BerGenBio ASA
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CLINICAL STUDY PROTOCOL

Investigational Product:	Bemcentinib (BGB324)
Protocol Number:	BGBC003
Phase	Phase Ib/II
Protocol Title:	An open label, multicenter, phase Ib/II study of BGB324 (bemcentinib) administered as a single agent or in combination with cytarabine or decitabine in patients with acute myeloid leukemia or as a single agent in patients with myelodysplastic syndrome
EudraCT Number:	2014-000165-46
IND Number:	124255
Version and Date:	10.0 (US); 14 July 2021

CCI

This study will be conducted in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements

1. Protocol Approval Signatures

Protocol BGBC003 Version 10.0 (US), 14 July 2021

Sponsor's Approval:

This protocol has been approved by BerGenBio ASA

Signature: **Date:**

Prof PPD
PPD

Investigator's Approval:

I, the undersigned, have reviewed the Protocol, including Appendices and I will conduct the BGBC003 clinical study as described and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and all the ethical and regulatory considerations stated. I have read and understood the contents of the bemcentinib Investigator's Brochure

Signature: **Date:**

2. Study Personnel

Full contact details for each Investigational site, the Sponsor and other key coordinating and operational personnel involved in this clinical trial (including vendors), are maintained and available for reference in each Site Study File and in the Trial Master File.

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5. List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APTT	Activated Partial Thromboplastin Time
Ara-C	Cytosine arabinoside, cytarabine
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the curve from time zero to infinity
AUC_{0-48h}	Area under the curve from time zero to 48 hours
AUC_{0-t}	Area under the concentration-time curve
AUC_{0-tau}	Area under the curve within a dosing interval
BM	Bone marrow
BP	Blood pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CI	Confidence interval
C_{max}	Maximum concentration achieved
CNS	Central nervous system
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Clinical Trials Directive
CV	Cardiovascular
DHA	Directions for Handling and Administration
DLT	Dose limiting toxicity
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EU	European Union
FCM	Flow cytometry
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
h	Hour
hERG	Human ether-à-go-go related gene
HIV	Human immunodeficiency virus
HPMC	Hydroxypropyl methylcellulose
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product

IMPD	Investigational medicinal product dossier
IND	Investigational new drug
IP	Inorganic phosphate
IRB	Institutional Review Board
IWG	International Working Group
K	Potassium
LC/MS/MS	Liquid chromatography/tandem mass spectrometry
LDAC	"Low-dose” cytarabine
MCH	Mean cell hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA	Multi Gated Acquisition Scan
Na	Sodium
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OR	Objective response
ORR	Objective response rate
OS	Overall Survival
pAXL	Phospho AXL
PBMC	Peripheral blood mononuclear cell(s)
PCR	Polymerase chain reaction
PD	Progressive Disease
PII	Personally identifiable information
PK	Pharmacokinetic
PR	Partial Remission
PT	Prothrombin time
QA	Quality Assurance
QTcF	QTc interval according to Fridericia’s correction
REC	Research Ethics Committee
RP2D	Recommended Phase 2 dose
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety analysis set
sAXL	Soluble AXL
SD	Stable disease
SMC	Safety Monitoring Committee
SmPC	summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
$T_{½}$	Terminal half-life
TdP	Torsade de Pointes
TEAE	Treatment Emergent Adverse Events
T_{max}	Time to maximum concentration

TMF	Trial Master File
ULN	Upper limit of normal
WT	Wild Type

6. Protocol Synopsis

PROTOCOL TITLE:	An open label, multicenter, phase Ib/II study of BGB324 (bemcentinib) administered as a single agent or in combination with cytarabine or decitabine in patients with acute myeloid leukemia or as a single agent in patients with myelodysplastic syndrome
PROTOCOL No:	BGBC003
SPONSOR:	BerGenBio ASA, Jonas Lies vei 91, 5009, Bergen, Norway
INVESTIGATIONAL PRODUCT:	Bemcentinib (BGB324)
PHASE OF DEVELOPMENT:	Phase Ib/II
INDICATION AND RATIONALE:	Acute myeloid leukemia (AML) (with the exception of AML M3) and myelodysplastic syndrome (MDS) with the exception of deletion 5q MDS. This is the first clinical study of bemcentinib in patients. Bemcentinib is a potent selective small molecule inhibitor of AXL, a surface membrane protein receptor tyrosine kinase which is overexpressed in up to half of AML cases. AXL expression has been identified as a marker of a poor prognosis in AML. *In vitro* studies indicate that signaling through AXL stimulates a number of pro-survival pathways some of which are mediated by AKT phosphorylation and up-regulation of the epithelial receptor kinase pathway. *In vitro* studies indicate that activation of AXL enables malignant cells to develop resistance to conventional chemotherapies. Preliminary *in vitro* studies using AML cell lines indicate that treatment with bemcentinib is at least additive in effect when administered with cytarabine). Early *in vitro* and *ex vivo* studies also indicate that AXL inhibition with bemcentinib inhibits proliferation of mononucleated bone marrow (BM) derived from patients with MDS.
OBJECTIVES:	**Part A** PRIMARY • To identify the maximum tolerated dose (MTD) of bemcentinib in AML patients who have received previous treatment with cytotoxic chemotherapy (with or without hematopoietic stem cell transplantation) or a targeted or biologic agent (e.g. hypomethylating agent, tyrosine kinase

	inhibitor, antibody), and have relapsed after or have been refractory to treatment with such prior therapy SECONDARY • To identify the dose limiting toxicity (DLT) profile of bemcentinib • To explore the safety and efficacy of bemcentinib • To characterize the pharmacokinetic (PK) profile of bemcentinib **Part B** PRIMARY • To identify the safety and tolerability of bemcentinib as a single agent in patients with AML or MDS (Parts B1 and B4), in combination with low dose cytarabine in patients with AML (Part B2 and Part B5), or in combination with decitabine in patients with AML (Part B3) SECONDARY • To explore the efficacy of bemcentinib as a single agent in patients with AML or MDS (Parts B1 and B4), in combination with low dose cytarabine in patients with AML (Part B2 and Part B5), or in combination with decitabine in patients with AML (Part B3) • To assess bemcentinib PK (all Part B cohorts) EXPLORATORY (Parts A and B1, B2, B3, B4 and B5) • To identify and evaluate potential predictive biomarkers, e.g. soluble AXL [sAXL] and other associated soluble biomarkers. Pre-treatment levels of biomarkers will be correlated with clinical endpoints • To establish the effects of bemcentinib on relevant biological endpoints in peripheral blood (including sAXL, peripheral blood mononuclear cells [PBMC]) and BM samples • To assess pharmacodynamic biomarkers in tissue and blood to support the clinical development of bemcentinib

	• To evaluate other biomarkers relevant to the investigational agents for exploratory purposes
ENDPOINTS:	SAFETY: Treatment emergent adverse events (TEAE), physical examination. Vital signs (i.e. blood pressure (BP) and heart rate (HR), respiration rate and temperature), electrocardiogram (ECG), echocardiograms and laboratory findings including clinical chemistry, hematology and urinalysis. EFFICACY: AML Response criteria: • Objective response (OR) or Stable Disease (SD) according to the revised recommendations of the International Working Group (IWG) in AML Appendix 5 [Cheson, 2003 and Döhner, 2017]. SD is defined as having unchanged disease for at least 3 treatment cycles. • Proportion of patients with an OR + SD as an estimate of clinical benefit • Relapse Free Survival • Event Free Survival • Overall Survival • To explore the correlation between baseline biomarker levels and clinical endpoints MDS Response criteria: • OR or SD according to the revised recommendations of the IWG in MDS Appendix 6 [Cheson, 2006]. SD is defined as failure to achieve at least Partial Remission (PR), but not evidence of Progressive Disease (PD) for at least 3 treatment cycles. • Proportion of patients with an OR + SD as an estimate of clinical benefit • Relapse Free Survival • Event Free Survival • Overall Survival • To explore the correlation between baseline biomarker levels and clinical endpoints PHARMACOKINETIC: As a minimum, area under the curve within a dosing interval ($AUC_{0\text{-}tau}$), maximum concentration achieved

	(C_{max}) and time to maximum concentration (T_{max}) for bemcentinib will be determined from plasma. Additional parameters may also be reported, as deemed appropriate once data are reviewed. PHARMACODYNAMIC AND PREDICTIVE BIOMARKERS: The effects of bemcentinib on pharmacodynamic endpoints of AXL inhibition will be determined in BM aspirates and blood samples: • To identify and evaluate potential predictive biomarkers, e.g. sAXL and other associated soluble biomarkers. Pre-treatment levels of biomarkers will be correlated with clinical endpoints • To establish the effects of bemcentinib on relevant biological endpoints in peripheral blood (including sAXL, PBMC) and BM samples • To assess pharmacodynamic biomarkers in tissue and blood to support the clinical development of bemcentinib • To evaluate other biomarkers relevant to the investigational agents for exploratory purposes • Effect of bemcentinib on AXL, sAXL and phospho AXL (pAXL) and downstream effectors of AXL signaling, such as Akt, pAkt, Erk, pErk, SLFN11, Bcl2, Puma by appropriate methods (e.g. flow cytometry (FCM), western blotting, proteomics, transcriptomics) • Effect of bemcentinib on gene expression by appropriate methods (e.g. FCM, western blotting, proteomics, transcriptomics, quantitative polymerase chain reaction (PCR), DNA-methylation analysis) • Effect of bemcentinib on relevant Immune cell populations • Effect of bemcentinib on the spectrum of mutations present within the cancer cell population by genomic analysis • To explore the correlation between baseline biomarker levels and clinical endpoints
STUDY DESIGN:	This Phase Ib/II open-label study will run at approximately 20 clinical sites (in Europe and the United States) and may enroll up to approximately 102 evaluable patients with AML or MDS. Additional

	countries and sites may be added as required to meet the enrolment needs of the study. In all parts of the study patients with AML who have a matched donor and who are candidates for allogeneic BM transplantation are not eligible to participate. In order to be eligible for Part A, patients must have received previous treatment with cytotoxic chemotherapy (with or without hematopoietic stem cell transplantation) or targeted or biologic agent (e.g. hypomethylating agent, tyrosine kinase inhibitor, antibody) and have relapsed after or have been refractory to treatment with such prior therapy. The study consists of a dose-escalation phase to determine the MTD of single agent bemcentinib in patients with relapsed or refractory AML (Part A). In the cohort expansion phase (Part B), bemcentinib will be investigated in up to four cohorts: In Part A dose-escalation will continue until DLT occurs, at which point an MTD will be selected and used in Part B. The dose of bemcentinib selected will be either the MTD or a Recommended Phase 2 dose (RP2D) as agreed by the Safety Monitoring Committee (SMC) and which is supposed to be clinically effective. Bemcentinib will be administered orally according to a daily schedule, with the first two to three doses of Cycle 1 serving as a 'loading' dose. Each 21-day (three week) period will constitute 1 cycle of treatment. As part of the development program the formulation has been enhanced to Formulation 2. Therefore from 2017 onwards Formulation 2 will be applied, first in an additional dose-escalation cohort. The starting dose for Formulation 1 consisted of a loading dose of 400 mg on Cycle 1, Days 1 and 2, followed by a daily maintenance dose of 100 mg. Dosing with Formulation 1 was completed in 2016. Currently, dosing with Formulation 2 will consist of a loading dose of 200 mg administered on Days 1, 2 and 3 followed by a daily maintenance dose of 100 mg. This dose may be escalated as agreed by the SMC to a maximum daily loading dose of 400 mg on Days 1, 2 and 3 followed by a maximum daily maintenance dose of 200 mg. Patients will be instructed to take bemcentinib on an empty stomach at a similar time each morning when they wake or more than 2 hours after a light meal with water.

	To maintain a fasted state, patients should be told not to eat or drink anything other than water for at least 1 hour after taking the drug. **Part A – Dose Escalation:** Open label, dose-escalation study of repeat doses of bemcentinib as a single agent. Escalation will be performed according to a "3+3" design to determine the MTD. Between 6-10 patients will be treated at the MTD or RP2D as determined by the SMC. The DLT assessment period will comprise the first 21-day treatment cycle. Patients who do not complete the DLT assessment period for reasons other than toxicity will be replaced for the purpose of toxicity evaluation. A patient must receive all loading doses and miss no more than 3 maintenance doses in Cycle 1 in order to be considered as informative to support dose escalation, unless missed doses are due to DLT. The decision to dose-escalate (or not) will be made by the SMC comprising a representative from each actively recruiting investigational site and a representative of the BerGenBio ASA study team. The decision to dose escalate will be based upon the tolerability of the bemcentinib loading dose and daily maintenance dose observed at the previous dose level. **Part B – Cohort Expansion** The decision to proceed to Part B of the study will be made by the SMC on the basis of the observed tolerability and efficacy seen in Part A. Up to 5 distinct patient cohorts of up to 14 evaluable patients per cohort in B1, B2, B3, B4 and up to 20 evaluable patients in cohort B5 may be explored. Depending upon the safety profile of bemcentinib observed in Part A, the initial starting dose in combination with cytarabine (Part B2) or decitabine (Part B3) may be reduced by a single dose level (i.e. MTD -1) which will be evaluated in at least three patients in each cohort before the introduction of the MTD identified in Part A. The bemcentinib dose level to be investigated in Part B2 and Part B3 will be dependent upon the MTD confirmed in Part A. A dose lower than 100 mg daily is not available. **Part B1:** Single agent bemcentinib in patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or co-morbidities. Patients should

	have relapsed following at least one line of therapy or be refractory to such prior therapy. **Part B2:** Bemcentinib will be administered in combination with low dose cytarabine in patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or existing co-morbidities. Cytarabine will be administered subcutaneously according to standard practice (i.e. 20 mg twice daily for 10 days followed by a rest period of ≤1 month according to persisting myelosuppression). Cytarabine should be administered approximately 30 minutes after the bemcentinib dose. The bemcentinib dose to be investigated in combination will be confirmed by the SMC. If the SMC-recommended dose of bemcentinib is less than the single agent MTD, further dose escalation of bemcentinib may be considered until an MTD for the combination is identified, although the dose administered will not escalate beyond the single-agent MTD. **Part B3:** Bemcentinib will be administered in combination with decitabine in patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or co-morbidities. Decitabine will be administered at a maximum dose of 20 mg/m^2 body surface area by intravenous infusion, repeated daily for 5 consecutive days (i.e. a total of 5 doses per 28-day treatment cycle). The total dose per treatment cycle must not exceed 100 mg/m^2. Decitabine should be administered within approximately 30 minutes of the bemcentinib dose. In Part B3 bemcentinib will be administered at a dose identified by the SMC in combination with decitabine. The dose of bemcentinib administered must not exceed the MTD. **Part B4:** Single agent bemcentinib in patients with previously treated MDS (including high risk and intermediate with the exception of deletion 5q MDS). The bemcentinib dose to be investigated will be confirmed by the SMC and will be no higher than the MTD dose explored in part A. **Part B5:** The Part B5 bemcentinib dose is based on the bemcentinib dose that was identified as safe and well tolerated in Part B2. Bemcentinib will be administered in combination with low dose cytarabine in patients with relapsed or refractory AML who have received at least

	one prior treatment for AML. Patients must be unsuitable for intensive chemotherapy as a result of advanced age or existing co-morbidities. The bemcentinib dose will be 400 mg orally daily for the first 3 days of treatment (loading dose) and 200 mg orally daily thereafter (maintenance dose). Cytarabine will be administered at a dose of 20 mg subcutaneously twice daily for 10 days every 28 days. Cytarabine should be administered approximately 30 minutes after the bemcentinib dose.
DOSE LIMITING TOXICITIES (Part A):	DLTs will be assessed during the first 3 weeks of treatment with bemcentinib (Cycle 1), according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) [NCI CTCAE] version 4 considered unrelated to leukemia progression or intercurrent illness, and defined as any of the following: • CTCAE Grade 3 or 4 nausea, vomiting, or diarrhea that persists despite maximum prophylactic and supportive care. • Any other CTCAE Grade 3 or 4 non-hematological toxicity that is considered to be clinically significant and causally related to bemcentinib, excluding isolated changes in laboratory results if no clinical significance or no clinical sequelae and adequately improve within 7 days. • Prolonged neutropenia with ANC <500 and platelet count <75000 after Day 42 from the start of treatment in the absence of residual leukemia • Treatment discontinuation, inability to administer one or more bemcentinib loading dose, or inability to administer three bemcentinib maintenance doses as a result of bemcentinib-related toxicity. • Any ventricular arrhythmia.
STUDY POPULATION: INCLUSION CRITERIA:	1. Provision of signed written informed consent 2. Histological, molecular, or cytological confirmation of: **AML (with the exception of AML M3)** • **Part A**: Patients with relapsed or refractory AML following treatment with cytotoxic chemotherapy or a targeted or biologic agent

	(e.g. hypomethylating agent, tyrosine kinase inhibitor, antibody) • **Part B1**: Patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or co-morbidities. Patients should have relapsed following at least one line of therapy or be refractory to such prior therapy • **Part B2**: Patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or co-morbidities and who are suitable to receive treatment with cytarabine • **Part B3**: Patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or co-morbidities and who are suitable to receive treatment with decitabine • **Part B4** Patients with previously treated MDS (with the exception of deletion 5q MDS) including intermediate and high risk patients who must have received prior treatment for their disease. Prior treatment may include those patients who have received hypomethylating agents, decitabine or other approved treatments for MDS. Or • **Part B5:** Patients with relapsed or refractory AML who are unsuitable for intensive chemotherapy as a result of advanced age or co-morbidities meeting the following criteria: o Must have received at least one prior treatment for AML. o Are suitable to receive treatment with "low-dose" cytarabine (LDAC). LDAC is defined as 20 mg cytarabine administered subcutaneously twice daily for 10 days every 28 days. The number of patients with refractory AML, defined as no hematological response to last AML treatment and/or patients who have received 2 or more prior treatments for AML, will be restricted to 1/3 of the sample size (i.e. no more than 6 evaluable patients).

	3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2 [Appendix 1] 4. Age 18 years or older 5. Female patients of childbearing potential must have a negative serum pregnancy test within 3 days prior to taking their first dose of bemcentinib. Male patients and female patients of reproductive potential must agree to practice highly effective methods of contraception (such as hormonal implants, combined oral contraceptives, injectable contraceptives, intrauterine device with hormone spirals, tubal ligation, total sexual abstinence, vasectomy) throughout the study and for ≥3 months after the last dose of bemcentinib. Female patients are considered NOT of childbearing potential if they have a history of surgical sterility or evidence of post-menopausal status defined as any of the following: a) Natural menopause with last menses >1 year ago b) Radiation induced oophorectomy with last menses >1 year ago c) Chemotherapy induced menopause with last menses >1 year ago
EXCLUSION CRITERIA:	1. Patients with a matched donor who are candidates for allogeneic BM transplantation 2. Pregnant or lactating 3. History of the following cardiac conditions: • Congestive cardiac failure of >Class II severity according to the New York Heart Association (NYHA) (Appendix 2: defined as symptomatic at less than ordinary levels of activity) • Ischemic cardiac event including myocardial infarction within 3 months prior to first dose. Patients with prior history or ECG evidence of old myocardial infarction should be discussed with the Sponsor to confirm eligibility. • Uncontrolled cardiac disease, including unstable angina, uncontrolled hypertension (i.e. sustained systolic BP >160 mmHg or diastolic BP >90 mmHg), or need to change

	medication within 6 weeks of provision of consent due to lack of BP control • History or presence of sustained bradycardia (≤55 beats per minute), left bundle branch block, cardiac pacemaker or ventricular arrhythmia. Note: Patients with supraventricular arrhythmia should be discussed with the Sponsor to confirm eligibility. • Family history of long QTc syndrome; personal history of long QTc syndrome or previous drug-induced QTc prolongation of at least Grade 3 (QTc >500 ms) • Presence of any factors that increase the risk for QTc prolongation, e.g. resistant or inadequately treated heart failure, presence of hypokalemia or hypomagnesemia not corrected by, or not responding to, replacement therapy or inadequately treated hypothyroidism as defined by the thyroid-stimulating hormone not within the expected range of the institution. 4. Abnormal left ventricular ejection fraction on echocardiography or Multi Gated Acquisition Scan (MUGA) (less than the lower limit of normal for a patient of that age at the treating institution or <45%, whichever is lower) 5. Current treatment with any agent known to cause QT prolongation and have a risk for Torsades de Pointes which cannot be discontinued at least five half-lives or two weeks prior to the first dose of study treatment. Please see Appendix 3 for list of relevant medications 6. Screening 12-lead ECG with a measurable QTc interval according to Fridericia's correction >450 ms 7. Ongoing infection requiring systemic treatment. Patients who are on prophylactic antimicrobials or who have been afebrile for 48 hours following the initiation of antimicrobials are eligible 8. Inadequate liver function as demonstrated by serum bilirubin ≥1.5 times the upper limits of normal range (ULN) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times the ULN (or ≥5 times the ULN for ALT or

	AST in the presence of liver involvement by leukemia) 9. Inability to tolerate oral medications 10. Existing gastrointestinal disease affecting drug absorption such as celiac disease or Crohn's disease 11. Known lactose intolerance 12. Requires vitamin K antagonists. Note: Patients receiving low doses prescribed to maintain the patency of venous access devices may be included 13. Treatment with any of the following; histamine receptor 2 inhibitors, proton pump inhibitors or antacids within 3 days or 5 half-lives of administration of bemcentinib, whichever is longer 14. Treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index 15. Previous bowel resection that would interfere with drug absorption 16. Evidence of ongoing gastrointestinal graft versus host disease 17. Hematopoietic stem cell transplantation within 6 months 18. Impaired renal function as demonstrated by a creatinine clearance of <30 mL/min determined by Cockcroft-Gault formula 19. Radiotherapy or chemotherapy within the 14 days prior to the first dose of bemcentinib being administered (other than hydroxyurea) 20. Receiving an investigational anti-cancer treatment concurrently or within 14 days or five half-lives (whichever is shorter) of either the parent drug or any known active metabolite prior to the start of bemcentinib 21. Unresolved CTCAE ≥Grade 2 toxicity (other than stable toxicity) from previous anti-cancer therapy excluding alopecia 22. Any evidence of severe or uncontrolled systemic conditions (e.g., severe hepatic impairment) or current unstable or uncompensated respiratory or cardiac conditions which makes it undesirable

	for the patient to participate in the study or which could jeopardize compliance with the protocol 23. Known active, uncontrolled central nervous system (CNS) disease including CNS leukemia 24. Known active infection with human immunodeficiency virus (HIV), hepatitis B or C viruses – screening for viral infections is **not** required for entry to this study 25. Major surgery within 28 days prior to the start of bemcentinib – excluding skin biopsies and procedures for insertion of central venous access devices 26. Hypersensitivity to cytarabine, decitabine or any of their excipients 27. Prior exposure to Astellas ASP2215 (FLT3/AXL inhibitor-Gilteritinib)
TREATMENT AND INTERVENTIONS:	Patient eligibility for the study will be determined within 14 days prior to the first dose of bemcentinib. Screening assessments will be conducted according to the Schedule of Events (Tables 4-6) in Section 11. Eligible patients will visit the study site to receive study treatment and protocol-specified procedures according to the relevant Schedule of Events (Tables 4-6) in Section 11. In order to reduce the risk of tumor lysis syndrome all patients will be asked to drink up to two liters of fluid in the 24-hour period prior to starting treatment with bemcentinib and on Day 0, Day 1, Day 2 and Day 3. All patients will receive treatment with allopurinol (or equivalent) for at least the first week of treatment or until their serum uric acid is within the normal range or considered as not clinically significant. If a patient has a pre-existing condition where uric acid levels are higher (i.e. gout) pre-bemcentinib uric acid levels may be considered as normal). The treatment period will consist of continuous 21-day treatment cycles. Patients will be intensively monitored throughout Day 1 to Day 4 inclusive of Cycle 1, and in addition will attend the clinic on Day 8, and Day 15. Patients will attend the clinic once a week during Cycle 2 (Day 1, 8 and 15) and then once per cycle thereafter. The study period will consist of screening, treatment, Final Study Visit, and follow-up. The Final Study Visit will occur 28 days after the patient has discontinued study treatment. The patients will be followed by the site for

	survival even after the final study visit. Follow-up can be conducted by phone or visit, contact with family members or community health care providers (family practitioner, nurse or family liaison/social worker), or public health records (where applicable). Every effort should be made to establish the patient's survival status at 3-monthly intervals, or less.
BEMCENTINIB: FORMULATION/DOSE/ROUTE OF ADMINISTRATION:	Bemcentinib is presented for oral dosing in capsules each containing 100 mg bemcentinib. Patients will be instructed to take bemcentinib on an empty stomach at a similar time each morning when they wake or more than 2 hours after a light meal, with water. To maintain a fasted state, patients should be told not eat or drink anything other than water for at least 1 hour after taking the drug. Bemcentinib will be administered orally according to a daily dosing schedule during each week of continuous 21-day treatment cycles. During Cycle 1 ONLY the first three doses may comprise of a 'loading' dose. **Part A**: Dose is ascending per dose cohort. The starting dose of bemcentinib (Cohort 1) will be 200 mg on Cycle 1, Days 1, 2 and 3 (loading dose), followed by a daily maintenance dose of 100 mg. This dose may be escalated as agreed by the SMC to a maximum daily loading dose of 400 mg on Days 1, 2 and 3 followed by a maximum daily maintenance dose of 200 mg. Please refer to Section 9.2.1.1 for more details on dose escalation rules. **Part B:** Bemcentinib will be administered at the MTD or RP2D in Part B1 and Part B4 In Parts B2 and B3 bemcentinib will be administered at a dose identified by the SMC, which may be lower than the bemcentinib dose confirmed in Part A. Depending upon the safety profile of bemcentinib observed in Part A the initial starting dose in combination with cytarabine or decitabine may be reduced by a single dose level (e.g., MTD -1) which will be evaluated in at least 3 subjects before introduction of the MTD or RP2D identified in Part A. The bemcentinib dose in Part B will be 400 mg orally daily for the first 3 days of treatment (loading dose) and 200 mg orally daily thereafter (maintenance dose).
DURATION AND FREQUENCY	Patients may continue to receive bemcentinib for as long as, in the opinion of the investigator, they continue to derive

	clinical benefit. When there is confirmed disease progression in the absence of clinical benefit, development of severe toxicity, or withdrawal of consent, study treatment must be discontinued. However, patients experiencing disease progression may be permitted to continue treatment with bemcentinib, where the investigator believes patients may continue to derive some clinical benefit from continued treatment. Clinical benefit in this context is defined as meeting one or several of the following criteria: evidence of disease stabilization after documented initial progression (patient is stably worse), tolerance of drug(s), absence of rapid progression based on peripheral or bone marrow blasts and clinical hematology and clinical chemistry parameters, maintenance of good performance status (PS of 2 or less and not deteriorating], absence of worsening clinical symptoms (i.e., no symptomatic deterioration) and/or improvements in patient's quality of life). The decision to continue treatment must be discussed and agreed between the treating investigator, the patient and the Sponsor. All decisions will be documented in writing. Patients dosed beyond progression will continue to be evaluated for potential clinical benefit and safety. This will not affect the time point of disease progression from the perspective of trial analysis. Patients who permanently discontinue treatment with one of the combination agents in Parts B2, B3 and B5 may continue to receive the other study drug alone if it is safe to do so (at investigator discretion) in the absence of disease progression or intolerable toxicity. The investigator may also decide to discontinue both study treatments at this time.
EVALUATION:	As outlined in the relevant Schedule of Events (Tables 6-8). <u>Safety:</u> Physical examination Vital signs ECG Echocardiogram

	Routine blood panel (hematology, clinical chemistry and coagulation panel) Adverse events (AEs) (CTCAE) <u>Efficacy:</u> Peripheral blood count; BM aspirate <u>Pharmacokinetics:</u> Bemcentinib PK parameters in plasma (Part A and Part B) <u>Pharmacodynamics:</u> The effects of bemcentinib on pharmacodynamic endpoints, gene expression and genomics in BM aspirates and PBMC.
FOLLOW UP:	AEs will be monitored for 28 days after the last dose of study treatment. If bemcentinib-related toxicities continue beyond the follow up period, patients will be followed until all bemcentinib-related toxicities have resolved to <u>≤</u>Grade 1 or less, stabilized or returned to baseline. Follow up monitoring for AEs may be conducted over the telephone. Serious adverse events (SAEs) with a suspected relationship to bemcentinib will be collected indefinitely. The study will be completed when all patients have completed their final study visit. All patients will be followed for survival after they have permanently discontinued from study treatment at ≤3 monthly intervals by the site. Subsequent anticancer therapies for AML or MDS must be collected in the electronic case report form (eCRF). The study will be completed when all patients have an OS event, unless the Sponsor terminates OS follow-up once all patients have discontinued study treatment.
STATISTICAL METHODS	As this is an early study of bemcentinib only descriptive analysis will be performed on safety data. Preliminary statistical analysis will be performed on objective response rates in Part B. **Safety:** All safety and tolerability assessments will be based on the safety analysis set (all patients who have received at least one dose of study medication). **Efficacy:** Efficacy assessments will be based on the safety analysis set.

	Note: patients treated with bemcentinib beyond disease progression will be followed for the same safety and efficacy assessments as for all other patients enrolled into the study until they are withdrawn from the study. The data for patients treated beyond progression will be presented in both a combined output (with all patients) and also a separate output (to reflect a new period of analysis). All data collected will be included in the study CSR. **Pharmacokinetics:** Individual and mean bemcentinib plasma concentration-time data will be presented in tabular and graphical form. PK parameters for bemcentinib will be derived from an appropriate PK model will be determined using a non-compartmental analysis. Full details of the PK analysis will be presented in a PK Analysis Plan. **Pharmacodynamics:** Pharmacodynamic data will be listed and summarized by dose cohort and time point as appropriate.

7. Introduction

This study is a dose-escalation of bemcentinib, an AXL kinase inhibitor, in patients with acute myeloid leukemia (AML), followed by a cohort expansion study of bemcentinib either as a single agent in patients with AML or MDS, or in combination with cytarabine (cytosine arabinoside, Ara-C) or decitabine in patients with AML.

7.1. Pre-clinical Studies with Bemcentinib

7.1.1. Summary of Pre-clinical Activity

Bemcentinib demonstrates potent inhibition of AXL in biochemical and cell-based kinase inhibition assays. The selectivity of bemcentinib for AXL is illustrated in Table 1.

Table 1: Bemcentinib Kinase Selectivity Profile

Kinase	Kinome Scan binding assay (Kd)		KinaseProfiler kinase activity assay (IC_{50})		BaF3 cell-based kinase activity assay (IC_{50})	
	nM	fold	nM	fold	nM	fold
AXL	0.4	1	4.6	1	63	1
Tie2	270	680	30	6.4	355	5.5
Ret	73	180	38	8.1	>316	>5
Flt1	400	>1000	40	8.7	>1000	>15
Flt4	460	>1000	41	8.8	>1000	>15
Yes	810	>1000	43	9.2	n/a	n/a

n/a = not applicable

Bemcentinib inhibits the growth and survival of tumor cell lines derived from a range of solid and leukemic tumors. *In vitro* activity of bemcentinib has been examined in a range of different AML cell lines where exposure-induced differentiation and arrest in the G1 phase of the cell cycle was accompanied by a reduction in levels of phosphorylated AXL and phosphorylated ERK. Early *in vitro* and *ex vivo* studies indicate that AXL inhibition with bemcentinib also inhibits proliferation of clonal cells derived from patients with MDS.

The *in vivo* efficacy of bemcentinib has been evaluated in two different murine models of AML. Studies in the MDV4-11 xenograft model showed a dose-dependent reduction in tumor burden following oral treatment with bemcentinib. A dose-dependent reduction in both AXL and ERK phosphorylation levels were noted. Bemcentinib treatment also significantly inhibited tumor growth in the OCI-AML5 xenograft model. Furthermore, bemcentinib has been shown to significantly prolong survival in the syngeneic bone marrow (BM) transplantation Hoxa9/Meis1 mouse model [Ben-Batalla, 2013].

As described by Ben-Batalla, BM cells from 7 out of 11 patients with primary AML were sensitive to bemcentinib (IC_{50} = 1.9 $\pm$ 0.5μM), and this inhibition was independent of FLT3 status since FLT3 WT AML cells were similarly sensitive to bemcentinib (n=3/8; p=0.4212).

Furthermore, the EC_{50} of response to bemcentinib correlated with AXL protein expression levels (n=10; R^2=0.84; p<0.05), with AXL negative cells being almost completely resistant to bemcentinib. Bemcentinib treatment also significantly sensitized BM cells from primary patient AML cells to cytarabine [Ben-Batalla, 2013].

Population studies have identified both AXL expression and circulating levels of Gas 6 as independent predictors of prognosis [Whitman, 2013].

A modest substrate and time-dependent inhibition of CYP3A4/5 activity by bemcentinib was observed in an *in vitro* study with human liver microsomes. Preliminary results from a cytarabine in vitro metabolism study indicate that cytarabine does not undergo extensive metabolism by CYP3A4. Consequently, it is considered unlikely that there will be an interaction between bemcentinib and cytarabine. Decitabine does not undergo CYP450 mediated metabolism; therefore, there is no rationale for the evaluation of its interaction with bemcentinib.

A comprehensive summary of the pre-clinical activity of bemcentinib is presented in the current version of the Investigator's Brochure (IB).

7.1.2. Summary of Pre-clinical Toxicology

To support clinical studies with bemcentinib a series of animal toxicology and safety studies, including 28-day repeat dosing studies in rodents and monkeys and a single dose telemetered cardiovascular (CV) safety study in monkeys, have been conducted. Comparisons of the data reported in the rodent and monkey studies indicate that primates are more sensitive to bemcentinib on a per body weight basis.

The results of the repeat dose 28-day study in monkeys identified the liver, reticuloendothelial system and hematopoietic system as target organs. These events were largely thought to be due to macrophage accumulation, consistent with phospholipidosis, and were only partially reversible across the planned 16-day recovery period, although this was anticipated to be due to the slow elimination of the compound. Similar findings were identified in mice treated across a range of dose levels with partial recovery noted 16 days later.

In the CV safety study, single oral administration of bemcentinib (7.5 mg/kg – 60 mg/kg) was associated with recoverable, non-adverse decreases in heart rate and corresponding increases in the RR interval durations. Dose-dependent increase in QTc interval was noted at all dose levels; the magnitude of the QTc effect at the highest dose level was 17%, whilst at 7.5 mg/kg and 15 mg/kg, the change generally fell below 10% compared to vehicle control

and pre-dose values. These observations were consistent with the previously identified IC_{50} for human ether-à-go-go related gene (hERG) channel inhibition of 0.53 μM bemcentinib.

Bemcentinib was negative in the Ames bacterial mutation assay, suggesting that bemcentinib is not mutagenic. Bemcentinib was also negative in an *in vitro* mammalian cell cytogenetic study in human lymphocytes suggesting that bemcentinib is not clastogenic.

7.1.3. High Dose Steroids and Mouse Model

In an academic model of osteoporosis, bemcentinib was administered in combination with high dose corticosteroids (12.5 mg/kg per day of prednisolone). In this research study, 6 out of 7 mice experienced severe toxicity after five continuous days of combination therapy. Four out of 7 animals died and the other 2 were euthanized for humane reasons. The exact mechanism of this effect is currently under investigation. The mice received very high levels of corticosteroids to induce rapid onset of osteoporosis – on a mg/kg basis, the corticosteroid dose was 20-fold higher than a typical high dose commonly used in clinical practice. Additionally, the dose of bemcentinib used in this model was 50 mg/kg which is 6-fold higher than the maximum exposure observed in human clinical studies.

In a follow-up study, the equivalent dose of prednisolone (0.208 mg/kg) was given as an oral bolus once a day for 9 days. The prednisolone dosed orally was well tolerated and no major issues were reported upon necropsy (336-TR-324-TOX). It was concluded that the toxicity observed when the prednisolone was continually administered by subcutaneous implantation, was a direct consequence of sustained exposure to steroid which would not occur when it is dosed orally once a day.

Please refer to the current version of the IB for further information on the results of the preclinical studies when bemcentinib was combined with steroids.

7.2. Clinical Studies with Bemcentinib

There has been one previous clinical study completed with bemcentinib (Protocol BGBC001). This study explored the effect of a single dose of bemcentinib (dose range: 50, 100, 150, 200, 400, 600, 1000 and 1500 mg) in healthy male volunteers under fasted conditions, with a sub-study in limited number of the volunteers to assess dosing under fed conditions. Eight dose levels (50 mg, 100 mg, 150 mg, 200 mg, 400 mg, 600 mg, 1000 mg and 1500 mg) were administered under fasted conditions to cohorts of four subjects (32 subjects in total). Seven of these subjects went on to receive the same dose of bemcentinib administered under fed conditions. Other studies with bemcentinib are being conducted in triple negative breast cancer or triple negative inflammatory breast cancer, Stage IIIb or Stage IV non-small cell lung

cancer (NSCLC), advanced adenocarcinoma of the lung and melanoma (please refer to the current version of the bemcentinib IB or clinicaltrials.gov for further details).

7.2.1. Summary of Clinical Safety

Please refer to the current version of the bemcentinib IB for the most up-to-date safety information.

In general exposure to bemcentinib in BGBC001 bemcentinib was well tolerated with all toxicities being spontaneously reversible and predominantly gastrointestinal in nature. No serious adverse events (SAE) were reported. Reported adverse events (AE) are summarized in Table 2.

Table 2: Bemcentinib-Related Adverse Events Reported Following a Single Oral Administration of Bemcentinib (50 mg to 1500 mg) to Healthy Male Subjects

Dose (mg)	Number of Subjects	Toxicity	Maximum Grade (CTCAE version 4.0)
50	4 fasted; 1 fed	Non-Cardiac Chest Pain	One
100	4 fasted; 2 fed	Paraesthesia Orthostatic hypotension	One
150	4 fasted; 1 fed	Abdominal Distension (n=2)	One
200	4 fasted; 1 fed	Respiratory tract infection	One
400	4 fasted; 2 fed	Diarrhoea	One
600	4 fasted	Diarrhoea Flatulence Nausea (n=2)	One One One
1000	4 fasted	Nausea	One
1500	4 fasted	Diarrhoea Nausea Vomiting Headache Dizziness Oropharyngeal pain	One Two Two One One One

7.2.1.1. ECG Findings

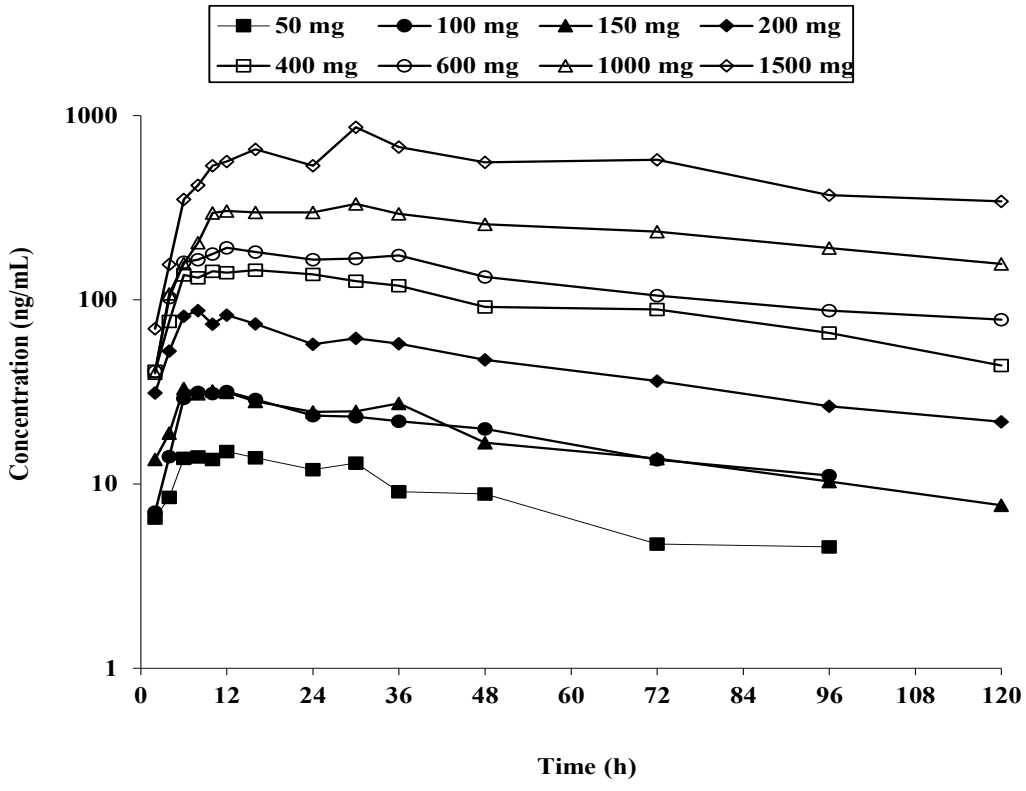
In light of the findings reported in the safety pharmacology studies described in Section 7.1.2, all subjects in study BGBC001 underwent serial ECG recordings following the administration of bemcentinib. The overall pattern indicated that bemcentinib administration was accompanied by a variable increase in QTc interval according to Fridericia's correction (QTcF), the magnitude of which was related to systemic exposure. The maximum QTcF recorded was Grade 1 in severity.

7.2.2. Summary of Clinical Pharmacokinetics

Concentrations of bemcentinib were quantified in plasma samples from subjects enrolled in Study BGBC001 using a fully validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method with a lower limit of quantification of 2.0 ng/mL. Pharmacokinetic (PK) parameters were derived by non-compartmental analysis using WinNonlin Phoenix Version 6.3 (Pharsight Corporation Inc., Mountain View, CA, USA, 2012).

Following a single oral dose of bemcentinib at doses between 50 mg and 1500 mg, administered under fasted conditions, mean maximal plasma concentrations of 7.63 ng/mL to 388 ng/mL were reached at 8 hours (h) to 23 h post-dose as presented in Figure 1.

Figure 1: Mean Plasma Concentrations of Bemcentinib Following a Single Oral Administration of Bemcentinib at 50, 100, 150, 200, 400, 600, 1000 and 1500 mg to Healthy Male Subjects



The mean apparent terminal half-life ($t_{1/2}$) of bemcentinib was 45.6 h to 88.7 h. Between-subject variability in systemic exposure (area under the curve from time zero to infinity ($AUC_{0-\infty}$) and maximum concentration achieved (C_{max})) to bemcentinib at 50 mg to 1500 mg was generally high (coefficient of variation of 25.8% to 96.7% for area under the concentration-

time curve (AUC_{0-t}) and C_{max}), most probably reflecting variable absorption. Across this dose range C_{max} of bemcentinib increased approximately dose proportionately, although the $AUC_{0-\infty}$ of bemcentinib increased slightly greater than dose proportionately.

Following administration of bemcentinib with food (whole milk and buttered toast) to 7 subjects who had previously received bemcentinib, there was an overall reduction in the between-subject variability with an increase in systemic exposure to bemcentinib in 3 subjects, no appreciable change in 3 subjects and an apparent reduction in 1 subject. It was estimated that administration with food would achieve an increase in exposure in some subjects of up to 2-fold.

7.2.3. Selection of the Starting Dose for Clinical Study BGBC003

Bemcentinib clinical development studies to date have involved two formulations. The first study in healthy volunteers, Study BGBC001, used Formulation 1. Study BGBC004, in patients with non-small cell lung cancer has used Formulation 2 and given bemcentinib when patients have fasted. This study, BGBC003, will evaluate both Formulation 1 (taken when patients are fed), and Formulation 2 (taken when patients are fasted). Please see Section 7.2.3.1 and the current version of the bemcentinib IB for more details.

In Study BGBC001, 32 subjects received doses of bemcentinib in the range 50 to 1500 mg under fasted conditions, of which seven also received the same dose of bemcentinib under fed conditions. The time to maximum concentration (t_{max}) and the apparent $t_{½}$ were generally comparable between fed and fasted conditions; t_{max} ranged from 6 to 30 hours and $t_{½}$ ranged from 30.2 to 77.2 hours (except in one subject where $t_{½}$ was reliably estimated as 165 hours). There was an increase in systemic exposure to bemcentinib in three subjects, no appreciable change in three subjects and an apparent reduction in systemic exposure in one subject when bemcentinib was given with food compared to under fasted conditions.

Overall, C_{max} and area under the curve from time zero to 48 hours (AUC_{0-48h}) under fed conditions were 29% and 21% greater, respectively compared to fasted conditions; however, the 95% confidence interval (CI) of the ratio (fed/fasted) included 100%, indicating that the apparent effect of food was not statistically significant. The elimination of bemcentinib was slow with a $t_{½}$ of longer than 24 hours. A consequence of this prolonged $t_{½}$ is the delay in the time taken to achieve steady state, which is estimated to be approximately two weeks following the initiation of bemcentinib administration. Such a delay would not be therapeutically acceptable in patients with advanced cancers.

The proposed starting dose and dosing schedule for clinical studies of bemcentinib in patients was therefore based on a one-compartment model, incorporated a lag time and no weighting to available clinical PK data. According to this model it was anticipated that the application of a loading dose (on Days 1 and 2) would enable a rapid achievement of therapeutic levels of bemcentinib, with a maintenance daily dosing from Day 3 to maintain optimum exposures whilst preventing wide changes in systemic concentration during therapy (see Figure 2 and Figure 3).

Current PK data suggest that bemcentinib would be best administered as a loading dose on up to the first three days of treatment, followed by a daily maintenance dose (see Figure 2 and Figure 3).

Figure 2: Simulated Plasma Concentrations of Bemcentinib for 600 mg Loading Dose on Days 1 and 2 and Daily Dose of 200 mg from Day 3 (fed)

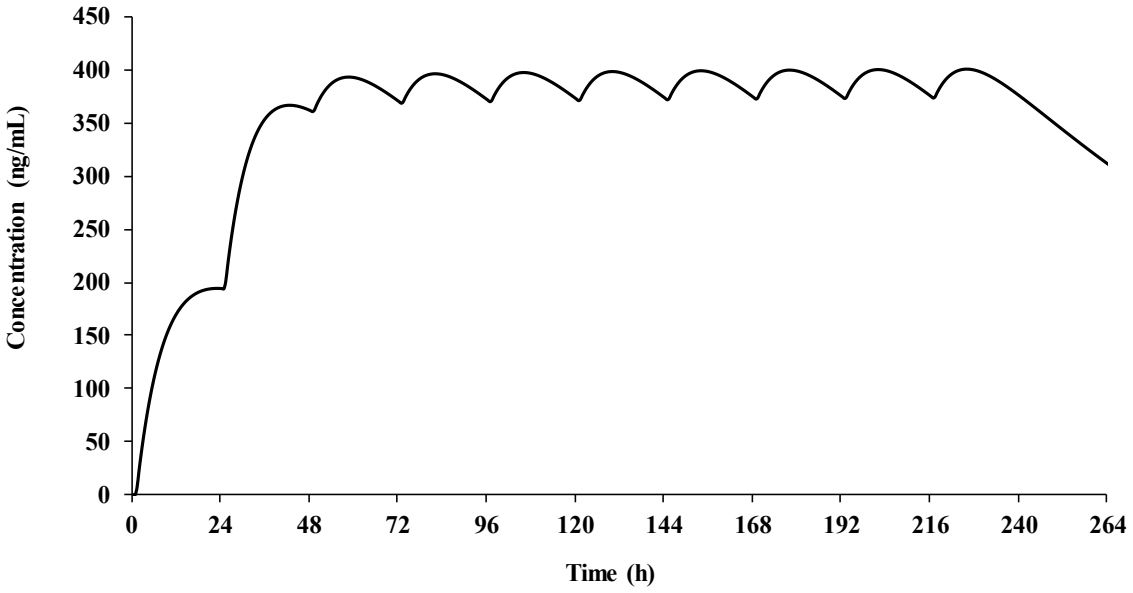
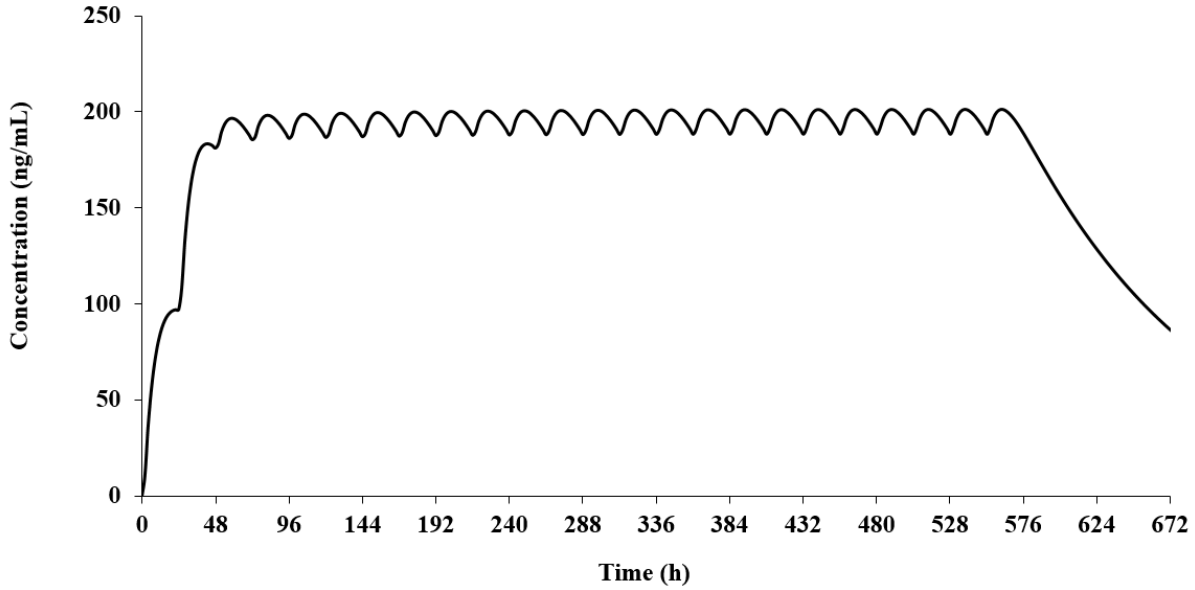
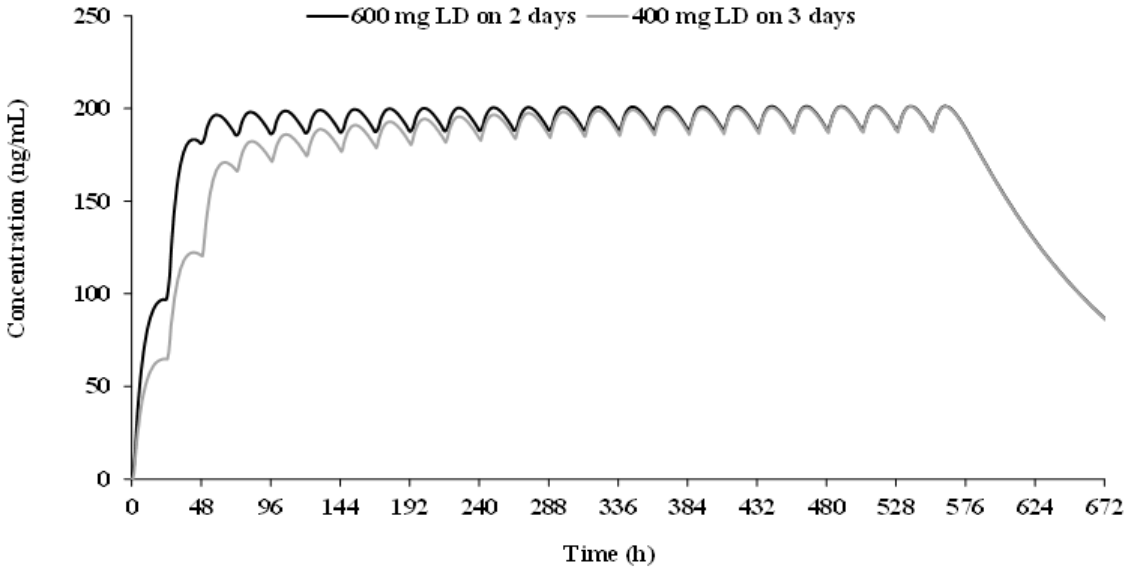


Figure 3: Simulated Plasma Concentrations of Bemcentinib for 600 mg Loading Dose on Days 1 and 2 and Daily Dose of 200 mg from Day 3 (fasted)



AE data to date suggest that gastrointestinal toxicities are more pronounced during and shortly after administration of the bemcentinib loading dose. It remains desirable to achieve bemcentinib steady-state as soon as possible in patients with advanced cancer, and in order to improve compliance during initial bemcentinib dosing, a 3-day loading dose is recommended, whilst ensuring steady-state is still reached by Day 4 (see Figure 4).

Figure 4: Predicted Plasma Concentrations of Bemcentinib after 1200 mg Loading Dose Given as 600 mg on Days 1 and 2 or 400 mg on Days 1, 2 and 3, followed by Daily Dose of 200 mg (fasted)



For study BGBC003, dosing will consist of a loading dose of 200 mg administered on Days 1, 2 and 3 followed by a daily maintenance dose of 100 mg. This dose may be escalated as agreed by the SMC to a maximum daily loading dose of 400 mg on Days 1, 2 and 3 followed by a maximum daily maintenance dose of 200 mg. A Recommended Phase 2 dose (RP2D) will be selected in Part A for further evaluation in Part B.

7.2.3.1. Formulation 1 and Formulation 2

As part of the formulation development program, recommendations for Formulation 1 consisted of a loading dose of 400 mg on Cycle 1, Days 1 and 2, followed by a daily maintenance dose of 100 mg. Dosing with Formulation 1 was completed in 2016.

Formulation 2 includes additional excipients resulting in an improved solubility profile when compared to Formulation 1. Repeated doses of Formulation 2 have already been administered to NSCLC patients in the fasting state in Study BGBC004, where drug absorption was increased and less variable when compared to data from patients receiving Formulation 1. pH studies suggest that bemcentinib exhibits increased solubility in an acid environment, thus patients should receive Formulation 2 in the fasted state upon waking and should not be receiving baseline gastric protectants including Proton Pump Inhibitors, Histamine Receptor two antagonists or antacids when starting therapy with bemcentinib. They may receive treatment with these agents in the evening if required for symptoms; but only when established on bemcentinib therapy (i.e. following at least one week of treatment with bemcentinib).

The increased absorption of bemcentinib seen with Formulation 2 in Study BGBC004 was well tolerated following a loading dose of 600 mg on Days 1 and 2, followed by a daily dose of 200 mg, but because of the increased bioavailability of this preparation, a starting loading dose of 200 mg administered on Days 1, 2 and 3 followed by a daily maintenance dose of 100 mg will be introduced for Formulation 2 in Study BGBC003.

This dose may be escalated as agreed by the SMC to a maximum daily loading dose of 400 mg on Days 1, 2 and 3 followed by a maximum daily maintenance dose of 200 mg.

Further details of the physicochemical properties of Formulation 1 and Formulation 2 and ongoing clinical studies with Formulation 2 can be found in the current version of the bemcentinib IB and the investigational medicinal product dossier (IMPD).

8. Study Objectives and Endpoints

8.1. Objectives

8.1.1. Primary Objectives

Part A

To identify the maximum tolerated dose (MTD) of bemcentinib in AML patients who have received previous treatment with cytotoxic chemotherapy (with or without hematopoietic stem cell transplantation) or a targeted or biologic agent (e.g. hypomethylating agent, tyrosine kinase inhibitor, antibody), and have relapsed after or have been refractory to treatment with such prior therapy.

Part B

To identify the safety and tolerability of bemcentinib as a single agent in patients with AML or MDS (Parts B1 and B4), or in combination with low dose cytarabine (Part B2 and Part B5) or decitabine (Part B3), in patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or existing co-morbidities.

8.1.2. Secondary Objectives

Part A

- To identify the Dose Limiting Toxicity (DLT) profile of bemcentinib
- To explore the safety and efficacy of bemcentinib
- To characterize the PK profile of bemcentinib

Part B

- To explore the efficacy of bemcentinib, as a single agent in patients with AML or MDS (Parts B1 and B4)
- To explore the efficacy of bemcentinib in combination with low dose cytarabine (Part B2 and Part B5) or decitabine (Part B3), in patients with AML who are unsuitable for intensive chemotherapy
- To evaluate bemcentinib PK (all Part B cohorts)

8.1.3. Exploratory Objectives

Parts A and B

- To identify and evaluate potential predictive biomarkers, e.g. soluble AXL (sAXL) and other associated soluble biomarkers. Pre-treatment levels of biomarkers will be correlated with clinical endpoints
- To establish the effects of bemcentinib on relevant biological endpoints in peripheral blood (including sAXL peripheral blood mononuclear cells [PBMC]) and BM samples
- To assess pharmacodynamic biomarkers in tissue and blood to support the clinical development of bemcentinib
- To evaluate other biomarkers relevant to the investigational agents for exploratory purposes

8.2. Endpoints

8.2.1. Safety Endpoints

Safety and tolerability will be assessed by conducting the following safety assessments at pre-defined time-points during the study:

- Treatment emergent AEs
- Physical examination
- Vital signs including blood pressure (BP), heart rate (HR), respiration rate and temperature
- Electrocardiogram (ECG)
- Echocardiogram
- Laboratory findings including clinical chemistry, hematology and urinalysis

8.2.2. Efficacy Endpoints

In AML, efficacy endpoints will be measured using the following response criteria.

- Objective Response (OR) or Stable Disease (SD) according to the revised recommendations of the International Working Group (IWG) in AML [Cheson, 2003

and Döhner, 2017] (see Appendix 5). SD is defined as having unchanged disease for at least 3 treatment cycles.

- Proportion of patients with an OR + SD as an estimate of clinical benefit.
- Relapse Free Survival
- Event Free Survival
- Overall Survival
- To explore the correlation between baseline biomarker levels and clinical endpoints

In MDS, efficacy endpoints will be measured using the following response criteria.

- OR or SD according to the revised recommendations of the IWG in MDS (see Appendix 6). SD is defined as failure to achieve at least PR but not evidence of PD for at least 3 treatment cycles.
- Proportion of patients with an OR + SD as an estimate of clinical benefit.
- Relapse Free Survival
- Event Free Survival
- Overall Survival
- To explore the correlation between baseline biomarker levels and clinical endpoints

8.2.3. Pharmacokinetic Endpoints

As a minimum, area under the curve within a dosing interval ($AUC_{0\text{-}tau}$), C_{max}, and time to maximum concentration (T_{max}) for bemcentinib will be determined from plasma. Additional parameters may also be reported, as deemed appropriate once data are reviewed.

8.2.4. Pharmacodynamic and Predictive Endpoints

The effects of bemcentinib on pharmacodynamic endpoints of AXL inhibition will be determined in BM aspirates and blood samples:

- To identify and evaluate potential predictive biomarkers, e.g. sAXL and other associated soluble biomarkers. Pre-treatment levels of biomarkers will be correlated with clinical endpoints

- To establish the effects of bemcentinib on relevant biological endpoints in peripheral blood (including sAXL PMBCs) and BM samples
- To assess pharmacodynamic biomarkers in tissue and blood to support the clinical development of bemcentinib
- To evaluate other biomarkers relevant to the investigational agents for exploratory purposes
- Effect of bemcentinib on AXL, sAXL and phospho AXL (pAXL) and downstream effectors of AXL signaling, such as Akt, pAkt, Erk, pErk, SLFN11, Bcl2, Puma by appropriate methods (e.g. flow cytometry (FCM), western blotting, proteomics, transcriptomics)
- Effect of bemcentinib on gene expression by appropriate methods (e.g. FCM, western blotting, proteomics, transcriptomics, quantitative polymerase chain reaction (PCR), DNA-methylation analysis)
- Effect of bemcentinib on relevant immune cell populations
- Effect of bemcentinib on the spectrum of mutations present within the cancer cell population by genomic analysis
- To explore the correlation between baseline biomarker levels and clinical endpoints

9. Study Design

9.1. Overview

This is a Phase Ib/II, open-label, dose-escalation and cohort expansion study to obtain a preliminary assessment of the safety, tolerability and efficacy of bemcentinib, a small molecule inhibitor of AXL kinase in patients with AML or MDS. The study will be conducted at up to approximately 20 sites in Europe and the US and will be performed in approximately 102 evaluable patients with AML or MDS. Additional countries and sites may be added as required to meet the enrolment needs of the study.

In Part A bemcentinib will be administered as monotherapy in patients with relapsed or refractory AML following previous treatment with cytotoxic chemotherapy (with or without hematopoietic stem cell transplantation) or a targeted or biologic agent (e.g. hypomethylating agent, tyrosine kinase inhibitor, antibody).

In Part B bemcentinib will be administered as a single agent in patients with AML who are unsuitable for intensive chemotherapy (i.e. cytarabine/anthracycline on a 3+7 dose or equivalent) as a result of advanced age and/or existing co-morbidities (Part B1) or in MDS patients who have previously received treatment (Part B4) and a further 3 cohorts of bemcentinib administered in combination with low dose cytarabine (Part B2 and Part B5) or decitabine (Part B3) in patients with AML who are unsuitable for intensive chemotherapy because of advanced age or existing co-morbidities will be investigated

In all parts of the study, AML patients with a matched donor and who are candidates for allogeneic BM transplantation are not eligible to participate.

Bemcentinib will be administered orally according to a daily schedule during continuous 21-day treatment cycles. During Cycle 1, Week 1 ONLY the first 3 doses of bemcentinib may serve as a ‘loading’ dose.

Dosing will consist of a loading dose of 200 mg administered on Days 1, 2 and 3 followed by a daily maintenance dose of 100 mg. This dose may be escalated as agreed by the SMC to a maximum daily loading dose of 400 mg on Days 1, 2 and 3 followed by a maximum daily maintenance dose of 200 mg.

Patients will be instructed to take bemcentinib on an empty stomach at a similar time each morning when they wake or more than 2 hours after a light meal, with water. To maintain a fasted state, patients should be told not eat or drink anything other than water for at least 1 hour after taking the drug.

In Part A the study will follow a 3+3 design to explore the safety and tolerability of repeat dosing of bemcentinib, and to identify the MTD. A minimum of 6-10 patients will be treated at the MTD or RP2D, as determined by the SMC. Depending upon the results of this phase of the study, the safety and efficacy of bemcentinib may be established in up to 4 disease-specific cohorts in Part B.

Part B1

Single agent bemcentinib will be administered to patients with AML who are unsuitable for intensive chemotherapy (i.e. cytarabine/anthracycline on a 3+7 dose or equivalent) as a result of advanced age and/or existing co-morbidities. In order to be eligible patients should have received at least one line of previous therapy.

Part B2

Bemcentinib will be administered in combination with low dose cytarabine in patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or existing co-morbidities.

Part B3

Bemcentinib will be administered in combination with decitabine in patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or existing co-morbidities.

Part B4

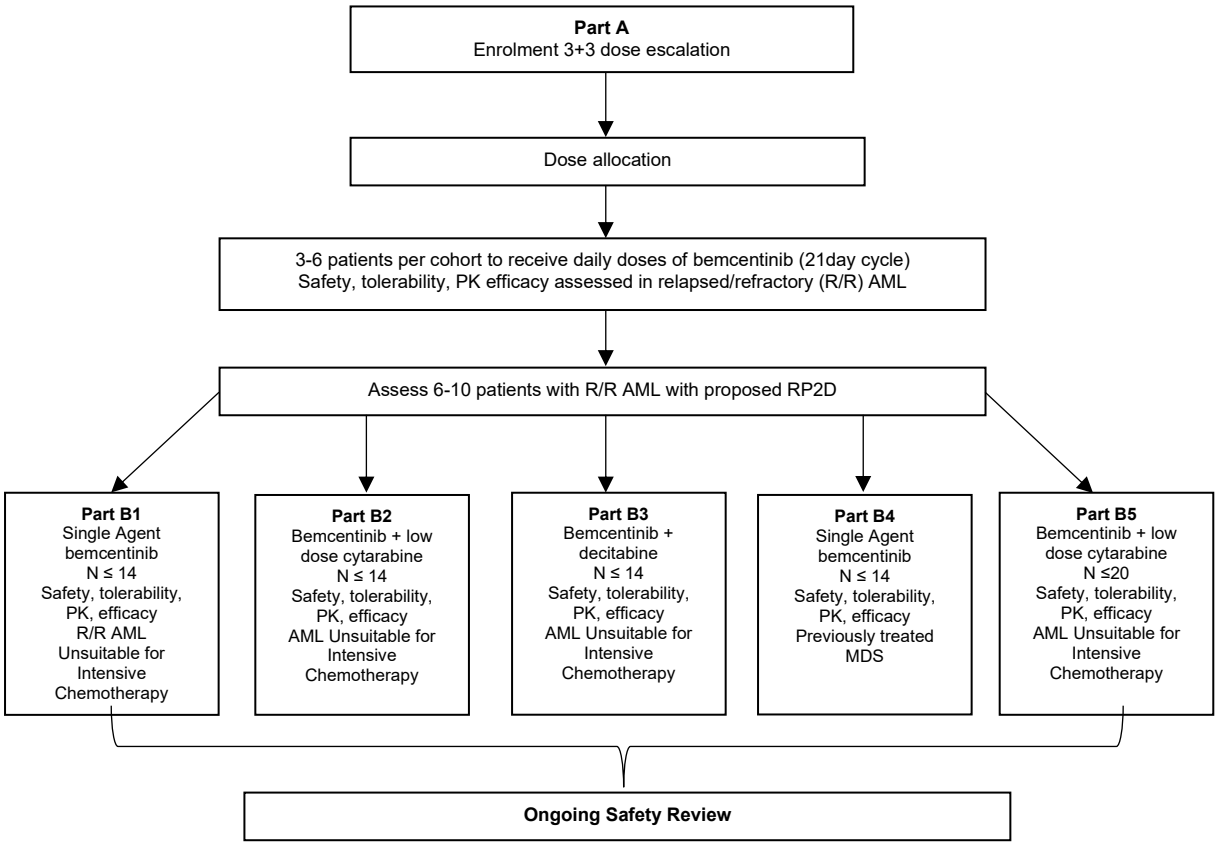
Single agent bemcentinib will be administered to patients with previously treated MDS (including high risk and intermediate with the exception of deletion 5q MDS).

Part B5

Bemcentinib will be administered in combination with cytarabine in patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or existing co-morbidities. Patients must have received at least one prior treatment for AML.

Please refer to Figure 5 for an outline of the overall study design.

Figure 5: BGBC003 Study Design



9.2. Study Specifics

9.2.1. Phase I DLT Assessment Period

During the dose-escalation phase (Part A), safety, tolerability, PK, and preliminary clinical activity of bemcentinib will be assessed, and the MTD established, in patients who have received previous treatment with cytotoxic chemotherapy or a targeted or biologic agent (e.g. hypomethylating agent, tyrosine kinase inhibitor, antibody) and have relapsed after or have been refractory to treatment with such prior therapy. Patients receiving an allograft in first remission would be eligible at the time of relapse.

A loading dose (Cohort 1) of 200 mg administered on Cycle 1, Days 1, 2 and 3 followed by a daily maintenance dose of 100 mg during continuous 21-day treatment cycles will be evaluated. This dose may be escalated as agreed by the SMC to a maximum daily loading dose of 400 mg on Days 1, 2 and 3 followed by a maximum daily maintenance dose of 200 mg (see Section 9.2.1.2). At least 3 evaluable patients will be entered per cohort.

9.2.1.1. Dose Escalation Scheme

Initially three patients will be recruited into Cohort 1 and will complete 1 cycle of treatment before a dose-escalation evaluation is made. A patient must receive all loading doses and miss no more than 3 maintenance doses in Cycle 1 in order to be considered as informative to support dose escalation, unless the missed doses are due to bemcentinib toxicity (see Section 9.2.1.2. Dose Limiting Toxicity).

The decision to dose-escalate (or not) will be made by the SMC comprising a representative from each actively recruiting investigational site and a representative of the BerGenBio ASA study team. Minutes of the SMC meeting will be recorded and circulated for final approval before being placed in the Trial Master File (TMF). The decision to dose escalate will be based upon the tolerability of bemcentinib.

Where dose escalation occurs, 3 patients will be recruited to the next cohort (dose level) and will complete 1 cycle of treatment before a dose-escalation evaluation is made, as outlined above.

If one patient in a cohort experiences a DLT during Cycle 1, the cohort will be expanded to 6 patients. If 2 of 3 or 2 of 6 patients in a cohort experience DLT no further dose-escalation will take place and the dose below will be nominated as the MTD. If the starting dose exceeds the MTD, a lower dose may be explored if recommended by the SMC. Provided treatment with the starting dose is considered safe by the SMC according to DLT evaluation, dose escalation may proceed.

Possible dosing levels are illustrated in Table 3. Dosing with Formulation 2 will consist of a loading dose of 200 mg administered on Days 1, 2 and 3 followed by a daily maintenance dose of 100 mg. This dose may be escalated as agreed by the SMC to a maximum daily loading dose of 400 mg on Days 1, 2 and 3 followed by a maximum daily maintenance dose of 200 mg. The maximum daily dose that may be explored in this study will be 400 mg.

Table 3: Possible Bemcentinib Dosing Levels Involving A Loading Dose and Daily Dose for Part A

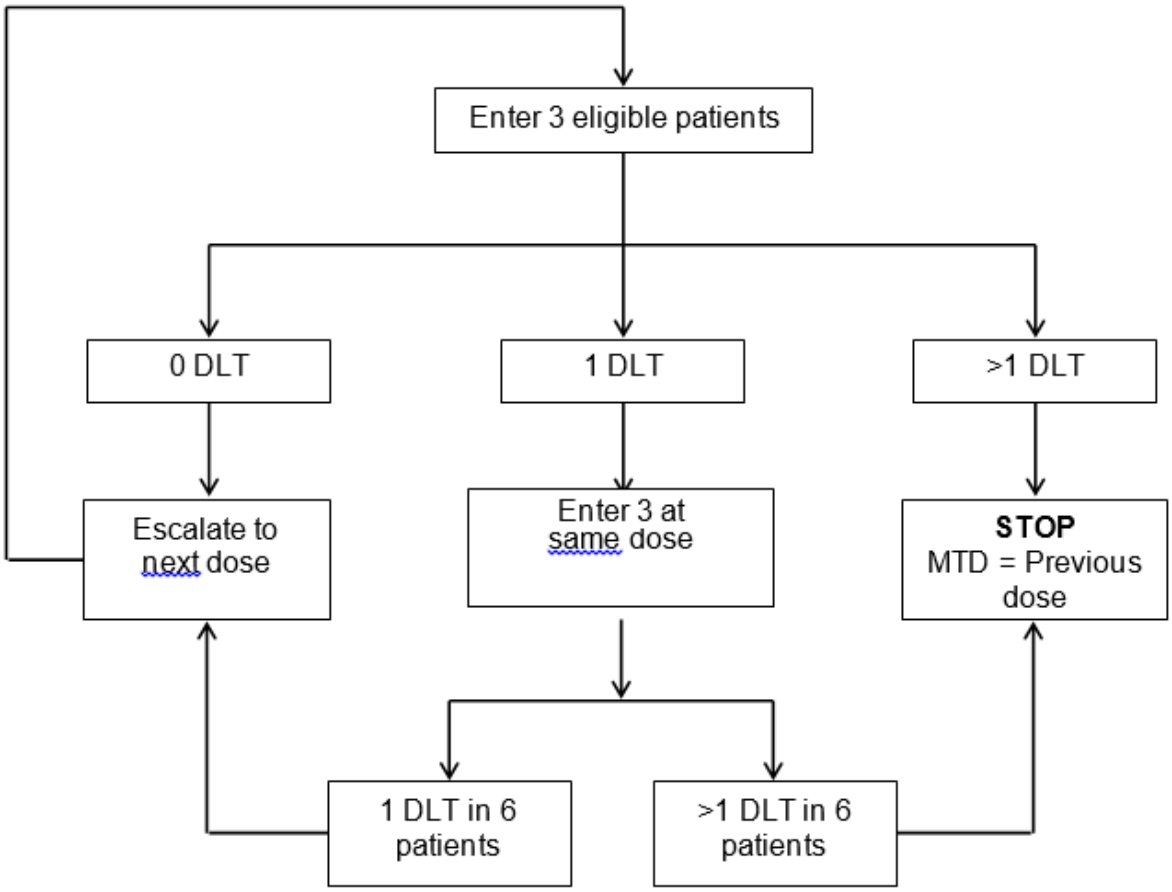
Total Loading Dose over 3 days (mg)	Days 1, 2 and 3 Loading Dose (mg)	Daily maintenance dose (mg)
600	200*	100*
1200	400	200

**starting dose*

If a patient withdraws or is withdrawn for reasons other than DLT prior to completing Cycle 1, the patient will be replaced for the purposes of toxicity evaluation.

Please refer to Figure 6 for the operating characteristics of the Dose Escalation process.

Figure 6: The 3+3 Dose Escalation Design



9.2.1.2. Dose Limiting Toxicity

DLT will be assessed during the first 3 weeks of treatment with bemcentinib (Cycle 1), according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) [NCI CTCAE] version 4 considered unrelated to leukemia progression or intercurrent illness, and defined as any of the following:

- CTCAE Grade 3 or 4 nausea, vomiting, or diarrhea that persists despite maximum prophylactic and supportive care.
- Any other CTCAE Grade 3 or 4 non-hematological toxicity that is considered to be clinically significant and causally related to bemcentinib, excluding isolated changes

in laboratory results if no clinical significance or no clinical sequelae and adequately improve within 7 days.

- Prolonged neutropenia with ANC <500 and platelet count <75000 after Day 42 from the start of treatment in the absence of residual leukemia.

- Treatment discontinuation, inability to administer one or more bemcentinib loading dose, or inability to administer three bemcentinib maintenance doses as a result of bemcentinib-related toxicity.

- Any ventricular arrhythmia.

9.2.2. Part B

Following SMC review of all treatment emergent safety and efficacy data from Part A, up to 14 evaluable patients (up to 20 evaluable patients in Part B5) will be recruited into each of up to five cohorts (Parts B1, B2, B3, B4 and B5). Depending upon the safety profile of bemcentinib observed in Part A the initial starting dose in combination with cytarabine (Part B2) or decitabine (Part B3), may be reduced by a single dose level (i.e. MTD -1) which may be evaluated in at least three subjects before introduction of the MTD or RP2D identified in Part A.

Recruitment into Part B5 will be overseen by the Sponsor's study team or designee. The number of recruitment slots for patients with refractory AML, defined as no hematological response to last AML treatment and/or patients who have received 2 or more prior treatments for AML, will be restricted to 1/3 of the sample size (i.e. no more than 6 evaluable patients).The study team will notify investigators when recruitment restrictions are applied.

AML Treatment Status	Pre-Screening Approval Requirement
One prior treatment for AML and NOT refractory	Sponsor approval not required prior to screening
Two or more prior treatments for AML	Sponsor approval mandatory prior to screening
Refractory AML*	Sponsor approval mandatory prior to screening

* Refractory AML is defined as no hematological response to last AML treatment and/or patients who have received 2 or more prior treatments for AML (see Appendix 5 of Protocol BGBC003: Modified International Working Group Response Criteria in Acute Myeloid Leukaemia [Cheson , 2003, Döhner, 2017])

9.3. Overall Study Duration and Follow Up

The study period will consist of screening, treatment period, Final Study Visit, and follow-up period. The Final Study Visit will occur 28 days after the patient has discontinued study

treatment. All subjects will be followed up for survival after the Final Study Visit unless they withdraw consent or are lost to follow-up. Subsequent anti-cancer therapy for AML or MDS will be reported in the electronic case report form (eCRF)

9.3.1. Screening

Patient eligibility for the study will be determined within 14 days prior to the first dose of study treatment. Screening assessments will be conducted according to the Schedule of Events tables in Section 11.

9.3.2. Treatment

Eligible patients will visit the study site to receive study treatment and protocol-specified procedures according to the relevant Schedule of Events table in Section 11. The treatment period will consist of continuous 21-day treatment cycles of bemcentinib.

Patients will be intensively monitored throughout Day 1 to Day 4 inclusive of Cycle 1, and in addition will attend the clinic on Day 8, and Day 15. Patients will attend the clinic once per week during Cycle 2 and then once per cycle thereafter. All patients will continue to receive bemcentinib or the combination for as long as, in the opinion of the investigator, they continue to derive clinical benefit. When there is unacceptable toxicity, confirmed disease progression in the absence of clinical benefit, or withdrawal of consent, bemcentinib or combination treatment must be discontinued. For patients in the combination arms (Part B2, B3 or B5), if treatment related toxicity requires permanent discontinuation, and the toxicity can be clearly assigned to one of the study treatments, the other study drug in the combination can be continued if it is safe to do so (investigator discretion) in the absence of disease progression or intolerable toxicity. The investigator may also decide to discontinue both study treatments at this time.

9.3.2.1 Dosing patients beyond progression

An important clinical observation in the last decade is that immune activation does not necessarily result in complete cancer regression for all patients, but nonetheless, clinical improvements are observed. In this context and for elderly patients with R/R AML, unfit for intensive chemotherapy and with no alternative treatments available for their disease, achieving stable disease and/or becoming transfusion independent, together with performance status improvement, can be viewed as a positive signal. Thus, where in the investigator's opinion, the patient's disease is considered "clinically stable" with clear improvement in the patient's symptomatology and with no other treatment options available,

other than palliative care, it may be in the patient's best interests to remain on treatment with bemcentinib.

Therefore, patients experiencing disease progression are permitted to continue treatment with bemcentinib where the investigator believes patients may continue to derive clinical benefit from continued treatment.

Clinical benefit in this context is defined as meeting one or several of the following criteria: evidence of disease stabilization after documented initial progression (patient is stably worse), tolerance of drug(s), absence of rapid progression based on peripheral or bone marrow blasts and clinical hematology and clinical chemistry parameters, maintenance of good performance status (PS of 2 or less and not deteriorating], absence of worsening clinical symptoms (i.e., no symptomatic deterioration) and/or improvements in patient's quality of life).

Importantly, the decision to continue treatment must be discussed and agreed by the treating investigator, the patient and the Sponsor. All decisions will be documented in writing. Patients dosed beyond progression will continue to be evaluated for potential clinical benefit and safety. This will not affect the time point of disease progression from the perspective of trial analysis.

9.3.3. Final Study Visit

Patients should return to the study site for the Final Study Visit 28 days after permanent discontinuation of all study treatments.

9.3.4. Follow Up

An AE will be monitored for 28 days after the last dose of bemcentinib although only events considered to be related to treatment need to be recorded in the eCRF between the last administration of bemcentinib and the end of the 28 day follow up period. If bemcentinib-related toxicities continue beyond the follow up period, patients will be followed until all bemcentinib-related toxicities have resolved to <Grade 1, stabilized or returned to baseline. If necessary, follow up monitoring for AEs may be conducted over the telephone.

SAEs with a suspected relationship to bemcentinib will be collected beyond the 28-day follow-up period until the event is resolved to ≤ Grade 1, stabilized or returned to baseline.

All patients that have permanently discontinued study treatment for whatever reason must be followed for survival. The investigator or designee must confirm with the patient at the time of the Final Study Visit how the patient will be followed for survival (e.g. contact with family or

health care provider). Survival follow-up must be conducted at least every 3 months by the investigator or designee and the date-of-death reported in the eCRF.

All subsequent anticancer therapy for AML or MDS must be reported in the eCRF.

9.4. Study Stopping Rules

BerGenBio ASA reserves the right to close a site or terminate the study at any time. The investigator may also terminate the study at their site at any time, provided there is reasonable cause for the intended termination. This action may be taken after appropriate consultation with the Sponsor and the Investigator. Conditions that may warrant termination of the study or involvement of a study site include, but are not limited to:

- The discovery of an unexpected, serious or unacceptable risk to patients enrolled in the study
- Failure of the investigator to comply with the protocol and Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of patients
- Attainment of the study objectives
- As a result of commercial considerations including discontinuation of further clinical development of bemcentinib in AML

9.5. End of Study

Except in the case of early termination (Section 9.4), the end of the study is defined as the date when all patients have an OS event, unless the Sponsor terminates OS follow-up once all patients have discontinued study treatment. Should the last patient enrolled to the study be continuing to receive bemcentinib 52 weeks from their Cycle 1 Day 1, the Sponsor may choose to lock the data base to that point and prepare the clinical study report (CSR). Data collected as part of this study after this point, will be reported as an addendum to the CSR.

A final CSR will be prepared when the last patient has completed their Final Study Visit and the database is locked. The Statistical Analysis Plan (SAP) will be finalized and signed before database lock.

Patients will continue to be followed for suspected SAEs until these are resolved to ≤ Grade 1, stabilized or returned to baseline. Refer to Section 15.2.2 for SAE reporting after the end of study.

10. Selection of Subjects

10.1. Inclusion Criteria

1. Provision of signed written informed consent

2. Histological or cytological confirmation of:

AML (with the exception of AML M3)

a) **Part A**: Patients with relapsed or refractory AML following treatment with cytotoxic chemotherapy (with or without hematopoietic stem cell transplantation) or a targeted or biologic agent (e.g. hypomethylating agent, tyrosine kinase inhibitor, antibody)

b) **Part B1**: Patients with AML who are unsuitable for intensive chemotherapy as a result of advanced age or co-morbidities. Patients should have relapsed following at least one line of therapy or be refractory to such prior therapy

c) **Part B2**: Patients with diagnosed AML who are unsuitable for intensive chemotherapy as a result if advancing age or co-morbidities and who are suitable to receive treatment with cytarabine

d) **Part B3**: Patients with AML who are unsuitable for intensive chemotherapy as a result if advancing age or co-morbidities who are suitable to receive treatment with decitabine

MDS (with the exception of deletion 5q MDS)

e) **Part B4:** Patients with previously treated MDS (with the exception of deletion 5q MDS) including intermediate and high-risk patients who must have received prior treatment for their disease. Prior treatment may include those patients who have received hypomethylating agents, decitabine or other approved treatments for MDS.

f) **Part B5**: Patients with relapsed or refractory AML who are unsuitable for intensive chemotherapy as a result of advanced age or co-morbidities meeting the following criteria:

- Must have received at least one prior treatment for AML

- Are suitable to receive treatment with "low-dose" cytarabine (LDAC). LDAC is defined as 20 mg cytarabine administered subcutaneously twice daily for 10 days every 28 days.

The number of patients with refractory AML, defined as no hematological response to last AML treatment and/or patients who have received 2 or more prior treatments for AML, will be restricted to 1/3 of the sample size (i.e. no more than 6 evaluable patients). Please refer to table in Section 9.2.2.

3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2 [Appendix 1]

4. Age 18 years or older

5. Female patients of childbearing potential must have a negative serum pregnancy test within 3 days prior to taking their first dose of bemcentinib. Male patients and female patients of reproductive potential must agree to practice highly effective methods of contraception (such as hormonal implants, combined oral contraceptives, injectable contraceptives, intrauterine device with hormone spirals, tubal ligation, total sexual abstinence, vasectomy) throughout the study and for ≥3 months after the last dose of bemcentinib. Female patients are considered NOT of childbearing potential if they have a history of surgical sterility or evidence of post-menopausal status defined as any of the following:

a) Natural menopause with last menses >1 year ago

b) Radiation induced oophorectomy with last menses >1 year ago

c) Chemotherapy induced menopause with last menses >1 year ago

10.2. Exclusion Criteria

1. Patients who have a matched donor and are candidates for allogeneic BM transplantation

2. Pregnant or lactating

3. History of the following cardiac conditions:

   - Congestive cardiac failure of >Class II severity according to the NYHA (Appendix 2: defined as symptomatic at less than ordinary levels of activity)

- Ischemic cardiac event including myocardial infarction within 3 months prior to first dose. Patients with prior history or ECG evidence of old myocardial infarction should be discussed with the Sponsor to confirm eligibility.

- Uncontrolled cardiac disease, including unstable angina, uncontrolled hypertension (i.e. sustained systolic BP >160 mmHg or diastolic BP >90 mmHg), or need to change medication within 6 weeks of provision of consent due to lack of BP control

- History or presence of sustained bradycardia (≤55 beats per minute), left bundle branch block, cardiac pacemaker or ventricular arrhythmia. Note: Patients with supraventricular arrhythmia should be discussed with Sponsor to confirm eligibility.

- Family history of long QTc syndrome; personal history of long QTc syndrome or previous drug-induced QTc prolongation of at least Grade 3 (QTc >500 ms)

- Presence of any factors that increase the risk for QTc prolongation, e.g. resistant or inadequately treated heart failure, presence of hypokalemia or hypomagnesemia not corrected by, or not responding to, replacement therapy or inadequately treated hypothyroidism as defined by the thyroid-stimulating hormone not within the expected range of the institution.

4. Abnormal left ventricular ejection fraction on echocardiography or Multi Gated Acquisition Scan (MUGA) (less than the lower limit of normal for a patient of that age at the treating institution or <45%, whichever is lower)

5. Current treatment with any agent known to cause QT prolongation and have a risk for Torsades de Pointes which cannot be discontinued at least five half-lives or two weeks prior to the first dose of study treatment. Please see Appendix 3 for list of relevant medications

6. Screening 12-lead ECG with a measurable QTcF >450 ms

7. Ongoing infection requiring systemic treatment. Patients who are on prophylactic antimicrobials or who have been afebrile for 48 hours following the initiation of antimicrobials are eligible

8. Inadequate liver function as demonstrated by serum bilirubin ≥1.5 times the upper limits of normal range (ULN) or alanine aminotransferase (ALT) or aspartate

aminotransferase (AST) ≥2.5 times the ULN (or ≥5 times the ULN for AST or ALT in the presence of liver involvement by leukemia)

9. Inability to tolerate oral medication
10. Existing gastrointestinal disease affecting drug absorption such as celiac disease or Crohn's disease
11. Known lactose intolerance
12. Requires vitamin K antagonists. Note: Patients receiving low doses prescribed to maintain the patency of venous access devices may be included
13. Treatment with any of the following; histamine receptor 2 inhibitors, proton pump inhibitors or antacids within 3 days or 5 half-lives of administration of bemcentinib, whichever is longer
14. Treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index. Please see Appendix 4 for details of CYP3A4 substrates.
15. Previous bowel resection that would interfere with drug absorption
16. Evidence of ongoing gastrointestinal graft versus host disease
17. Hematopoietic stem cell transplantation within 6 months
18. Impaired renal function as demonstrated by a creatinine clearance of <30 mL/min determined by Cockcroft-Gault formula
19. Radiotherapy or chemotherapy within the 14 days prior to the first dose of bemcentinib being administered (other than hydroxyurea)
20. Receiving an investigational anti-cancer treatment concurrently or within 14 days or five half-lives (whichever is shorter) of either the parent drug or any known active metabolite prior to the start of bemcentinib
21. Unresolved CTCAE ≥Grade 2 toxicity (other than stable toxicity) from previous anti-cancer therapy excluding alopecia

22. Any evidence of severe or uncontrolled systemic conditions (e.g., severe hepatic impairment) or current unstable or uncompensated respiratory or cardiac conditions which makes it undesirable for the patient to participate in the study or which could jeopardize compliance with the protocol

23. Known active, uncontrolled central nervous system (CNS) disease including CNS leukemia

24. Active infection with human immunodeficiency virus (HIV), hepatitis B or C viruses – screening for viral infections is **not** required for entry to this study

25. Major surgery within 28 days prior to the start of bemcentinib – excluding skin biopsies and procedures for insertion of central venous access devices

26. Hypersensitivity to cytarabine, decitabine or any of their excipients

27. Prior exposure to Astellas ASP2215 (FLT3/AXL inhibitor Gilteritinib)

11. Study Procedures and Assessments

The Schedule of Events for specific parts of the study are summarized in the following tables as outlined below:

- Part A in Table 4
- Parts B1 and B4 in Table 5
- Parts B2, B3 and B5 in Table 6

Table 4: Part A Schedule of Events

Cycle		1						2			≥3	End of Study
Week		1				2	3	4	5	6	>7	
Visit	Screen	1	2	3	4	5	6	7	8	9	≥10	
Cycle Day	-14 to 0	1	2	3	4	8	15	1	8	15	1	28 days after last dose
Visit window (+/-) days		0	0	0	0	0	0	2	1	1	2	1
Informed consent	X											
Demographics	X											
Medical history	X											
Inclusion/exclusion	X											
ECOG	X							X			X	X
Physical examination[a]	X	X[e]				X	X	X			X	X
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[c]	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[d]	X	X[e]										
Clinical chemistry[f]	X	X[e]	X	X	X	X	X	X	X	X	X	X
Hematology[g]	X	X[e]	X	X	X	X	X	X	X	X	X	X
Coagulation screen[h]	X	X[e]				X	X	X			X	X
Urinalysis	X	X[e]				X	X	X	X	X	X	X
Bone marrow aspirate	X							X[k]			X[k]	
Bone marrow aspirate (Pharmacodynamic)	X[i]	(X[i])			(X[j])			X[k]			X[k]	
Echocardiogram/MUGA	X										X[l]	
PK blood sampling[m]		X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamic blood sampling[n]		X	X	X	X	X	X	X	X	X	X	X
Response criteria[o]								X			X	
Bemcentinib administration[p]		X	X	X	X	X	X	X	X	X	X	
Bemcentinib accountability						X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Overall survival		If the patient dies during the study period, report the date-of-death in the eCRF.										X[q]

a. A full physical examination, excluding gynecological and rectal examinations, will be conducted at the Screening and End of Study visits. A symptom-directed examination will be conducted at selected visits
b. Vital signs (systolic and diastolic blood pressure (BP), heart and respiration rate and temperature) will be taken at every visit
c. Triplicate 12-lead ECGs will be taken, ≤5 minutes apart, after resting for ≥10 minutes in supine position at every visit. During Cycle 1 Days 1-4 ECGs will coincide with selected PK sampling time-points i.e. pre-dose and 2, 4, 6 hr post-dose (Day 1); 24 (pre 2nd dose) and 30 hr post-Day 1 dose (Day 2); 48 hr (pre 3rd dose) post-Day 1 dose (Day 3); pre-dose, 2, 4 and 6 hr post-dose (Day 4). Patients who re-start bemcentinib following interruption for >7 days are recommended to recommence with a loading dose, with ECGs performed per this intensive schedule. Patients who do not receive the loading dose should attend the clinic for additional ECG assessments between Day 8 and 15, and between Day 15 and the end of Cycle 1. All time-points are approximate, but every effort must be made to make ECG assessment at specified time-points
d. For women of child-bearing potential
e. Unless conducted as part of the screening procedures within 3 days prior to Day 1
f. Clinical chemistry laboratory parameters (uric acid, electrolytes, blood urea nitrogen (BUN), total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, creatine phosphokinase, alkaline phosphatase, albumin, calcium, magnesium, phosphorus, glucose,)
g. Hematology laboratory parameters (full blood count including differential white cell count and blast count, hemoglobin, hematocrit and platelets)
h. Coagulation parameters: prothrombin time (PT) and activated partial thromboplastin time (APTT)
i. Bone marrow aspirate for diagnosis and baseline sample for pharmacodynamic biomarker analyses. If diagnostic bone marrow aspirate is routinely frozen, a repeat (fresh) bone marrow aspirate should be taken on Day -1 or Day 0 (pre-dose) for pharmacodynamic biomarker analyses
j. Optional bone marrow aspirate for pharmacodynamic biomarker analyses.
k. Bone marrow aspirate for clinical response assessment and pharmacodynamic biomarker analyses is mandatory at Cycle 2 Day 1 (pre-dose); optional assessments may be performed on Day 1 of every cycle thereafter and as clinically indicated.
l. Echocardiogram/MUGA scan Cycle 4 Day 1 ONLY
m. Blood sampling for the determination of bemcentinib in plasma will be conducted at the following Cycle 1 time-points:
3-day loading dose schedule or no loading dose: pre-dose and 2, 4, 6 hr post-dose (Day 1); 24 (pre 2nd dose) and 30 hr post-Day 1 dose (Day 2); 48 hr (pre 3rd dose) and 2, 4, 6, 8 hr post-dose (Day 3); and pre-dose (Day 4)
A pre-dose sample will be collected at ALL study visits (including ≥3 Cycle 3 (up to and including Cycle 15) and End of Study). All time-points are approximate, but every effort must be made to take samples at specified time-points. Actual times must be recorded. Maximum sampling time-points are described. Please refer to the local Laboratory Manual for time-points required at each site
n. Blood sampling for pharmacodynamic biomarker analyses will involve a maximum 33 mL blood volume at Cycle 1 Day 1 and Day 4, Day 1 of each cycle thereafter, (up to and including Cycle 15), and End of Study visit, or a multiple number of 4.5 mL blood samples to match the pharmacokinetic samples (see Tables 12-14). Please refer to the local Laboratory Manual for time-points required at each site.
o. Assessment of clinical response (% blasts; neutrophil count; platelet count). Response assessment should be performed by the investigator according to the modified response criteria in Appendix 5 (Cheson, 2003 and Döhner, 2017).
p. Bemcentinib should be taken on an empty stomach at a similar time each morning when they wake, or more than 2 hours after a light meal, with water. To maintain a fasted state, patients should be told not eat or drink anything other than water for at least 1 hour after taking the drug. Patients should record dosing in the dosing diary provided. On study visit days, bemcentinib should be administered on the unit.
q. All patients that have not died prior to the Final Study Visit should be followed for survival at ≤3-monthly intervals. The date of death must be reported for all patients in the eCRF (unless they are lost to follow-up or withdraw consent.

Table 5: Parts B1 and B4 Schedule of Events

Cycle		1						2			≥3	End of Study	Follow-Up
Week		1				2	3	4	5	6	>7		
Visit	Screen	1	2	3	4	5	6	7	8	9	≥10		
Cycle Day	-14 to 0	1	2	3	4	8	15	1	8	15	1	28 days after last dose	
Visit window (+/-) days		0	0	0	0	0	0	2	1	1	2	1	
Informed consent	X												
Demographics	X												
Medical and surgical history	X												
Inclusion/exclusion	X												
ECOG	X							X			X	X	
Physical examination[a]	X	X[e]				X	X	X			X	X	
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead triplicate ECG[c]	X	X	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test[d]	X	X[e]											
Clinical chemistry[f]	X	X[e]	X	X	X	X	X	X	X	X	X	X	
Hematology[g]	X	X[e]	X	X	X	X	X	X	X	X	X	X	
Coagulation screen[h]	X	X[e]				X	X	X			X	X	
Urinalysis	X	X[e]				X	X	X	X	X	X	X	
Bone marrow aspirate	X							X[k]			X[k]		
Bone marrow aspirate (Pharmacodynamic)	X	(X[i])			(X[j])			X[k]			X[k]		
Echocardiogram/MUGA	X										X[l]		
PK blood sampling[m]		X	X	X	X	X	X	X	X	X	X	X	
Pharmacodynamic blood sampling[n]		X			X			X			X	X	
Response assessment[o]								X			X	X[o]	X[o]
Bemcentinib administration[p]		X	X	X	X	X	X	X	X	X	X		
Bemcentinib accountability						X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	

Cycle		1						2			≥3	End of Study	Follow-Up
Week		1				2	3	4	5	6	>7		
Visit	Screen	1	2	3	4	5	6	7	8	9	≥10		
Cycle Day	-14 to 0	1	2	3	4	8	15	1	8	15	1	28 days after last dose	
Record subsequent AML/MDS treatment in eCRF													X[q]
Overall Survival		If the patient dies during study period, please report the date-of-death in the eCRF											

a. A full physical examination, excluding gynecological and rectal examinations, will be conducted at the Screening and End of Study visits. A symptom-directed examination will be conducted at selected visits
b. Vital signs (systolic and diastolic blood pressure (BP), heart and respiration rate and temperature) will be taken at every visit
c. Triplicate 12-lead ECGs will be taken, ≤5 minutes apart, after resting for ≥10 minutes in supine position at every visit. During Cycle 1 Days 1-4 ECGs will coincide with selected PK sampling time-points i.e. pre-dose and 2, 4, 6 hr post-dose (Day 1); 24 (pre 2nd dose) and 30 hr post-Day 1 dose (Day 2); 48 hr (pre 3rd dose) post-Day 1 dose (Day 3); pre-dose, 2, 4 and 6 hr post-dose (Day 4). All time-points are approximate, but every effort must be made to make ECG assessment at specified time-points
d. For women of child-bearing potential
e. Unless conducted as part of the screening procedures within 3 days prior to Day 1
f. Clinical chemistry laboratory parameters (uric acid, electrolytes, blood urea nitrogen (BUN), total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, creatine phosphokinase, alkaline phosphatase, albumin, calcium, magnesium, phosphorus, glucose)
g. Hematology laboratory parameters (full blood count including differential white cell and blast count, hemoglobin, hematocrit and platelets)
h. Coagulation parameters: prothrombin time (PT) and activated partial thromboplastin time (APTT)
i. Bone marrow aspirate for diagnosis and baseline sample for pharmacodynamic biomarker analyses. If diagnostic bone marrow aspirate is routinely frozen, a repeat (fresh) bone marrow aspirate should be taken on Day -1 or Day 0 (pre-dose) for pharmacodynamic biomarker analyses
j. Optional bone marrow aspirate for pharmacodynamic biomarker analyses.
k. Bone marrow aspirate for response assessment and pharmacodynamic biomarker analyses are mandatory at Cycle 2 Day 1 (pre-dose), Cycle 4 Day 1 and every 3rd cycle thereafter until PD is confirmed. For patients that remain on study for more than 12 months without PD, response assessments can be performed after every 5 cycles until the patient experiences PD or permanently withdraws from study treatment for other reasons. Optional assessments may be performed at any time during the study as clinically indicated.
l. Echocardiogram Cycle 4 Day 1 ONLY
m. Blood sampling for the determination of bemcentinib in plasma will be conducted at the following Cycle 1 time-points:
3-day loading dose schedule or no loading dose: pre-dose and 2, 4, 6 hr post-dose (Day 1); 24 (pre 2nd dose) and 30 hr post-Day 1 dose (Day 2); 48 hr (pre 3rd dose) and 2, 4, 6, 8 hr post-dose (Day 3); and pre-dose (Day 4)

A pre-dose sample will be collected at ALL study visits (including ≥3 Cycle 3 (up to and including Cycle 15) and End of Study). All time-points are approximate, but every effort must be made to take samples at specified time-points. Actual times must be recorded. Maximum sampling time-points are described. Please refer to the local Laboratory Manual for required time-points.

n. Blood sampling for pharmacodynamic biomarker analyses will involve a maximum 33 mL blood volume taken at pre-dose at Cycle 1 Day 1 and Day 4, Day of each cycle thereafter (up to and including Cycle 15) and End of Study visit
o. Assessment of response (% blasts; neutrophil count; platelet count) until treatment failure is confirmed. Response assessment should be performed by the investigator according to the modified response criteria in Appendix 5 (Cheson, 2003 and Döhner, 2017) for AML and Appendix 6 (Cheson, 2006) for MDS.
p. Bemcentinib should be taken on an empty stomach at a similar time each morning when they wake, or more than 2 hours after a light meal, with water. To maintain a fasted state, patients should be told not eat or drink anything other than water for at least 1 hour after taking the drug. Patients should record dosing in the dosing diary provided. On study visit days, bemcentinib should be administered on the unit. The bemcentinib dose in Part B will be 400 mg orally daily for the first 3 days of treatment (loading dose) and 200 mg orally daily thereafter (maintenance dose).
q. All patients that have not died prior to the Final Study Visit should be followed for survival at ≤3-monthly intervals. The date of death must be reported for all patients in the eCRF (unless they are lost to follow-up or withdraw consent.

Table 6: Parts B2, B3 and B5 Schedule of Events

Cycle		1						2			≥3	End of Study	Follow-Up
Week		1				2	3	4	5	6	>7		
Visit	Screen	1	2	3	4	5	6	7	8	9	≥10		
Cycle Day	-14 to 0	1	2	3	4	8	15	1	8	15	1	28 days after last dose	
Visit window (+/-) days		0	0	0	0	0	0	2	1	1	2	1	
Informed consent	X												
Demographics	X												
Medical and surgical history	X												
Inclusion/exclusion	X												
ECOG	X							X			X	X	
Physical examination[a]	X	X[e]				X	X	X			X	X	
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead triplicate ECG[c]	X	X	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test[d]	X	X[e]											
Clinical chemistry[f]	X	X[e]	X	X	X	X	X	X	X	X	X	X	
Hematology[g]	X	X[e]	X	X	X	X	X	X	X	X	X	X	
Coagulation screen[h]	X	X[e]				X	X	X			X	X	
Urinalysis	X	X[e]				X	X	X	X	X	X	X	
Bone marrow aspirate	X							X[k]			X[k]		
Bone marrow aspirate (Pharmacodynamic)	X	(X[i])			(X[j])			X[k]			X[k]		
Echocardiogram/MUGA	X										X[l]		
PK blood sampling (bemcentinib)[m]	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacodynamic blood sampling[n]	X	X			X			X			X	X	
Response assessment[o]								X			X	X[o]	X[o]
Bemcentinib administration[p]		X	X	X	X	X	X	X	X	X	X		
Bemcentinib accountability						X	X	X	X	X	X	X	
Cytarabine/decitabine administration[q]		X											

Cycle		1						2			≥3	End of Study	Follow-Up
Week		**1**				**2**	**3**	**4**	**5**	**6**	**>7**		
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**≥10**		
Cycle Day	**-14 to 0**	**1**	**2**	**3**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**28 days after last dose**	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	
Record subsequent AML treatment in eCRF													X
Overall Survival		If the patient dies during study period, please report the date-of-death in the eCRF										X	X[r]

a. A full physical examination, excluding gynecological and rectal examinations, will be conducted at the Screening and End of Study visits. A symptom-directed examination will be conducted at selected visits
b. Vital signs (systolic and diastolic blood pressure (BP), heart and respiration rate and temperature) will be taken at every visit
c. Triplicate 12-lead ECGs will be taken, ≤5 minutes apart, after resting for ≥10 minutes in supine position at every visit. During Cycle 1 Days 1-4 ECGs will coincide with selected PK sampling time-points i.e. pre-dose and 2, 4, 6 hr post-dose (Day 1); 24 (pre 2nd dose) and 30 hr post-Day 1 dose (Day 2); 48 hr (pre 3rd dose) post-Day 1 dose (Day 3); pre-dose, 2, 4 and 6 hr post-dose (Day 4). All time-points are approximate, but every effort must be made to make ECG assessment at specified time-points
d. For women of child-bearing potential
e. Unless conducted as part of the screening procedures within 3 days prior to Day 1
f. Clinical chemistry laboratory parameters (uric acid, electrolytes, blood urea nitrogen (BUN), total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, creatine phosphokinase, alkaline phosphatase, albumin, calcium, magnesium, phosphorus, glucose)
g. Hematology laboratory parameters (full blood count including differential white cell and blast count, hemoglobin, hematocrit, and platelets)
h. Coagulation parameters: prothrombin time (PT) and activated partial thromboplastin time (APTT)
i. Bone marrow aspirate for diagnosis and baseline sample for pharmacodynamic biomarker analyses. If diagnostic bone marrow aspirate is routinely frozen, a repeat (fresh) bone marrow aspirate should be taken on Day -1 or Day 0 (pre-dose) for pharmacodynamic biomarker analyses
j. Optional bone marrow aspirate for pharmacodynamic biomarker analyses.
k. Bone marrow aspirate for response assessment and pharmacodynamic biomarker analyses are mandatory at Cycle 2 Day 1 (pre-dose), Cycle 4 Day 1 and every 3rd cycle thereafter until PD is confirmed. For patients that remain on study for more than 12 months without PD, response assessments can be performed after every 5 cycles until the patient experiences PD or permanently withdraws from study treatment for other reasons. Optional assessments may be performed at any time during the study as clinically indicated.
l. Echocardiogram to be performed at Screening and on Cycle 4 Day 1 ONLY; or at any time during the study as clinically indicated.

m. Blood sampling for the determination of bemcentinib in plasma will be conducted at the following Cycle 1 time-points:
3-day loading dose schedule or no loading dose: pre-dose and 2, 4, 6 hr post-dose (Day 1); 24 (pre 2nd dose) and 30 hr post-Day 1 dose (Day 2); 48 hr (pre 3rd dose) and 2, 4, 6, 8 hr post-dose (Day 3); and pre-dose (Day 4)
A pre-dose sample will be collected at ALL study visits (including ≥3 Cycle 3 (up to and including Cycle 15) and End of Study). All time-points are approximate, but every effort must be made to take samples at specified time-points. Actual times must be recorded. Maximum sampling time-points are described. Please refer to the local Laboratory Manual for required time-points
n. Blood sampling for pharmacodynamic biomarker analyses will involve a maximum 33 mL blood volume taken at pre-dose at Cycle 1 Day 1 and Day 4, Day 1 of each cycle thereafter, (up to and including Cycle 15), and End of Study visit
o. Assessment of response (% blasts; neutrophil count; platelet count) until treatment failure is confirmed. Response assessment should be performed by the investigator according to the modified response criteria in Appendix 5 (Cheson, 2003 and Döhner, 2017)
p. Bemcentinib should be taken on an empty stomach at a similar time each morning when they wake, or more than 2 hours after a light meal, with water. To maintain a fasted state, patients should be told not eat or drink anything other than water for at least 1 hour after taking the drug. Patients should record dosing in the dosing diary provided. On study visit days, bemcentinib should be administered on the unit. The bemcentinib dose in Part B will be 400 mg orally daily for the first 3 days of treatment (loading dose) and 200 mg orally daily thereafter (maintenance dose).
q. Please refer to Section 12.1.2 for administration details.
r. All patients that have not died prior to the Final Study Visit should be followed for survival at ≤3-monthly intervals. The date of death must be reported for all patients in the eCRF (unless they are lost to follow-up or withdraw consent.

11.1. Enrolment

Patients must provide written informed consent before any study-specific screening procedures are performed. Patients who meet all inclusion/exclusion criteria will be allocated a study-specific patient number.

11.1.1. Blinding Procedures

This is an open-label study and consequently there are no blinding procedures in operation.

11.2. Screening

During screening, the following procedures will be performed:

- Obtain written informed consent
- Demographic data, including date of birth, sex, height, and race
- Medical and surgical history
- Concomitant medication
- Physical examination, including weight
- Echocardiogram or MUGA scan
- Vital sign measurements (systolic and diastolic BP, heart and respiration rate and temperature)
- Serial 12-lead ECGs, in triplicate (<5 minutes apart), performed after the patient has been supine for >10 minutes)
- ECOG performance status [Appendix 1]
- Collection of blood sample for hematology (including neutrophil and platelet count), clinical chemistry profile
- Coagulation panel
- Routine urinalysis
- Serum pregnancy test, where appropriate
- BM aspirate for confirmation of the diagnosis and baseline sample for pharmacodynamic biomarker analyses

Male patients and female patients of reproductive potential must agree to practice highly effective methods of contraception throughout the study and for ≥3 months after the last dose of bemcentinib. Highly effective methods of contraception are defined as:

- Hormonal implants, combined oral contraceptives, injectable contraceptives,

- An intrauterine device with hormone spirals
- Tubal ligation
- True total sexual abstinence
- Vasectomy

If it is not possible to use one of these highly effective methods of contraception two barrier methods used in conjunction are acceptable.

In order to reduce the risk of tumor lysis syndrome all patients will be asked to drink up to two liters of fluid in the 24-hour period prior to starting treatment with bemcentinib and on Day 0, Day 1, Day 2 and Day 3. All patients will receive treatment with allopurinol (or equivalent) for at least the first week of treatment or until their serum uric acid is within the normal range or has returned to baseline levels.

11.3. Treatment Period

The following sections outline the assessments to be conducted in each part of the study. For Cycle 2 and beyond a visit window of +/-48 hours is allowed for the Day 1 visit and +/-24 hours for other visits, per protocol. For details of allowable windows around specific PK/PD sampling time-points please refer to the relevant footnotes for Tables 4-6. The timing of the Cycle 1 Day 1 and Day 4 post-dose ECGs should approximate to the PK sampling time-points. Details of allowable windows around visits and specific procedures will be included in the eCRF completion guidance documentation.

11.3.1. Part A

Please refer to the Schedule of Events outlined in Table 4.

11.3.1.1. Cycle 1

In addition to the assessments below, AEs and concomitant medications will be recorded on each visit. Patients will be intensively monitored throughout Day 1 to Day 4 inclusive during Cycle 1.

Visit 1 (Day 1):

- Physical examination, including weight (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- BM aspirate for baseline sample for pharmacodynamic biomarker analyses (pre-dose) ONLY if the diagnostic BM aspirate was frozen (and therefore unsuitable for PD analyses)

- Collection of additional PD biomarker blood sample (pre-dose) ONLY if BM aspirate sample is not collected
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- Coagulation panel (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- Routine urinalysis unless conducted as part of the screening procedures within 3 days prior to Day 1)
- Serum pregnancy test, where appropriate (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- 12-lead ECGs per screening procedures (pre-dose and 2, 4, and 6 hr post-dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 4)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 4)
- Bemcentinib administration

Visit 2 (Day 2):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- 12-lead ECGs per screening procedures (24 and 30 hr post Day 1 dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 4)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 4)
- Bemcentinib administration

Visit 3 (Day 3):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- 12-lead ECGs per screening procedures (48 hr post Day 1 dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 4)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 4)
- Bemcentinib administration

Visit 4 (Day 4):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- 12-lead ECGs per screening procedures (pre-dose and 2, 4, and 6 hr post-dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 4)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 4)
- BM aspirate for pharmacodynamic biomarker analyses (OPTIONAL)
- Bemcentinib administration

Visit 5 (Day 8):

- Physical examination, including weight
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Coagulation panel
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Routine urinalysis
- Collection of PK blood sample (pre-dose)
- Collection of pharmacodynamic biomarker blood sample (pre-dose)
- Bemcentinib administration
- Bemcentinib accountability

Interim Visit for additional ECG assessment (for patients who do not receive a loading dose only)

Visit 6 (Day 15):

- Physical examination, including weight
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Coagulation panel
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood samples (pre-dose)
- Collection of pharmacodynamic biomarker blood samples (pre-dose)
- Routine urinalysis

- Bemcentinib administration
- Bemcentinib accountability

Interim Visit for additional ECG assessment (for patients who do not receive a loading dose only)

11.3.1.2. Cycle 2

In addition to the assessments below, AEs and concomitant medications will be recorded on each visit.

Visit 7 (Day 1):

- Physical examination, including weight
- ECOG performance status [Appendix 1]
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Coagulation panel
- Routine urinalysis
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose)
- Collection of pharmacodynamic biomarker blood sample (pre-dose)
- Bemcentinib administration
- Bemcentinib accountability
- BM aspirate for clinical response criteria review and PD biomarker analyses (pre-dose) unless there is clear evidence of progression in the peripheral blood
- Collection of additional pharmacodynamic biomarker blood sample (pre-dose) ONLY if BM aspirate sample is not collected
- Clinical response criteria review according to IWG criteria (refer to Appendix 5)

Visit 8 (Day 8) and Visit 9 (Day 15):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Routine urinalysis
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose)
- Collection of pharmacodynamic biomarker blood sample (pre-dose)

- Bemcentinib administration
- Bemcentinib accountability

11.3.1.3. Cycle 3 and Subsequent Cycles

In addition to the assessments below, AEs and concomitant medications will be recorded on each visit.

BM aspirates, ECGs and laboratory investigations should be taken more frequently if clinically indicated.

Visit ≥10 (Day 1):

- Physical examination, including weight
- ECOG performance status [Appendix 1]
- Echocardiogram (Cycle 4 ONLY)
- Collection of blood sample for hematology (including neutrophil and platelet count for clinical response criteria review) and clinical chemistry profile
- Coagulation panel
- Routine urinalysis
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose) up to and including Cycle 15
- Collection of pharmacodynamic biomarker blood sample (pre-dose) up to and including Cycle 15
- BM aspirate for clinical response criteria review and pharmacodynamic biomarker analyses (pre-dose) unless there is clear evidence of progression in the peripheral blood (CYCLE 3 ONLY)
    - On Day 1 of Cycle 4 and beyond BM aspirate will be done only if clinically indicated
- Clinical response criteria review according to IWG criteria (refer to Appendix 5)
- Collection of additional pharmacodynamic biomarker blood sample (pre-dose) ONLY if BM aspirate sample is not collected
- Bemcentinib administration
- Bemcentinib accountability

11.3.2. Parts B1 and B4

Please refer to the Schedule of Events outlined in Table 5.

11.3.2.1. Cycle 1

In addition to the assessments below, AEs and concomitant medications will be recorded on each visit. Patients will be intensively monitored throughout Day 1 to Day 4 inclusive of Cycle 1.

Visit 1 (Day 1):

- Physical examination, including weight (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- BM aspirate for baseline sample for pharmacodynamic biomarker analyses (pre-dose) ONLY if the diagnostic BM aspirate was frozen (and therefore unsuitable for pharmacodynamic analyses)
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- Coagulation panel (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- Routine urinalysis unless conducted as part of the screening procedures within 3 days prior to Day 1)
- Serum pregnancy test, where appropriate (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- 12-lead ECGs per screening procedures (pre-dose and 2, 4, and 6 hr post-dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 5)
- Collection of pharmacodynamic biomarker blood sample (pre-dose)
- Bemcentinib administration

Visit 2 (Day 2):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- 12-lead ECGs per screening procedures (24 and 30 hr post Day 1 dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 5)
- Bemcentinib administration

Visit 3 (Day 3):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile

- 12-lead ECGs per screening procedures (48 hr post Day 1 dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 5)
- Bemcentinib administration

Visit 4 (Day 4):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- 12-lead ECGs per screening procedures (pre-dose and 2, 4, and 6 hr post-dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 5)
- BM aspirate for pharmacodynamic biomarker analyses (OPTIONAL)
- Bemcentinib administration

Visit 5 (Day 8):

- Physical examination, including weight
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Coagulation panel
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose)
- Routine urinalysis
- Bemcentinib administration
- Bemcentinib accountability

Visit 6 (Day 15):

- Physical examination, including weight
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Coagulation panel
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose)
- Routine urinalysis
- Bemcentinib administration
- Bemcentinib accountability

11.3.2.2. Cycle 2

In addition to the assessments below, AEs and concomitant medications will be recorded on each visit.

Visit 7 (Day 1):

- Physical examination, including weight
- ECOG performance status [Appendix 1]
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Coagulation panel
- Routine urinalysis
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose)
- Collection of pharmacodynamic biomarker blood samples (pre-dose)
- Bemcentinib administration
- Bemcentinib accountability
- BM aspirate for clinical response criteria review and pharmacodynamic biomarker analyses (pre-dose) unless there is clear evidence of progression in the peripheral blood
- Clinical response criteria review according to IWG criteria (refer to Appendix 5 for AML and Appendix 6 for MDS)

Visit 8 (Day 8) and Visit 9 (Day 15):

- Physical examination, including weight
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Routine urinalysis
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose)
- Bemcentinib administration
- Bemcentinib accountability

11.3.2.3. Cycle 3 and Subsequent Cycles

In addition to the assessments below, AEs and concomitant medications will be recorded on each visit.

BM aspirate for response assessment and pharmacodynamic biomarker analyses are mandatory at Cycle 2 Day 1 (pre-dose), Cycle 4 Day 1 and every 3rd cycle thereafter until PD is confirmed. For patients that remain on study for more than 12 months without PD, response assessments can be performed after every 5 cycles until the patient experiences PD or permanently withdraws from study treatment for other reasons.

Optional assessments may be performed at any time during the study as clinically indicated.

Visit ≥10 (Day 1):

- Physical examination, including weight
- ECOG performance status [Appendix 1]
- Echocardiogram (Cycle 4 ONLY)
- Collection of blood sample for hematology (including neutrophil and platelet count for clinical response criteria review) and clinical chemistry profile
- Coagulation panel
- Routine urinalysis
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose) up to and including Cycle 15
- Collection of pharmacodynamic biomarker blood samples (pre-dose) up to and including Cycle 15
- BM aspirate for clinical response criteria review and pharmacodynamic biomarker analyses (pre-dose) as per relevant Schedule of Events (Table 5) in Section 11
- Clinical response criteria review according to IWG criteria (refer to Appendix 5 for AML and Appendix 6 for MDS)
- Bemcentinib administration
- Bemcentinib accountability

11.3.3. Part B2, Part B3 and Part B5

Please refer to the Schedule of Events outlined in Table 6, Section 12.1.2 for cytarabine administration and Section 12.1.3 for decitabine administration.

To accommodate the dosing schedules of decitabine and cytarabine patients will need to attend the clinic / unit more frequently than required by the dosing/ assessment schedules of bemcentinib. Patients are only required to take bemcentinib capsules at clinic/ unit on those study days where study related procedures are being conducted.

In Part B2 and Part B5, bemcentinib should be administered prior to cytarabine (i.e. approximately 30 minutes) and in Part B3, decitabine should be administered within 30 minutes of the bemcentinib dose.

Please refer to the Schedule of Events outlined in Table 6. Cytarabine will be administered at a dose of 20 mg administered subcutaneously twice daily for up to ten consecutive days repeated approximately every 28 days.

Decitabine will be administered at a dose of 20 mg/m^2 body surface area by intravenous infusion over 1 hour repeated daily for 5 consecutive days (i.e., a total of 5 doses per treatment cycle).

11.3.3.1. Cycle 1

In addition to the assessments below, AEs and concomitant medications will be recorded on each visit. Patients will be intensively monitored throughout Day 1 to Day 4 inclusive of Cycle 1.

Visit 1 (Day 1):

- Physical examination, including weight (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- BM aspirate for baseline sample for pharmacodynamic biomarker analyses (pre-dose) ONLY if the diagnostic BM aspirate was frozen (and therefore unsuitable for pharmacodynamic analyses)
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- Coagulation panel (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- Routine urinalysis unless conducted as part of the screening procedures within 3 days prior to Day 1)
- Serum pregnancy test, where appropriate (unless conducted as part of the screening procedures within 3 days prior to Day 1)
- 12-lead ECGs per screening procedures (pre-dose and 2, 4, and 6 hr post-dose)

- Vital signs per screening procedures
- Collection of PK blood samples for bemcentinib and cytarabine analysis (at time-points outlined in Table 6 as appropriate)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 6)
- Bemcentinib administration
- Commence cytarabine (Part B2) or decitabine (Part B3) administration and continue per local practice

Visit 2 (Day 2):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- 12-lead ECGs per screening procedures (24, and 30 hr post Day 1 dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 6)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 6)
- Bemcentinib administration

Visit 3 (Day 3):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- 12-lead ECGs per screening procedures (48 hr post Day 1 dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 6)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 6)
- Bemcentinib administration

Visit 4 (Day 4):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- 12-lead ECGs per screening procedures (pre-dose and 2, 4, and 6 hr post-dose)
- Vital signs per screening procedures
- Collection of PK blood samples (at time-points outlined in Table 6)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 6)
- BM aspirate for pharmacodynamic biomarker analyses (OPTIONAL)

- Bemcentinib administration

Visit 5 (Day 8):

- Physical examination, including weight
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Coagulation panel
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Routine urinalysis
- Collection of PK blood sample (pre-dose)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 6)
- Bemcentinib administration
- Bemcentinib accountability

Visit 6 (Day 15):

- Physical examination, including weight
- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Coagulation panel
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood samples (pre-dose)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 6)
- Routine urinalysis
- Bemcentinib administration
- Bemcentinib accountability

11.3.3.2. Cycle 2

In addition to the assessments below, AEs and concomitant medications will be recorded on each visit.

Visit 7 (Day 1):

- Physical examination, including weight
- ECOG performance status [Appendix 1]

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Coagulation panel
- Routine urinalysis
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose)
- Collection of pharmacodynamic biomarker blood sample (pre-dose)
- Bemcentinib administration
- Bemcentinib accountability
- BM aspirate for clinical response criteria review and pharmacodynamic biomarker analyses (pre-dose) unless there is clear evidence of progression in the peripheral blood
- Clinical response criteria review according to IWG criteria (refer to Appendix 5)

Visit 8 (Day 8) and Visit 9 (Day 15):

- Collection of blood sample for hematology (including neutrophil and platelet count) and clinical chemistry profile
- Routine urinalysis
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose)
- Collection of pharmacodynamic biomarker blood samples (at time-points outlined in Table 6)
- Bemcentinib administration
- Bemcentinib accountability

11.3.3.3. Cycle 3 and Subsequent Cycles

In addition to the assessments below, AEs and concomitant medications will be recorded on each visit. BM aspirate for response assessment and pharmacodynamic biomarker analyses are mandatory at Cycle 2 Day 1 (pre-dose), Cycle 4 Day 1 and every 3rd cycle thereafter until PD is confirmed. For patients that remain on study for more than 12 months without PD, response assessments can be performed after every 5 cycles until the patient experiences PD or permanently withdraws from study treatment for other reasons.

Optional assessments may be performed at any time during the study as clinically indicated.

Visit ≥10 (Day 1):

- Physical examination, including weight
- ECOG performance status [Appendix 1]
- Echocardiogram (Cycle 4 ONLY)
- Collection of blood sample for hematology (including neutrophil and platelet count for clinical response criteria review) and clinical chemistry profile
- Coagulation panel
- Routine urinalysis
- 12-lead ECGs per screening procedures
- Vital signs per screening procedures
- Collection of PK blood sample (pre-dose)
- Collection of pharmacodynamic biomarker blood sample (pre-dose)
- BM aspirate for clinical response criteria review and pharmacodynamic biomarker analyses (pre-dose) as per relevant Schedule of Events (Table 6) in Section 11
- Clinical response criteria review if BM aspirate conducted according to IWG criteria (refer to Appendix 5)
- Bemcentinib administration
- Bemcentinib accountability

11.4. Final Study Visit

The following assessments will be carried out for every patient enrolled into the study 28 days after the last dose of study medication or at study withdrawal:

- Collection of blood sample for hematology (including neutrophil and platelet count for clinical response criteria review) and clinical chemistry profile
- Coagulation panel
- Routine urinalysis
- Recording of AEs
- Concomitant medications
- Physical examination, including weight
- ECOG performance status [Appendix 1]
- Vital signs per screening procedures
- 12-lead ECGs per screening procedures
- Collection of PK blood sample
- Collection of pharmacodynamic biomarker blood sample

- Bemcentinib accountability

11.5. Survival Follow-up

- All patients must have follow-up at ≤3-monthly intervals to confirm their survival status following the Final Study Visit unless they withdraw consent or are lost to follow-up.
- All subsequent therapies must be recorded in the eCRF if the patient has received treatment of AML following permanent discontinuation of study treatment.

12. Treatment of Subjects

BerGenBio ASA will provide bemcentinib to each study site.

Please refer to Section 14 for the procedures for preparation, storage, handling, disposal and accountability of bemcentinib.

In Part B2 cytarabine will be administered at a dose of 20 mg subcutaneously twice daily for up to 10 consecutive days repeated approximately every 28 days.

In Part B3 decitabine will be administered per standard local practice up to a maximum dose of 20 mg/m^2 body surface area by intravenous infusion over 1 hour, repeated daily for 5 consecutive days (i.e., a total of 5 doses per treatment cycle).

12.1. Treatment Schedule and Administration

12.1.1. Bemcentinib

In Part A, the starting dose of bemcentinib (Cohort 1) will be 200 mg on Cycle 1, Days 1, 2 and 3 (loading dose), followed by a daily maintenance dose of 100 mg.

Patients will take bemcentinib orally, fasted every day of continuous 21-day treatment cycles. Patients receiving Formulation 2 will be instructed to take bemcentinib on an empty stomach at a similar time each morning when they wake, or more than 2 hours after a light meal, with water. To maintain a fasted state, patients should be told not eat or drink anything other than water for at least 1 hour after taking the drug.

Please note that patients in Parts B2 and B3 will also take bemcentinib according to a 21-day treatment cycle i.e. the length of the bemcentinib treatment cycle will not be change to reflect the cytarabine or decitabine treatment cycle described in Section 12.1.2.

The bemcentinib dose in Part B5 (combination with low dose cytarabine) will be 400 mg orally daily for the first 3 days of treatment (loading dose) and 200 mg orally daily thereafter (maintenance dose).

Patients will record their dosing at home in a dosing diary that will be reviewed regularly by the site staff. Patients will be instructed as to the importance of following the dosing instructions they have been provided with, and for maintaining an accurate and up to date dosing record. Patients will also be instructed to bring their dosing diary and all bemcentinib

bottles, including unused and empty bottles, with them to each study visit. The site staff will record the amount of used and unused bemcentinib capsules at selected study visits.

12.1.2. Cytarabine

In Part B2 cytarabine will be administered subcutaneously according to standard practice (i.e. 20 mg/m^2 twice daily for 10 days followed by a rest period of $\leq$1 month according to persisting myelosuppression). Cytarabine should be administered approximately 30 minutes after the bemcentinib dose.

For Part B5, cytarabine will be administered at a dose of 20 mg subcutaneously twice daily for 10 days every 28 days. Cytarabine should be administered approximately 30 minutes after the bemcentinib dose.

If toxicity presents then the cytarabine dose may be modified in accordance with the approved prescribing information or Summary of Product Characteristics (SmPC) and in accordance with local treatment guidelines.

Cytarabine is considered to be standard of care for these patients and will not be supplied or reimbursed by BerGenBio ASA.

12.1.3. Decitabine

In Part B3 decitabine (Dacogen®) will be administered per standard local practice up to a maximum dose of 20 mg/m^2 body surface area by intravenous infusion over 1 hour, repeated daily for 5 consecutive days (i.e., a total of 5 doses per treatment cycle). The total daily dose must not exceed 20 mg/m^2 and the total dose per treatment cycle must not exceed 100 mg/m^2. The cycle should be repeated every 4 weeks depending on the patient's clinical response and observed toxicity. It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial remission may take longer than 4 cycles to be obtained. Treatment may be continued as long as the patient shows response, continues to benefit or exhibits stable disease, i.e., in the absence of overt progression, in accordance with local treatment practice. Decitabine is considered to be standard of care for these patients and will not be supplied or reimbursed by BerGenBio ASA.

12.2. Dose Modification

12.2.1. Bemcentinib

If a patient experiences drug-related toxicity which requires treatment with bemcentinib to be interrupted, a delay of up to 14 days is permitted to allow for resolution of toxicity. Toxicities must have resolved to Grade ≤1 or to baseline for treatment to recommence. For Grade 1 or Grade 2 (tolerable) toxicity, the patient may resume dosing at the same dose level. For ≥Grade 2 (intolerable) toxicity, the patient may resume dosing at a dose level defined by the grade of the toxicity and the number of occurrence(s) of prior toxicity as outlined in Table 7. A maximum of two dose reductions are permitted.

Table 7: Dose Modification of Bemcentinib Daily Dose for Toxicity

Grade (CTCAE)	Recommended Dose Modification
Grade 1 and Grade 2 (tolerable)	
Any occurrence	Maintain dose if toxicity is tolerated by the patient
Grade 2 (intolerable)	
1st or 2nd occurrence of same adverse event	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2 Resume dosing at same dose
3rd occurrence of same adverse event	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2 Dose reduce by 100 mg
4th occurrence of same adverse event	Discontinue permanently
Grade 3	
1st occurrence	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2 Dose reduce by 100 mg or Discontinue permanently if dose has already been reduced
2nd occurrence of same adverse event at G3	Discontinue permanently
Grade 4	
1st occurrence	Discontinue permanently

Notes:
- Treatment interruption for bemcentinib-related toxicity should be limited to 14 days
- Dose reduction below 100 mg daily is not possible (a single capsule contains 100 mg bemcentinib)
- Patients being considered for dose reduction or permanent discontinuation of bemcentinib, should be discussed with the Medical Monitor

If after a 14-day delay, toxicity has not resolved to Grade ≤1 or to baseline the patient should be withdrawn from the study.

In clinical study BGBC001 bemcentinib exhibited evidence of exposure-related QTc prolongation, and it is anticipated that QTc prolongation could be dose-limiting in this study. In order to reduce the risk of QTc prolongation, all efforts should be made to maintain the patient's serum potassium levels at >4 mmol/L during treatment with bemcentinib and for 2 weeks following completion of therapy. Serum calcium and magnesium should be measured and reasonable efforts made to maintain at normal levels throughout treatment. Patients with a QTc of ≥480 ms should be closely monitored on the clinical trial unit until their QTc falls below 480 ms and their electrolytes should be measured and corrected as necessary.

If a patient experiences QTc prolongation despite normal serum potassium and magnesium levels, bemcentinib dosing should be modified as outlined in Table 8. All values refer to the mean of triplicate serial ECG recordings. If a patient experiences a ventricular arrhythmia at any time, they should be withdrawn from the study.

Table 8: Dose Modification of Bemcentinib Daily Dose for QTc Prolongation

QTcF	Recommended Bemcentinib Dose Modification
Grade 1 (451-480 ms)	
Any occurrence	No dose modification required
Grade 2 (481-500 ms)	
1st occurrence	Continue dosing and conduct weekly ECGs; i) if QTcF reduces to ≤Grade 1 by 14 days from initial recording, no dose modification is required ii) if QTcF does not reduce to ≤Grade 1 by 14 days from initial recording, dose reduce by 100 mg
≥2nd occurrence (without dose modification)	Repeat procedure for "1st occurrence"
≥2nd occurrence (at reduced dose)	Continue dosing and conduct weekly ECGs; i) if QTcF reduces to ≤Grade 1 by 14 days from initial recording, no further dose modification is required ii) if QTcF does not reduce to ≤Grade 1 by 14 days from initial recording, interrupt treatment for ≤14 days - if QTcF reduces to ≤Grade 1, no dose modification is required and dosing can recommence; if treatment interruption is required on more than 2 occasions at reduced dose, dose reduce by another 100 mg or discontinue treatment if dose reduction is not possible - if QTcF does not reduce to ≤Grade 1, dose reduce by another 100 mg or discontinue treatment if dose reduction is not possible

≥Grade 3 (≥501 ms)	
1st occurrence	Interrupt treatment for ≤14 days; i) if QTcF reduces to ≤Grade 1, dose reduce by 100 mg or discontinue treatment if dose reduction is not possible ii) if QTcF does not reduce to ≤Grade 1, discontinue treatment
2nd occurrence	Discontinue permanently
Ventricular arrhythmia	
1st occurrence	Discontinue permanently

Notes:

- Serum calcium, magnesium and potassium should be measured regularly whilst receiving bemcentinib; all abnormal results should be corrected; check for use of concomitant medication that are associated with QT prolongation.
- The mean QTcF value from triplicate ECG readings should be used when considering dose modification
- Treatment interruption for bemcentinib-related toxicity should be limited to 14 days
- Dose reduction below 100 mg daily is not possible (a single capsule contains 100 mg bemcentinib)
- Patients being considered for dose reduction or permanent discontinuation of bemcentinib should be discussed with the Medical Monitor

12.3. Concomitant Medication and Procedures

All prescription, non-prescription, or over-the-counter medications including herbal remedies given to, or taken by, the patient at entry and during the study must be clearly documented in the eCRF.

The patients must be instructed that no additional medication will be allowed without the prior consent of the investigator. Any medication considered necessary for the patient's safety and well-being may be given at the discretion of the investigator. Hematopoietic growth factors may be administered for the treatment of AEs such as neutropenic infections but should not be used to maintain the dose intensity of bemcentinib in Part A. Patients who have evidence of treatment benefit after ≥1 cycle of treatment in Part B may receive hematopoietic growth factors to maintain bemcentinib dosing.

Concurrent treatment with any agent known to cause QT prolongation and have a risk for Torsades de Pointes is an exclusion criterion for the study. A comprehensive list of these prohibited medications is provided in Appendix 3. Patients being treated with antacid histamine receptor 2 inhibitors or proton pump inhibitors within 3 days of administration of bemcentinib will be excluded. The Investigator may initiate treatment with these medications during the study, providing they are taken in the evening.

12.4. Continuation of Treatment

It is acknowledged that the R/R AML setting is a high unmet need for effective therapies, more so for those elderly patients unsuitable for intensive chemotherapy enrolled into this study. Unlike intensive chemotherapy approaches where a clinical response may be observed relatively early in the treatment phase, the Sponsor has observed clinical responses occurring later in patients treated with bemcentinib in its immunotherapeutic mode of action when given as monotherapy or in combination with other agents. Given that AXL mediates multiple survival mechanisms used by cancers (chemotherapy drug resistance, immune evasion) and given AXL is found at high levels on immune cells in proximity to some tumors and on the tumor cells themselves, it is not unexpected that it may take longer to observe some clinical responses in some patients as bemcentinib inhibits the expression of AXL and allows the body's own immune system to kill tumor cells. This would explain both the early (cytotoxic like consequences of reversal of EMT) and the late (activation of innate immune anti-tumor responses) responses which have been observed in this study. Therefore, it is recommended that study treatment is administered for at least 3 cycles as the time-to-response may be delayed. Patients will continue to receive study treatment for as long as, in the opinion of the investigator, they continue to derive clinical benefit.

12.5. Discontinuation of Treatment and Withdrawal of Patients

Patients may withdraw informed consent and discontinue from the study at any time, or for any reason, without prejudice to their future treatment. In addition, a patient must be discontinued from the study if any of the following criteria are met:

- Significant patient non-compliance with the protocol, as agreed by the investigator and the sponsor
- Patient lost to follow-up
- Termination of the study by the sponsor
- Patient experiences an unacceptable toxicity that precludes them from continuing in the study e.g. patient experiences a ventricular arrhythmia (see Section 12.2.1), as agreed by the investigator and the sponsor
- Lack of adequate recovery from a first cycle DLT, see Section 9.2.1.2
- Failure of toxicity to adequately resolve, as outlined in Table 7
- Female patient becomes pregnant

- Patient experiences PD (unless in the opinion of the investigator, they continue to derive clinical benefit and are permitted to continue on study after discussion and agreement between investigator, the patient and Sponsor. All decisions will be documented in writing).

Note: Clinical benefit in this context is defined as meeting one or several of the following criteria: evidence of disease stabilization after documented initial progression (patient is stably worse), tolerance of drug(s), absence of rapid progression based on peripheral or bone marrow blasts and clinical hematology and clinical chemistry parameters, maintenance of good performance status (PS of 2 or less and not deteriorating], absence of worsening clinical symptoms (i.e., no symptomatic deterioration) and/or improvements in patient's quality of life). This will not affect the time point of disease progression from the perspective of trial analysis.

- Patient and/or investigator decide that it is in the patient's best interest to withdraw from study treatment or the patient withdraws consent

AEs resulting in discontinuation will be followed as outlined in Section 9.3.4.

Patients who discontinue during the DLT assessment period (Part A), for any reason other than a DLT, will be replaced. All other patients who discontinue study treatment will not be replaced.

If a patient discontinues study treatment prior to study completion, and for reasons other than progression or non-tolerability, every effort should be made to conduct the Final Study Visit assessments as outlined in Section 11.5. The reason for the patient's withdrawal from the study must be recorded in the eCRF. Patients that permanently discontinue either bemcentinib or the combination agent must continue to undergo all study assessments until all study treatments have been permanently discontinued after which they must attend the Final Study Visit.

13. Study Assessments

Study assessments will be conducted according to the relevant Schedule of Events (Tables 4-6) in Section 11.

13.1. Clinical Safety Assessments

Before being entered into the study, patients will be assessed to ensure that eligibility criteria are met. Patients not meeting the criteria must not be entered into the study.

The following tests and assessments will be performed at times specified in the relevant Schedule of Events (Tables 4-6) in Section 11 and at any other time required in the opinion of the investigator:

- Serum pregnancy test on women of childbearing potential (Screening only)
- Physical examination
- Vital sign measurements (systolic and diastolic BP, heart and respiration rate and temperature)
- Serial 12-lead ECGs, in triplicate ($\leq$5 minutes apart), performed after the patient has been supine for $\geq$10 minutes)
- AE and SAE recording
- Concomitant medication and procedures recording
- Echocardiogram or MUGA scan

13.1.1. Resting 12-lead ECG

For timing of individual measurements please refer to relevant Schedule of Events (Tables 4-6) in Section 11.

Twelve-lead ECGs will be obtained after the patient has rested in a supine position for >10 minutes in each case. All 12-lead ECGs should be recorded while the patient is in the supine position. The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected. ECGs will be conducted in triplicate and performed <5 minutes apart.

ECGs will be recorded at 25 mm/sec. A clinically significant ECG finding must be recorded as part of the medical history, if observed prior to start of dosing, and as an AE post-dose, where the finding represents a change from baseline.

13.1.2. Physical Examination

The physical examination will be symptom-directed and will exclude rectal and gynecological (where applicable) examinations.

13.1.3. Vital Signs

For timing of individual measurements please refer to relevant Schedule of Events (Tables 4-6) in Section 11.

BP and HR will be measured using a BP recording device with an appropriate cuff size. Measurements will be made after the patient has been resting supine for ≥10 minutes. Temperature and respiration rate will be measured as per clinical practice.

13.1.4. Subject Symptomatology

Symptoms reported spontaneously by the patient will be recorded throughout the study period. Symptoms reported will be reviewed by the investigator and recorded as an AE where this is a change from baseline or a new symptom reported. Please note that every effort should be made to report the actual medical condition rather than a symptom in the eCRF (see Section 15.1.1 Adverse Event for guidance).

13.2. Laboratory Safety Assessments

Blood and urine samples will be taken at times specified in the relevant Schedule of Events (Tables 4-6) in Section 11, and at any other time required in the opinion of the investigator, and analyzed at the designated local laboratory.

13.2.1. Hematology and Clinical Chemistry

Blood samples for the determination of clinical chemistry, hematology and coagulation parameters to be measured are outlined in Table 9.

Table 9: Hematology, Clinical Chemistry and Coagulation Parameters

Biochemistry	Hematology
Bilirubin	Hemoglobin
Aspartate aminotransferase (AST)	Mean cell hemoglobin (MCH)
Alanine aminotransferase (ALT)	Mean corpuscular hemoglobin concentration (MCHC)
Alkaline phosphatase (ALP)	Total white cell count
Creatine phosphokinase (CK)	Differential white cell count
Creatinine	Platelets
	Peripheral blast percentage

Biochemistry	Hematology
Albumin	**Coagulation**
Total protein	Prothrombin time (PT)
Potassium (K)	Activated Partial Thromboplastin Time (APTT)
Sodium (Na)	
Calcium (Ca)	
Magnesium (Mg)	
Glucose	
Inorganic phosphate (IP)	
Uric acid	
Additional parameters may be performed as clinically indicated and per local practice	

13.2.2. Urinalysis

Dipstick urinalysis for measurement of the parameters outlined in Table 10 will be conducted by the local laboratory:

Table 10: Urinalysis Parameters

pH	Nitrite
Glucose	Blood
Proteins	Leukocytes
Ketones	Specific gravity
Bilirubin	Urine microscopy (if indicated)
Additional parameters may be performed as clinically indicated and per local practice	

13.3. Pharmacokinetic Assessments

Venous blood samples for the determination of concentrations of bemcentinib (all Parts) in plasma will be taken at times specified in the relevant Schedule of Events (Tables 4-6) in Section 11. Detailed procedures for the collection, processing, storage and shipment of the samples will be provided in the Study Laboratory Manual.

Table 11: Bemcentinib PK Sampling Time Points and Permitted Windows

Study Day	Time Point (hr)	Permitted Time Window
Cycle 1 Day 1	Pre-dose	
	2.0	+/-15 mins (from C1D1 dose)
	4.0	+/- 30 mins (from C1D1 dose)
	6.0	+/- 45 mins (from C1D1 dose)
Cycle 1 Day 2	24.0	+/-2 hrs (from C1D1 dose)

	30.0	+/-3 hrs (from C1D1 dose)
Cycle 1 Day 3	48.0 (0)	+/-4 hrs (from C1D1 dose)
	2.0	+/-15 mins (from C1D3 dose)
	4.0	+/- 30 mins (from C1D3 dose)
	6.0	+/- 45 mins (from C1D3 dose)
	8.0	+/-1 hrs (from C1D3 dose)
Cycle 1 Day 4	Pre-dose	+/-2 hrs (from C1D3 dose)
Day 1 of each cycle up to and including Cycle 15	Pre dose	
EOS		As collected- not time specific

13.3.1. Determination of Bemcentinib Concentration in Plasma

Plasma samples for determination of bemcentinib concentration will be analyzed by BerGenBio's Bioanalytical Services vendor using the validated LC/MS/MS method.

13.4. Clinical Efficacy Assessments

All patients must undergo baseline disease assessments at Screening (peripheral blood and BM). Response assessments will be performed at Cycle 2 Day 1 (pre-dose), Cycle 4 Day 1 and then repeated after every 3 cycles or when clinically indicated. Patients that complete 12 months on study treatment, and have not experienced PD, will undergo response assessment every 5 cycles until PD is confirmed. A BM assessment may be performed at any time during the study as clinically indicated as outlined in the relevant Schedule of Events (Tables 4-6) in Section 11. Response assessment will be performed by the investigator according to the modified IWG response criteria for AML (Cheson, 2003 and Döhner, 2017). Please refer to Appendix 5.

The assessment of the clinical efficacy of bemcentinib in AML will be made, according to the revised recommendations of the IWG in AML [Cheson, 2003 and Döhner, 2017] as follows:

- Assessment of the % of blasts in a peripheral blood and BM aspirate sample
- Measurement of absolute neutrophil count (ANC)
- Measurement of Platelet count≥
- Red cell transfusion requirement

The assessment of clinical efficacy of bemcentinib in patients with MDS will be made according to the modified IWG response criteria in myelodysplasia [Cheson, 2006]. Please refer to Appendix 6.

- Assessment of the % of blasts in a peripheral blood and BM aspirate sample
- Measurement of ANC
- Measurement of Platelet count
- Red cell transfusion requirement

BM aspirate and PBMC samples will be analyzed at the designated local laboratory. Wherever possible, an aliquot of BM aspirate will be taken for pharmacodynamic biomarker assessment (see Section 13.5.1).

13.5. Pharmacodynamic and Predictive Biomarkers

The effects of bemcentinib on pharmacodynamic endpoints of AXL inhibition will be determined in BM aspirates with blood samples:

- To identify and evaluate potential predictive biomarkers, e.g. sAXL and other associated soluble biomarkers. Pre-treatment levels of biomarkers will be correlated with clinical endpoints.
- To establish the effects of bemcentinib on relevant biological endpoints in peripheral blood (including sAXL PBMC) and BM samples.
- To assess pharmacodynamic biomarkers in tissue and blood to support the clinical development of bemcentinib.
- To evaluate other biomarkers relevant to the investigational agents for exploratory purposes.
- Effect of bemcentinib on AXL, sAXL and pAXL and downstream effectors of AXL signaling, such as Akt, pAkt, Erk, pErk, SLFN11, Bcl2, Puma by appropriate methods (e.g. FCM, western blotting, proteomics, transcriptomics)
- Effect of bemcentinib on gene expression by appropriate methods (e.g. FCM, western blotting, proteomics, transcriptomics, quantitative PCR, DNA-methylation analysis)
- Effect of bemcentinib on relevant immune cell populations.
- Effect of bemcentinib on the spectrum of mutations present within the cancer cell population by genomic analysis.
- To explore the correlation between baseline biomarker levels and clinical endpoints.

Biomarker samples will be collected at the time-points outlined in the relevant Schedule of Events (Tables 4-6) in Section 11. Detailed procedures for the collection, processing, storage and shipment of the samples will be provided in the Study Laboratory Manual.

13.5.1. Bone Marrow Aspirates

Aliquots of the BM aspirate samples collected for the assessment of clinical efficacy, as outlined in Section 13.4, will be processed for the pharmacodynamic investigation of AXL inhibition by bemcentinib.

A BM aspirate sample will be taken on Cycle 1 Day 4 from patients who consent to this optional procedure.

The samples collected will be analyzed for the following:

- To identify and evaluate potential predictive biomarkers. Pre-treatment levels of biomarkers will be correlated with clinical endpoints.
- To evaluate other biomarkers relevant to the investigational agents for exploratory purposes.
- Effect of bemcentinib on AXL, sAXL and pAXL and downstream effectors of AXL signaling, such as Akt, pAkt, Erk, pErk, SLFN11 Bcl2, Puma by appropriate methods (e.g. western blotting, proteomics, transcriptomics)
- Genomic analysis of normal tissue, and of cancer cells prior to and during treatment with bemcentinib, to investigate whether the spectrum of mutations present within the cancer cell population changes with bemcentinib treatment
- BM mononuclear cells (CD34+) will be analyzed by transcriptomics and by the methods described by Ben-Batalla, 2013

13.5.2. Pharmacodynamic Blood Samples

Blood samples will be collected at the time-points outlined in the relevant Schedule of Events (Tables 4-6) in Section 11.

- To assess pharmacodynamic biomarkers in tissue and blood to support the clinical development of bemcentinib
- Effect of bemcentinib on AXL, sAXL and pAXL and downstream effectors of AXL signaling, such as Akt, pAkt, Erk, pErk, SLFN11 Bcl2, Puma by appropriate methods (e.g. FCM, western blotting, proteomics, transcriptomics)

13.6. Volume of Blood and Bone Marrow Sampling

The approximate, maximum volume of blood and BM aspirate that will be drawn from each patient per cycle is detailed in the tables below:

Table 12: Volume of blood and BM aspirate to be drawn per Patient during Screening and at Cycle 1

Assessment	Sample volume (mL)	Part A		Part B	
		n	Total volume (mL)	n	Total volume (mL)
Pharmacokinetics	4.5	14	63	14	63
Pharmacodynamics	33	2	66	2	66
Coagulation	5	4	20	4	20
Clinical chemistry	5	7	35	7	35
Hematology	2.5	7	17.5	7	17.5
Total blood volume (mL) for screen and Cycle 1		**201.5**		**201.5**	
Pharmacodynamics	20	1(3)[a]	20(60)	1(3)[a]	20(60)
Clinical efficacy assessment[b]	1	1	1	1	1
Total BM volume (mL) for screen and Cycle 1		**20(60)**		**20(60)**	

maximum of 3 samples if patient consents to optional BM aspirate on Day 4 and diagnostic BM aspirate is routinely frozen
[b] 1 mL aliquot of total 20 mL BM aspirate draw

Table 13: Volume of Blood and BM aspirate to be drawn per Patient during Cycle 2

Assessment	Sample volume (mL)	Part A		Part B	
		n	Total volume (mL)	n	Total volume (mL)
Pharmacokinetics	4.5	3	13.5	3	13.5
Pharmacodynamics	33	1	33	1	33
Coagulation	5	1	5	1	5
Clinical chemistry	5	3	15	3	15
Hematology	2.5	3	7.5	3	7.5
Total blood volume (mL) for Cycle 2		**74**		**74**	
Pharmacodynamics	20	1	20	1	20
Clinical efficacy assessment[a]	1	1	1	1	1
Total BM volume (mL) for Cycle 2		**20**		**20**	

[a] 1 mL aliquot of total 20 mL BM aspirate draw

Table 14: Volume of Blood and BM aspirate to be drawn per Patient per Cycle >3 (up to and including Cycle 15 for PK and Blood Pharmacodynamics) & at Final Study Visit

Assessment	Sample volume (mL)	Part A		Part B	
		n	Total volume (mL)	n	Total volume (mL)
Pharmacokinetics	4.5	1	4.5	1	4.5
Pharmacodynamics	33	1	33	1	33
Coagulation	5	1	5	1	5
Clinical chemistry	5	1	5	1	5
Hematology	2.5	1	2.5	1	2.5
Total blood volume (mL) per Cycle & Final Visit		**50**		**50**	
Pharmacodynamics	20	1	20	1	20
Clinical efficacy assessment[a]	1	1	1	1	1
Total BM volume (mL) per Cycle		**20**		**20**	

1 mL aliquot of total 20 mL BM aspirate draw; optional assessment performed as clinically indicated

14. Study Treatment Management

Every patient enrolled in the study will receive bemcentinib. Patients enrolled in Part B2 and B5 will receive bemcentinib in combination with low dose cytarabine.

14.1. Study Medication

The investigational medicinal product (IMP) bemcentinib must be stored in a secure location. Accountability for study treatment is the responsibility of the investigator. The investigator/designee must ensure that the IMP will only be dispensed to patients in accordance with the protocol and that any unused IMP will be disposed of or, if unopened, returned in accordance with the written instructions of the sponsor.

Study staff should refer to the sponsor's Directions for Handling and Administration (DHA) document for specific instructions regarding the handling, storage, dispensing and destruction of the IMP.

Bemcentinib has been manufactured according to appropriate Good Manufacturing Practice (GMP) standards. Bemcentinib will be labelled in compliance with GMP Annex 13 requirements, Food and Drug Administration (FDA) requirements and local regulatory guidelines.

14.1.1. Bemcentinib

Bemcentinib will be supplied in hydroxypropyl methylcellulose (HPMC) capsules at a dose strength of 100 mg for oral dosing. Please refer to Section 4 of the current version of the bemcentinib IB for additional information on the physical, chemical and pharmaceutical properties of bemcentinib.

14.1.1.1. Bemcentinib Storage

Bemcentinib will be shipped to the site and must be stored at the site in a secure location under ambient temperature conditions (<25 °C/ <77 °F).

Detailed instructions for the storage of dispensed IMP at home will be provided to every patient enrolled in the clinical study.

14.1.1.2. Bemcentinib Accountability

The investigator/designee must maintain complete and accurate IMP accountability records showing the date of receipt and quantity of all supplies of IMP. These records must include

accurate patient-specific dispensing information including quantity of capsules/bottles dispensed, date dispensed, and quantity and date returned (or disposed of).

At the end of the study, reconciliation must be made between the amount of IMP supplied, dispensed and subsequently returned to the sponsor or destroyed at site and any discrepancies accounted for.

Destruction of the IMP at site will only be performed by authorized personnel following written receipt of approval from the sponsor. The procedure should be fully documented as outlined in the DHA.

14.1.2. Cytarabine and Decitabine

All patients in Part B2 and Part B5 will receive subcutaneous low-dose cytarabine.

Name: Cytarabine
Brand name: Ara-C
Active Substance: Cytosine Arabinoside
Pharmaceutical form: Solution for injection
Route of administration: Subcutaneous
Investigational Medicinal Product Status: Non-IMP
ATC code: L01BC01

Cytarabine will have commercial packaging and labels in accordance with its marketing authorization. It will be purchased by the participating hospital via their normal purchasing procedure and will not be reimbursed by BerGenBio ASA.

All patients in Part B3 will receive intravenous decitabine per standard practice.

Name: Decitabine
Brand name: Dacogen
Active Substance: Decitabine (5-aza-2'-deoxycytidine)
Pharmaceutical form: Solution for injection
Route of administration: Intravenous
Investigational Medicinal Product Status: Non-IMP
ATC code: L01BC08

Decitabine will be packaged and labelled in the standard manner according to the current marketing authorization by the manufacturer. It will be purchased by the participating hospital via their normal purchasing procedure and will not be reimbursed by BerGenBio ASA.

14.1.2.1. Cytarabine and Decitabine Storage

Cytarabine and decitabine will be stored in accordance with the specific manufacturer's SmPC or US prescribing information. A copy of the SmPC or US prescribing information for the product used should be kept in the BGBC003 Pharmacy file, Investigator Site File and the TMF.

14.1.2.2. Cytarabine and Decitabine Accountability

The investigator/designee must maintain complete and accurate cytarabine and decitabine dispensing logs including the actual dose administered and the date.

15. Safety Definitions, Monitoring and Reporting

Safety reporting in this clinical study will be undertaken in accordance with current regulatory and national requirements.

15.1. Definitions

The following definitions are according to the Directive 2001/20/EC.

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable or unintended sign, symptom or disease temporally associated with the use of the IMP whether or not considered related to the IMP. This includes any occurrence that is new, an exacerbation of an existing disease (a worsening of the character, frequency or severity of a known condition) or abnormal results of diagnostic procedures, including clinically significant laboratory test abnormalities.

Suggested criteria for the assessment of clinical significance for laboratory abnormalities are as follows.

The laboratory abnormality:

- is clearly consistent with the pattern of leukemia disease or progression;
- is accompanied by clinical symptoms;
- requires study drug dose modification or interruption or permanent discontinuation of study treatment;
- requires more frequent follow-up assessments, further diagnostic investigation, etc.;
- requires a change in concomitant medication, therapy, or treatment.

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g. alkaline phosphatase and bilirubin 5X ULN associated with cholecystitis), only the diagnosis (e.g. cholecystitis) needs to be recorded on the AE eCRF. If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.” Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly

recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

For all AEs, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases) wherever possible. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single syndrome at the time of reporting, each individual sign and/or symptom should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, the reported event term should be updated to reflect the medical diagnosis.

Note that AEs occurring secondary to an initiating event that are separated in time or medically significant should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to a renal failure, both events should be recorded separately on the eCRF.

A pre-existing medical condition which is present at the start of the study and described in the Medical History eCRF, should only be recorded as an AE or SAE if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g. “more frequent headaches”).

15.1.2. Adverse Reaction

An adverse drug reaction (ADR) is defined as all untoward and unintended responses to an IMP related to any dose administered. The definition implies a reasonable possibility of a causal relationship between the event and the IMP i.e. there are facts (evidence) or arguments to suggest a causal relationship.

15.1.3. Serious Adverse Event

An SAE as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is any untoward medical occurrence that meets any of the following conditions:

- Results in death
- Is life-threatening (i.e. the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

15.2. Monitoring and Reporting Events

15.2.1. Adverse Events

Any AE experienced by a patient between signing the informed consent form (ICF) and 28 days after the last administration of bemcentinib is to be recorded in the eCRF regardless of the severity and causality of the event, although only events considered to be related to treatment need to be recorded between the last administration of bemcentinib and the end of the 28-day follow up period. If bemcentinib-related toxicities continue beyond the Follow-up period, patients will be followed until all bemcentinib-related toxicities have resolved to Grade ≤1, stabilized or returned to baseline.

15.2.2. Serious Adverse Events

Any SAE experienced by a patient between the time of the first administration of bemcentinib and 28 days after the last administration is to be recorded on an SAE Report Form as well as in the eCRF within 24 hours of knowledge by the investigator of its occurrence, regardless of the severity and causality of the event. The exception to this will be patients who experience an SAE due to a Screening assessment. Such events should also be reported and will be recorded in the CSR. SAEs with a suspected relationship with bemcentinib will be collected indefinitely. The SAE Report Form should be e-mailed to the Syneos Health Safety and Pharmacovigilance Global Safety Mailbox safetyreporting@syneoshealth.com.

All SAEs that have not resolved by the end of the study, or that have not resolved upon the patient's discontinuation from the study, must be followed until any of the following occur:

- The event resolves
- The event stabilizes
- The event returns to baseline status
- The event can be attributed to agents other than the IMP or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a patient's participation in a clinical study must be reported as an SAE. Exclusions to this are hospitalizations:

- For pre-scheduled or routine elective procedures (as long as the qualifying condition did not worsen or progress, in the opinion of the investigator, since signing the ICF)
- For social reasons, in the absence of an AE e.g. for respite care
- Due to expected deterioration caused by disease progression

15.2.3. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.2.2
- The severity of the event as defined in Section 15.3.1
- The relationship to bemcentinib as defined in Section 15.3.2

15.3. Safety Classifications

15.3.1. Assessment of Severity

The investigator/designee will rate the severity of each AE according to CTCAE. For each sign or symptom, the maximum or highest grade observed since the last visit should be reported. If the symptom or event cannot be graded according to CTCAE, the following grade (severity) rating guideline will be used:

Grade 1	Mild	The AE is transient and easily tolerated by the subject
Grade 2	Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities
Grade 3 or 4	Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening

15.3.2. Assessment of Causality

The investigator will assess the causality of the AE with respect to the IMP according to the following guidance:

Unrelated	The Adverse Event is clearly unrelated to bemcentinib

Unlikely	The Adverse Event is doubtfully related to bemcentinib
Possible	The Adverse Event may be related to bemcentinib
Probable	The Adverse Event is likely to be related to bemcentinib
Definite	The Adverse Event is clearly related to bemcentinib

If in the opinion of the investigator an SAE is considered not related an alternate etiology must be provided. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the sponsor should be provided with the report.

15.3.3. Assessment of Expectedness

An unexpected adverse event is an event, the nature or severity of which is not consistent with the reference safety information (RSI) presented in the IB for the IMP. The responsibility for determining expectedness of an ADR falls to the sponsor.

15.3.4. Immediate Reporting of Serious Adverse Events

Expedited safety reporting within this clinical study complies with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A), investigational new drug (IND) application safety reporting (under 21CFR312.32), and with applicable local regulatory requirements.

The sponsor assumes responsibility for appropriate reporting of AEs to the Regulatory Authorities and main Research Ethics Committees (REC)/Institutional Review Boards (IRB). Although this responsibility can be delegated to the sponsor's Contract Research organization (CRO), the sponsor retains ultimate responsibility for safety reporting.

All SAEs that are unexpected and associated with the use of the IMP are classified as suspected unexpected serious adverse reactions (SUSARs) and must be reported to the main RECs/IRBs and Regulatory Authorities within 7 calendar days if fatal or life threatening, or within 15 calendar days if non-life threatening and non-fatal. The sponsor/designee must also report SUSARs to all investigational sites.

Any safety information from other observations that could change the risk-benefit evaluation of the IMP should be promptly communicated to the Regulatory Authorities and main RECs/IRBs. Any other SUSARs associated with the IMP should be reported as soon as the sponsor becomes aware of them including SUSARs which occur in another clinical study

conducted by the same sponsor or which are identified by spontaneous reports, a publication, or which are transmitted to the sponsor by another Regulatory Authority.

Other safety issues that also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of the IMP (sufficient to consider changes in the administration or in the overall conduct of the trial), for instance include:

- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important
- Post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the sponsor
- New events relating to the conduct of the trial or the development of the IMP likely to affect the safety of the patients, such as:
    - An SAE which could be associated with the trial procedures and which could modify the conduct of the trial
    - A major safety finding (such as carcinogenicity, which differs to the underlying disease)

Expedited reporting is not usually required for reactions which are serious but expected, and it is inappropriate to report events that are considered unrelated to the IMP.

15.3.5. Annual Safety Updates

Once a year the sponsor/designee will submit an annual Development Safety Update Report (DSUR) to the Regulatory Authorities and main RECs/IRBs that lists all suspected serious adverse reactions occurring throughout the time period.

15.3.6. Deaths

The cause of death of a patient in a clinical study, unless it is associated with disease progression, is considered a SAE whether the event is expected or associated with the IMP. The reporting periods for SAEs are detailed in Section 15.2.2.

15.3.7. Procedures for Handling Special Situations

15.3.7.1. Pregnancy

As detailed in the inclusion/exclusion criteria, patients of childbearing potential who are not using adequate contraception will not be invited to participate in this study. Female patients of childbearing potential must have a negative serum pregnancy test within 3 days prior to the first dose of bemcentinib. In the event of any pregnancies occurring in female patients, or in

the partners of male patients during the study, the pregnancy must be reported to the Syneos Health Safety and Pharmacovigilance Global Safety mailbox safetyreporting@syneoshealth.com by the investigational staff within one working day of their knowledge of the event using a Pregnancy Notification Form.

The reporting period for pregnancies will start with the first study-related procedure and end 28 days after the final administration of bemcentinib.

Any female patients who become pregnant whilst taking part in the study will be withdrawn, whilst patients whose partners become pregnant can remain in the study. A patient who completes or withdraws from the trial before the full term of their/their partner's pregnancy will be asked to consent to their doctor providing the sponsor with follow-up information concerning the pregnancy and its outcome.

15.3.8. Medical Emergency

In a medical emergency requiring immediate attention, study staff will apply appropriate medical intervention according to standard medical practice. The investigator/designee should contact BerGenBio's Medical Monitor if guidance is needed to manage a case particularly if the medical emergency is suspected to be related to the IMP.

15.3.8.1. Unblinding for a Medical Emergency

Not applicable.

15.4. Investigator's Safety Responsibilities

The investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to bemcentinib
- Determine the seriousness, relationship and severity of each event
- Determine the onset and resolution of each event
- Complete an SAE form for each SAE as outlined in Section 15.2.2
- Pursue SAE follow-up information actively and persistently
- Ensure all AE and SAE reports are supported by documentation in the patient medical records
- Report SAEs to their local REC/IRB, as required by local law

15.5. Sponsor's Safety Responsibilities

The sponsor's responsibilities include the following:

- The ongoing safety evaluation of the IMP
- Reporting of SUSARs to the Regulatory Authorities, main REC/IRB and investigators according to required timelines as outlined in Section 15.3.4
- Submission of the annual DSUR to the Regulatory Authorities and main REC/IRB

15.6. Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects. An overdose is defined by a boundary of 15% above the prescribed dose of any medicinal product.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

16. Statistical Methods and Determination of Sample Size

Detailed statistical analysis information will be provided separately in the SAP. Any deviations to the planned analyses specified within the SAP, will be justified in writing and presented within the final CSR.

In the Tables, Listings and Figures presented in the CSR, patients enrolled in Part A will be reported separately. Where appropriate, the data for patients who received the MTD during Part A will be combined with that for patients who received the MTD in Part B for the purpose of data summarization. A clear distinction will be made in the relevant Tables to differentiate between the cohort who received the MTD during the dose escalation phase of Part A, the MTD cohort from the cohort expansion phase in Part A, and the combined MTD cohort.

If necessary, after the clinical phase of the study has been completed, a decision will be made between the sponsor and the study statistician regarding management of missing values, data for withdrawn patients and data for protocol violators.

Interim reports will be prepared as required during the study. The study will be completed when all patients have an OS event, unless the Sponsor terminates OS follow-up once all patients have discontinued study treatment. The database lock will take place when all data to this point, are reconciled, and the CSR will be generated. Should the last patient enrolled to the study be continuing to receive bemcentinib 52 weeks from their Cycle 1 Day 1, the Sponsor may choose to lock the data base to that point and prepare the CSR. Data collected as part of this study after this point, will be reported as an addendum to the CSR.

16.1. Description of Objectives

Please refer to Section 8.1.

16.2. Description of Endpoints

Please refer to Section 8.2.

16.3. Demography and Baseline Disease Characteristics

The Enrolled Population will include all patients who have signed the ICF and enrolled into the study. The enrolment date will be defined as the date of the first protocol-defined screening procedure. All patients in the Enrolled Population will be accounted for in patient disposition. Patient disposition will be summarized by dose group. Medical history and prior medications will be tabulated.

Data from patients who fail screening will not be collected. The exception to this will be patients who experience an SAE due to a Screening assessment. Such events should be reported and will be recorded in the CSR.

16.4. Safety

16.4.1. Analysis Population

The safety analysis set (SAS) will be defined as all patients who receive at least one dose of bemcentinib. The SAS will be analyzed by dose group or combination in Part B.

Patients enrolled to Part A who meet the eligibility criteria for Part B1 and who receive the RP2D, may contribute to the Part B1 analysis.

Any patient who continues treatment with bemcentinib beyond confirmed disease progression will be followed for safety (AEs/SAEs) as well as general condition, performance status etc., as defined in protocol section 13.

16.4.2. Methods of Analysis

No formal statistical analysis will be performed. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0 or above. The number and percentage of patients reporting treatment-emergent AEs will be tabulated by preferred term and system organ class and summarized by both CTCAE grade and relationship to study drug. All AEs commencing prior to dosing with study medication will be excluded from the tabulation but will be fully listed. AEs that have missing onset dates will be considered to be treatment-emergent, unless the stop date is known to be prior to the first administration of bemcentinib.

Separate listings will be produced for DLTs, SAEs, discontinuations due to related AEs, and events of $\geq$Grade 3 severity.

Summary statistics by dose cohort and time point will be produced for vital signs, ECG parameters and laboratory safety data, together with changes from baseline. The incidence of laboratory test results outside the normal range will be summarized by dose cohort and time point. Laboratory test results outside the normal range will be individually listed for clinical review. Abnormal ECG results will be summarized by dose cohort.

Changes in PR, QT interval and QTcF duration will be analyzed according to administered dose and ultimately modelled with corresponding plasma concentrations of bemcentinib when available.

Any patient treated with bemcentinib beyond disease progression will be followed for the same safety and efficacy assessments as for all other patients enrolled into the study. The data for patients treated beyond progression will be presented in both a combined output (with all patients) and also a separate output (reflecting a new period of analysis with the data collected in this period). All data collected will be included in the study CSR and may be presented at congress/symposia.

16.5. Efficacy

16.5.1. Analysis Population

The Efficacy Analysis Population will include all subjects who receive >1 dose of bemcentinib (Full Analysis Set).

Any patient who continues treatment with bemcentinib beyond confirmed disease progression will be followed for efficacy assessments (hematology testing, physical examinations and bone marrow biopsy, if clinically indicated), as defined in protocol section 13.

For the Per Protocol analysis set, the population will be defined as follows:

Patients that

- Meet key eligibility criteria, have assessable disease at baseline and have at least one post-baseline response assessment
- Have received >1 dose of bemcentinib (and combination agent in Part B2, B3 and B5)

16.5.2. Methods of Analysis

Although all efficacy analysis for this study is to be regarded as essentially exploratory, there will be formal hypothesis tests for the objective response rate (ORR). These will consist of one-sided, within-group tests of proportion of responders for each criterion, against the null hypothesis of a response rate $\leq$5% (this being the observed response rate under current treatment). Values of P <0.2 will be taken as sufficient evidence of a trend to justify further study and significant efficacy will support the justification to proceed to pivotal studies of bemcentinib.

Patients who on review have received at least 1 dose of bemcentinib or have a major protocol violation that will impact on the safety or efficacy analysis (e.g. do not meet key eligibility criteria or do not have evaluable disease for response assessment at baseline) may be replaced.

Data relating to efficacy response will be listed and summarized by dose cohort and time point, as appropriate.

16.6. Pharmacokinetics

16.6.1. Analysis Population

The Pharmacokinetics Analysis Population will include all patients who receive ≥1 dose of bemcentinib and have evaluable PK data available.

16.6.2. Methods of Analysis

The PK parameters listed in Table 15 (but not limited to) will be derived from the relevant concentration data of bemcentinib in each part of the study, derived from a PK model. Full details of the PK methodology will be written in a PK Analysis Plan.

Table 15: Plasma PK parameters

C_{max}	The observed maximum plasma concentration after single dose administration
t_{max}	The time to reach C_{max}
$AUC_{0\text{-}tau}$	The area under the curve within a dosing interval, calculated by the linear up-log down trapezoidal method.
λ_z	The apparent terminal rate constant estimated from individual linear regression of the terminal part of the log concentration vs. time curve
$t_{½}$	The apparent terminal half-life, calculated by $0.693/\lambda_z$

Where possible, individual, mean and median bemcentinib plasma concentration-time data will be presented in tabular and/or graphical form.

16.7. Pharmacodynamics

16.7.1. Analysis Population

The Pharmacodynamic Analysis Population will include all patients who receive ≥1 dose of bemcentinib and have ≥1 pharmacodynamic sample collected for analysis.

16.7.2. Methods of Analysis

All pharmacodynamic biomarkers will be listed and summarized by dose cohort and time-point as appropriate. No formal statistical analysis will be performed, although descriptive terms will be used to describe the results.

16.8. Safety Monitoring Committee

No formal statistical interim analyses are planned.

Data will be monitored by the SMC, in an on-going manner, to assess patient safety as outlined in Section 9.2.1.1. During Part A, the SMC will be responsible for:

- Reviewing the safety data from Cycle 1 of each dose cohort to determine whether dose escalation can proceed
- Determining the MTD prior to commencing Part B
- Defining the starting dose of bemcentinib to be administered with cytarabine/ decitabine in Part B2/Part B3.

During the execution of Part B the SMC will convene after every 10 patients have completed Cycle 1 of treatment or 6 months have elapsed, whichever occurs first. Part A and Part B3 have been fully completed (i.e. last patient last visit has been achieved in both parts). Enrolment in Part B2 has been completed with a number of patients ongoing, whereas Parts B1, B4 and B5 continue to enroll as of 17 Mar 2020.

Independent Data Monitoring Committee (IDMC) has been established since 30 Oct 2019 at the request of The Federal Institute for Drugs and Medical Devices (BfArM). During execution of the remainder of Parts B1, B2, B4 and B5, patient safety data will be monitored and assessed by the IDMC in an on-going manner in accordance with the IDMC charter.

16.9. Sample Size Considerations

Part A of the study follows a conventional algorithm (3+3 patients per dose level) to identify the MTD, escalating on 0/3 or 1/6 patients experiencing a DLT. Under this design, there is a 71% chance of escalation if the true but unknown rate of DLT is 20%, and <50% chance of escalation if the true but unknown rate of DLT is >30%. The operating characteristics of this 3+3 design are outlined in Table 16.

Table 16: Operating Characteristics of the 3+3 Study Design

True but Unknown Rate of DLT (%)	Probability of Escalation (%)
20	71
30	49
40	31
50	17
60	8

The total sample size of Part A depends upon whether DLT(s) is experienced at a given dose level (i.e. whether 3 or 6 patients have been treated) and how many dose levels are tested in order to reach the MTD. A minimum of 6- 10 patients will be treated at the MTD.

The sample size of up to 14 evaluable patients for Parts B1, B2, B3 and B4 and up to 20 evaluable patients in Part B5 in this study has been calculated on the basis of the following assumptions for a one-sided, within-group test of proportions, comparing an anticipated ORR of $\geq$20% against the null hypothesis rate of 5%, with power 80% for a test of size 0.2. This calculation is based on statistical significance at the 0.2 level, since this will be taken as evidence of a trend worthy of further study. Although this is offered as a formal sample size calculation, it is acknowledged that for this early-stage study the analyses will be exploratory in nature, and that no account has been taken of multiplicity inherent in the assessment of several, presumably non-independent criteria, for ORR.

16.10. Clinical Study Report

The results of the study will be presented in an integrated CSR according to ICH guidelines.

17. Ethical Requirements

17.1. Good Clinical Practice Statement

The clinical study will be performed in accordance with the protocol, the Declaration of Helsinki, ICH Guidelines, GCP, the European Union (EU) Clinical Trials Directive (CTD) 2001/20/EC Guideline for GCP CPMP/ICH/135/95, and all applicable local regulatory requirements.

Authorization of a Clinical Trial Application, IND, or equivalent will be obtained from the relevant Regulatory Authority prior to initiation of the study within a specific country.

17.2. Ethics Committee

The final study protocol and ICF must be approved, in writing, by the relevant REC/IRB before patient enrolment commences.

The following information should be reported to the REC/IRB during the study:

- All amendments to the research (substantial and non-substantial amendments)
- Annual progress reports
- Individual SUSARs
- DSUR on an annual basis
- Urgent Safety Measures

The investigator/designee must notify the REC/IRB within 90 days of completion of the study. However if the study is terminated prematurely, written explanation of the reason(s) for the early termination must be provided within 15 days.

17.3. Patient Information and Consent

Prior to performing any study-related activities, including screening tests and procedures, written informed consent must be obtained from the patient, in accordance with local regulations.

The ICF must be in accordance with the principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements and sponsor policy and must be approved by the reviewing REC/IRB.

17.4. Subject Data Protection

Personally identifiable information (PII) i.e. identifiable information from or about an individual will not be collected by the sponsor. The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, tolerability, quality and utility of the IMP used in this study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The ICF must explain that identifying information will be kept on file and that portions of the patient's medical records pertinent to the study will be reviewed by sponsor personnel (or their designees) and possibly by Regulatory Agencies and the REC/IRB for data verification purposes.

18. Administrative Procedures

18.1. Quality Assurance

In compliance with GCP and regulatory requirements, the sponsor/designee, external Regulatory Agency and/or REC/IRB may conduct quality assurance (QA) audits at any time during or following completion of the study. The investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

18.2. Case Report Form and Source Document Verification

Electronic CRFs will be provided for recording clinical data. Designated site personnel will record data in the eCRF for observations, tests and assessments as specified in the protocol. The investigator must permit direct access to designated source documentation (e.g. medical records) for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data.

18.3. Study Monitoring

Before a patient can be screened for enrolment into the study, the sponsor/designee will conduct a study initiation visit to:

- Determine that the site facilities are adequate
- Discuss responsibilities with regard to the protocol with the investigator and study team
- Conduct training on completion of the eCRF and other study related documentation
- Review study procedures

During the conduct of the study, the sponsor/designee will provide support to the investigator and study team via telephone/e-mail communication. The sponsor/designee will conduct regular site visits, according to applicable ICH and GCP guidelines, to:

- Confirm the facilities remain acceptable
- Confirm the site study team are adhering to the protocol and regulatory requirements
- Confirm that the IMP is being properly maintained and accountability records are accurate and current
- Confirm data are being accurately recorded in the eCRF by performing source document verification

18.4. Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the sponsor of the trial is responsible for notifying the Regulatory Authorities in writing, within 7 days, of any serious breach of:

- The conditions and principles of GCP in connection with the study
- The protocol relating to the study

Whilst under investigation, the site is requested to cooperate with the sponsor/designee in providing sufficient information to report the breach to the Regulatory Authorities where required, and in undertaking any corrective and/or preventive action.

18.5. Retention of Study Data

A copy of all records and essential documents must be retained in the study files for a minimum of two years following the last approval of the drug in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or a minimum of two years have elapsed since the formal discontinuation of the clinical development of the drug. No documents should be destroyed without prior written agreement between the sponsor and the investigator.

Should the investigator wish to assign the documents to another party or move them to another location, the sponsor must be notified. The sponsor will notify the investigator in writing when the study-related documents are no longer needed.

18.6. Use of Information and Publication Policy

All information regarding bemcentinib and the sponsor's operations (e.g. patent applications, formulas, manufacturing processes, basic scientific data, or formulation information) supplied by the sponsor to the investigator and not previously published is considered confidential. This confidential information remains the sole property of the sponsor and shall not be disclosed to others without the written consent of the sponsor. The investigator agrees to use this information only to perform this study and will not use it for other purposes including publications and presentations without the sponsor's written consent. The full terms of confidentiality, intellectual property and publication policy are detailed in the current Clinical Trial Agreement between the sponsor and the site.

18.7. Contract Research Organizations

Monitoring, data management, statistics and programming, medical writing, auditing and QA services will be outsourced to the sponsor's CRO Covance

Pharmacovigilance services will be outsourced to Syneos Health

PK and pharmacodynamics analyses will be outsourced to the sponsor's Bioanalytical services vendor.

18.8. Changes to the Final Study Protocol

All protocol amendments must be submitted to the REC/IRB and, if applicable, to the Regulatory Authorities.

Protocol amendments that affect patient safety, the scope of the investigation, or the scientific quality of the study should not be implemented without prior Regulatory Authority/REC/IRB approval (where applicable), except where necessary to eliminate immediate hazards to the patients.

18.9. Investigator Responsibilities

By signing the protocol, the investigator agrees to:

- Conduct the study in accordance with the protocol and make changes only after notifying the Sponsor, except to protect the safety, rights or welfare of patients
- Personally conduct or supervise the study
- Inform any patients enrolled in the study that the drug is being used for investigational purposes
- Ensure that the requirements relating to obtaining informed consent and REC/IRB review and approval meet Federal guidelines, as stated in 21CFR50 and 21CFR56
- Report to the Sponsor any AEs that occur during the course of the study, in accordance with 21CFR312.32, as well as ICH guidelines
- Have read and understood the IB for bemcentinib, including potential risks and side effects of the drug
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments
- Maintain adequate and accurate records, in accordance with 21CFR312.62 and to make those records available for inspection by the sponsor, their designated

representative, relevant Regulatory Authorities/REC/IRB or any agency authorized by law

- Ensure that a REC/IRB that complies with the requirements of 21CFR56 will be responsible for initial and continuing review and approval of the clinical study
- Report promptly to the REC/IRB and the sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include protocol amendments and IND safety reports)
- Not make any changes in the research study without approval, except when necessary to eliminate hazards to the subject/subjects
- Comply with all other requirements regarding the obligations of the clinical investigators and all other pertinent requirements listed in 21CFR312

19. References

Ben-Batalla I, Schultze A, Wroblewski M, et al., AXL a prognostic and therapeutic target in acute myeloid leukemia mediates paracrine crosstalk of leukemia cells with bone marrow stroma. *Blood* (2013) 122(14): 2443–2452.

Cheson BD, Bennett JM, Kopecky KJ, *et al*., Revised recommendations of the International Working Group for Diagnosis, Standardisation of Response Criteria, Treatment Outcomes and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* (2003) 21(24): 4642–4649.

Cheson BD, Greenberg PL, Bennett JM *et al*., Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* (2006) 108(2): 419–425.

Döhner H, Estey E, Grimwade D, et al., Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* (2017) 129(4): 424-447.

Oken MM, Creech RH, Tormey DC, *et al.,* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* (1982) 5(6): 649–655.

Whitman SP, Kohlschmidt J, Maharry K, *et al.,* Gas6 expression identifies high-risk AML patients: potential implications for therapy. *Leukemia* (2013) Dec 11. doi: 10.1038/leu.2013.371. [Epub ahead of print].

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (1994). (9th ed.). Boston: Little, Brown & Co. 253–256.

20. Appendices

Appendix 1: Eastern Cooperative Oncology Group (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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

From Oken *et al., 1982* with credit to the ECOG Chair Robert Comis M.D

Appendix 2: The New York Heart Association (NYHA) Functional Classification in a Patient with Heart Disease

Overview: The New York Heart Association (NYHA) developed a functional classification for patients with heart disease.

Patients: Heart disease must be present.

Parameters:

1) Limitations on physical activity
2) Symptoms (undue fatigue palpitations dyspnea and/or anginal pain) with ordinary physical activity
3) Status at rest

Limitations on Physical Activity	Symptoms with Ordinary Physical Activity	Status at Rest	Class
none	none	comfortable	I
slight	symptomatic with ordinary activities	comfortable	II
marked	symptomatic at less than ordinary levels of activity	comfortable	III
unable to perform any activity	discomfort with any activity	symptomatic at rest	IV

From The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (1994). (9th ed.). Boston: Little, Brown & Co. 253 – 256

Appendix 3: Drugs Associated with a Risk of QT Prolongation and Cardiac Arrhythmias

For any concomitant medication, please check the following website for the drug's Torsades de Pointes (TdP) risk: https://crediblemeds.org/oncosupport/. Drugs with known TdP risk should be avoided. For drugs with a conditional risk, please review the product label and correct any abnormalities, e.g. hypokalemia.

Known Risk of TdP	Substantial evidence supports the conclusion that these drugs prolong the QT interval AND are clearly associated with a risk of TdP, even when taken as directed in official labelling.
Possible Risk of TdP	Substantial evidence supports the conclusion that these drugs can cause QT prolongation BUT there is insufficient evidence at this time that these drugs, when used as directed in official labelling, are associated with a risk of causing TdP.
Conditional Risk of TdP	Substantial evidence supports the conclusion that these drugs are associated with a risk of TdP BUT only under certain conditions (e.g. excessive dose, hypokalemia, congenital long QT or by causing a drug-drug interaction that results in excessive QT interval prolongation)

Generic Name	**Brand Name**
Amiodarone	Coradone/Pacerone
Anagrelide	Agrylin®, Xagrid®
Arsenic trioxide	Trisenox
Astemizole	Hismanal
Azithromycin	Zithromax®, Zmax®
Bepridil	Vascor
Chlorquine	Arelan
Chlorpromazine	Thorazine
Cisapride	Propulsid
Citalopram	Celexa®, Cipramil®
Clarithromycin	Biaxin
Cocaine	Cocaine
Disopyramide	Norpace
Dofetilide	Tikosyn
Domperidone	Motilium
Dronedarone	Multaq®
Droperidol	Inapsine
Erythromycin	Erythrocin/E.E.S.
Escitalopram	Cipralex®, Lexapro®
Flecainide	Tambocor®, Almarytm®
Halofantrine	Halfan
Haloperidol	Haldol
Ibutilide	Covert
Levomethadyl	Orlaam
Mesoridazine	Serentil
Methadone	Methadose/Dolophine
Moxifloxacin	Avelox
Ondansetron	Zofran®, Anset®

Petamidine	NebuPent/Pentam
Pimozide	Orap
Probucol	Lorelco
Procainamide	Pronestyl/Procan
Propofol	Diprivan
Quinidine	Cardioquin/Quinaglute
Sevoflurane	Ulane®, Sojourn®
Sotalol	Betapace
Sparfloxacin	Zagam
Sulpiride	Dogmatil®, Dolmatil®
Terfenadine	Seldane
Thioridazine	Mellaril
Vandetanib	Zactima

Woosley RL, Heise CW , Gallo T, Tate J, Woosley D and Romero KA, www.CredibleMeds.org, QTdrugs List, [Accession Date], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

Appendix 4: CYP3A4 Substrates

Examples of CYP3A4 substrates are provided below. For most up-to-date information on CYP3A4 substrates, please check the Drug Interactions Flockhart Table™ https://drug-interactions.medicine.iu.edu/Main-Table.aspx.

University of Indiana CYP3A4, 5, 7 P450 Drug Interactions Abbreviated "Clinically Relevant" Table of Substrates

Macrolide antibiotics:	**HIV Antivirals:**	**HMG CoA Reductase Inhibitors:**
clarithromycin	indinavir	atorvastatin
erythromycin (not 3A5)	ritonavir	lovastatin
NOT azithromycin	saquinavir	NOT pravastatin
telithromycin	nevirapine	NOT rosuvastatin
		simvastatin
Anti-arrhythmics:	**Prokinetics:**	
quinidine→3-OH	cisapride	**Others:**
		alfentanyl
Benzodiazepines:	**Antihistamines:**	aripiprazole
alprazolam	astemizole	boceprevir
diazepam→3OH	chlorpheniramine	buspirone
midazolam	terfenadine	carbamazepine
triazolam	**Calcium Channel Blockers:**	gleevec
	amlodipine	haloperidol
Immune Modulators:	diltiazem	pimozide
cyclosporine	felodipine	quinine
tacrolimus (FK506)	nifedipine	tamoxifen
sirolimus	nisoldipine	telaprevir
	nitrendipine	trazodone
PDE-5 Inhibitors:	verapamil	vincristine
sildenafil		diergotamine & ergotamine
tadalafil		fentanyl
vardenafil		

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "/clinpharm/ddis/clinical-table/" Accessed 20 October 2016.

Appendix 5: Modified International Working Group Response Criteria in Acute Myeloid Leukemia (Cheson, 2003, Döhner, 2017)

IWG Response Criteria in AML		Bone Marrow Blasts/Myeloblast	Circulating or Peripheral Blood Blasts[a]	Absolute Neutrophil Count	Platelet Count	EMD
Morphologic Complete Remission	CR	<5% and no myeloblasts with Auer rods	None	≥1.0 x 10^9/L or ≥1,000/µL	≥100 x 10^9/L or ≥100,000/µL	None
CR with Incomplete Blood Count Recovery	CRi	<5% and no myeloblasts with Auer rods	None	<1.0 x 10^9/L or <1,000/µL	<100 x 10^9/L or <100,000/µL	None
Morphologic leukemia-free state	MLFS	<5% and no myeloblasts with Auer rods[b]	No hematologic recovery required			None
Partial Remission	PR	Decrease of myeloblasts % to 5% to 25% and decrease of pretreatment myeloblast % by at least 50%	All hematologic criteria of CR			
Unchanged	UN	Absence of CR, CRi or PR and criteria for PD not met				
Progressive Disease[c]	PD	>50% increase in myeloblasts over the pretreatment value (a minimum 15% increase is required if <30% myeloblasts pretreatment)	>50% increase in PB to >25 × 10^9/L or >25 000/µL[d]			New EMD disease

a. PBs are quantified as an automated WBC times percentage of blasts by manual differential (100 cells) per standard clinical laboratory procedures.
b. BM examination should not be aplastic, and have at least 200 cells or cellularity should be at least 10%
c. PD is usually accompanied by a decline in ANC and platelets, increased transfusion requirement and decline in performance status and increase in symptoms.
d. Certain targeted therapies may cause a differentiation syndrome, that is, a transient increase in the percentage of BM blasts (myeloblasts) and an absolute increase in PBs; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

Abbreviations: AML, acute myeloid leukemia, ANC, Absolute Neutrophil Count; BL, EMD, Extramedullary Disease; IWG, International Working Group, PB, Peripheral Blood Blast; WBC, White Blood Cell.

References

- Cheson BD, Bennett JM, Kopecky KJ, *et al*. Revised Recommendations of the International Working Group for Diagnosis, Standardisation of Response Criteria, treatment Outcomes and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol (2003) 21 (24): 4642 – 4649.
- Döhner H, Estey E, Grimwade D, *et al*. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood (2017) Jan 26; 129(4): 424–447.

Appendix 6: International Working Group Response Criteria in Myelodysplastic Syndromes (Cheson, 2006)

Category A: Altering the natural history of disease			
IWG Response Criteria in MDS	**Bone Marrow[a]**	**Peripheral Blood[a]**	**Additional Considerations**
Complete Remission (CR)	≤5% myeloblasts with normal maturation of all cell lines with no evidence for dysplasia[b]	Normalization of blood counts as defined by: • Hb ≥11g/dL (not supported by EPO or transfusions) • Platelets ≥100 x 10^9/L or 100,000/µL (not supported by transfusions) • Neutrophils ≥1.5 x 10^9/L or 1,500/µL (not supported by G-CSF) • PB 0%	Responses to be confirmed in two successive assessments; response parameters in peripheral blood needs to be maintained for at least 6 weeks.
Partial Remission (PR)	All CR criteria met if abnormal before treatment except for: • Myeloblasts decrease by 50% or more over pretreatment value but still >5%, or • Less advanced FAB or IPPS category compared to pretreatment value	Hematologic improvement	Absolute values must last at least 6 weeks.
Marrow CR	≤5% myeloblasts and decrease by ≥50% over pretreatment value	If hematologic improved, these should be noted in addition to marrow CR (see Category B).	
Stable Disease (SD)	Failure to achieve at least PR, but no evidence of PD for at least 3 treatment cycles.		
Progressive Disease (PD)	• For patients with less than 5% myeloblasts: a 50% or more increase in myeloblasts to more than 5% myeloblasts. • For patients with 5% to 10% myeloblasts: a 50% or more increase to more than 10% myeloblasts.	Myeloblast increase plus at least one of the following: • ≥50% decrease in ANC or platelets • Reduction in Hb by ≥2g/dL • Transfusion dependence.	Death during treatment

	• For patients with 10% to 20% myeloblasts: a 50% or more increase to more than 20% myeloblasts. • For patients with 20% to 30% myeloblasts: a 50% or more increase to more than 30% myeloblasts.		
Relapse after CR or PR	Relapse is characterized by at least one of the following: • Return to pretreatment myeloblasts percentage • ≥50% decrease in ANC or platelets Reduction in Hb by ≥2g/dL or transfusion dependence.		
Disease transformation	Transformation to AML (30% or more blasts).		
Category B: Hematologic Improvement (HI)			
	Hematopoietic Lineage	**Response Criteria**	**Definition[a]**
	Erythroid (HI-E)	Major response	For patients with pretreatment Hb<11 g/dL, greater than 2 g/dL increase in Hb; for RBC transfusion-dependent patients, transfusion independence.
		Minor response	For patients with pretreatment Hb <11 g/dL, 1 to 2 g/dL increase in Hb; for RBC transfusion-dependent patients, 50% decrease in transfusion requirements.
	Platelet (HI-P)	Major response	For patients with pretreatment PLT counts of <100 x 10^9/L or 100,000/μL, an absolute increase of 30 x 10^9/L or 30,000/μL or more; for PLT transfusion-dependent patients, stabilization of PLT counts and PLT transfusion independence.

		Minor response	For patients with pretreatment PLT counts <100 x 10^9/L or 100,000/μL, a 50% or more increase in PLT count with a net increase >10 x 10^9/L or 10,000/μL but less than 30 x 10^9/L or 30,000/μL.
	Neutrophil (HI-N)	Major response	For ANC <1.5 x 10^9/L or 1,500/μL before therapy, ANC increase of at least a 100%, or an absolute increase of more than 0.5 x 10^9/L or 500/μL, whichever is greater.
		Minor response	For ANC less than 1.5 x 10^9/L or 1,500/μL before therapy, ANC increase of at least 100%, but absolute increase less than 0.5 x 10^9/L or 500/μL.
Category C: Cytogenetic Response (CRc)[b]			
	Major CRc	No detectable cytogenetic abnormality, if preexisting abnormality was present.	
	Minor CRc	≥50% reduction of abnormal metaphases	

a. Improvements in BM and PB must be based on ≥2 successive assessments; response in PBN must be maintained for at least 6 weeks.
b. IWG criteria require 20 analyzable metaphases assessed by conventional cytogenetic studies to diagnose or exclude the presence of a cytogenetic abnormality. For normal Karyotype, 20 metaphases are optimal to ensure that enough metaphases have been examined. For cytogenetic response, 20 metaphases are optimal, but not necessary, to define the degree of cytogenetic response. FISH to assess changes in a specific cytogenetic abnormality is acceptable.

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; EPO, erythropoietin; G-CSF, FAB, French-American-British (classification system); IPPS, International Prognostic Scoring System; granulocyte colony stimulating factor; Hb, hemoglobin; IWG, International Working Group; MDS, myelodysplastic syndrome; PB, peripheral blast; PLT, platelet; RBC, red blood cell.

Reference

Cheson BD, Greenberg PL, Bennett JM. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006; 108:419-425.