6.2.2 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common terminology criteria for adverse events (CTCAE, version 3.0) unless otherwise indicated.

A listing of laboratory values will be provided by laboratory parameter, patient, and initial dose cohort in the clinical study report (CSR). The frequency of notable lab abnormalities will be displayed by parameter, cycle and dose cohort in the CSR. Similarly, the frequency of all laboratory abnormalities will be displayed by parameter, worst CTCAE v3 grade experienced and dose cohort in the CSR.

Laboratory data will be also be displayed by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

10.1.6.2.3 Other safety data

Data from other tests (e.g. electrocardiogram or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

[redacted]

10.1.6.2.4 Tolerability

Not applicable.

10.1.7 Resource utilization

Not applicable.

10.1.8 Patient-reported outcomes

Not applicable.

10.1.9 Pharmacokinetics

Plasma panobinostat trough levels (C_{min} in ng/mL) will be summarized by study day.

[redacted]

10.1.12 Interim analysis

There is no plan for interim analysis.

10.1.13 Sample size calculation

Sample size is expected to be 26 in total.

Cohorts of at least three MTD evaluable patients per dose level will be enrolled in the phase Ib part including at least nine patients at the MTD and/or RPIID level.

Sample size is expected to be at least 26 assuming two cohorts of six patients each treated at dose levels distinct from the MTD and/or RPIID, and two cohorts of 7 patients each treated at the MTD and/or RPIID.

[redacted]

10.1.14 Power for analysis of critical secondary variables

There are no critical secondary variables in this study.

10.2 Phase IIb part

10.2.1 Population for analysis

Safety Set: The safety set includes all patients who received at least one dose of any one compound of the study treatment

Full analysis set: consists of all patients who were randomized to one of the two treatment arms.

10.2.2 Population and grouping for the analyses

For all safety analyses, the safety set will be used. For efficacy, demographics, and baseline characteristics analyses, the full analysis set will be used. All listings and tables will be presented by treatment arm ('as treated' for the safety analyses, and 'as randomized' for the efficacy analyses, demographics and baseline characteristics).

10.2.3 Patient demographics/other baseline characteristics

Demographic and other baseline data will be listed by patient and summarized descriptively by treatment arm for the full analysis set. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented.

10.2.4 Treatments (study drug, concomitant therapies, compliance)

The actual dose and duration in days of panobinostat and 5-Aza as well as the actual dose intensity (computed as cumulative dose received/actual duration) and relative dose intensity (computed as actual dose intensity/planned dose intensity [= planned cumulative dose/scheduled duration]), will be listed and summarized by means of descriptive statistics by treatment arm, component and cycle. The daily dose for each patient will be summarized using descriptive statistics (e.g. mean, median, and modal daily doses).

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized by ATC term and treatment arm descriptively.

10.2.5 Primary objective

The primary objective for the phase IIb part is given in Section 3.1.1.

10.2.6 Secondary objectives

The secondary objective for the phase IIb part is given in Section 3.1.2.

[redacted]

10.2.8 Efficacy variables and analysis

The primary efficacy endpoint will be the composite CR (CR or CRi or bone marrow CR) among all patients in the FAS.

The following efficacy endpoints will be considered.

- Clinical response for AML: CR, CRi, PR
- Clinical response for MDS/CMML: CR, bone marrow CR, PR and Hematologic Improvement (HI)
- 1-year survival rate
- Time to Progression (TTP)

Clinical responses will be summarized by treatment arm, overall and within disease type (i.e. AML or MDS/CMML). Percentage rates for the composite CR rate (CR or CRi or bone marrow CR), overall response rate (CR or CRi or bone marrow CR or PR) will be reported along with 95% confidence intervals for both arms. Exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated Clopper and Pearson 1934. Point estimates and confidence intervals for the difference in rates between the treatment arms will also be reported. The 1-year survival rate will be obtained from the Kaplan-Meier curve and its variance will be estimated by Greenwood's formula. Time to progression will also be analyzed through Kaplan Meier curves.

10.2.9 Safety variables and analysis

All adverse events recorded during the study will be summarized by treatment arm. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by body system, severity (based on CTCAE grades), type of adverse event, and relation to the study treatment. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient, type of adverse event, and treatment arm.

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs, and special tests) will be considered as appropriate.

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common terminology criteria for adverse events (CTCAE, v 3.0) unless otherwise indicated. Summary data will be reported by treatment arm.

A listing of laboratory values will be provided by laboratory parameter, patient, and treatment arm, in the clinical study report (CSR). The frequency of notable lab abnormalities will be displayed by parameter, cycle and treatment arm in the CSR. Similarly, the frequency of all laboratory abnormalities will be displayed by parameter, worst CTCAE v3 grade experienced and treatment arm in the CSR.

Laboratory data will be also be displayed by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

Data from other tests (e.g. electrocardiogram or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

[redacted]

10.2.10 Sample size calculation

The planned sample size is 40 per arm, or, in other words, 80 in total. It is deemed that an observed relative improvement of 50% in the composite CR rate (CR or CRi or bone marrow CR) in the investigational arm over the active control arm is clinically relevant in the phase IIb part of the study. Under the assumption that the composite response rate in the active control arm is 17% (estimate based on Fenaux et al 2009a), the following table gives the estimated probabilities of observing clinically relevant improvement , under different values of the true composite CR rate in the experimental arm. The chance of observing a clinically relevant improvement when there is actually no difference in the true composite CR rates between the arms) is estimated to be 23% while the chance of not observing a clinically relevant improvement when there is indeed a substantial difference in the true composite CR rates (true composite response rates in investigational and active control arms are 35% and 17% respectively) is estimated to be 19%. Since there is no hypothesis being tested, a formal power analysis has not been done. The aforementioned estimated probabilities of 23% and 19% are only analogous to the probabilities of type I and type II errors (in the setting of hypothesis testing). These probabilities (as well as, the others shown under [4] in the following table) have been derived by simulating response data using independent binomial distributions for the investigational and active control arms with the probability parameter of the distribution being specified according to the assumed true underlying composite CR rates as shown under [1], and [2] of the table below. Thus, given that the true composite CR rates are as in [1] and [2] (and, the true percentage improvement as in [3]), [4] represents the probability of observing clinically relevant improvement. More specifically, [4] represents the following:

Pr[(observed composite CR rate in investigational arm - observed composite CR rate in active control arm) ≥ 50% of observed composite CR rate in active control arm]

Table 10-3 Probability of observing clinically relevant improvement based on an assessment of composite CR (CR or CRi or bone marrow CR)

True composite CR rate in active control arm [1]	True composite CR rate in investigational arm [2]	True improvement (as a percentage of the true composite CR rate in the active control arm) [3]	Probability of observing clinically relevant improvement [4]
0.17	0.17	0	0.23
	0.20	18	0.33
	0.25	47	0.51
	0.30	76	0.68
	0.35	106	0.81

10.2.11 Interim analysis

There is no plan for interim analysis.

[redacted]

10.2.12 Power for analysis of critical secondary variables

There are no critical secondary variables.

10.2.13 Handling of missing values/censoring/discontinuations

Patients for whom clinical response is unknown will be treated as non-responders. Patients for whom the post-baseline response assessments cannot be determined because of missing baseline response assessment, will be excluded from the relevant efficacy analyses. Patients for whom disease progression status cannot be determined because of missing baseline assessment, will be censored at baseline for the time to progression analysis. Other missing data will be noted as missing on appropriate tables/listings.

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, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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. 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

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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.

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 is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov, before study start. In addition, results of interventional clinical trials in adult patients are posted on ...novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV).

Novartis follows the ICMJE authorship guidelines (...icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to ...novartis.com.

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.

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

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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 trial 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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